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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Enbrel® / Etanercept

PROTOCOL NO.: 0881A5-401 (B1801271)

PROTOCOL TITLE: A Randomised, Double-Blind, Two-Period Study to Evaluate the Safety and Efficacy of Etanercept on Skin and Joint Disease in Psoriasis Subjects with Psoriatic Arthritis

Study Centers: A total of 102 centers took part in this study and randomized subjects; 5 in Argentina, 2 in Australia, 2 in Austria, 2 in Belgium, 2 in Colombia, 3 in Czech Republic, 5 in Denmark, 3 in Finland, 12 in France, 15 in Germany, 1 in Greece, 6 in Hungary, 7 in Italy, 2 in Republic of Korea, 2 in Mexico, 4 in Netherlands, 4 in Poland, 2 in Portugal, 1 in Serbia, 3 in Serbia and Montenegro, 5 in Spain, 2 in Sweden, 2 in Switzerland, 2 in Taiwan, 1 in Turkey, 7 in the United Kingdom.

Study Initiation Date and Final Completion Dates: 25 December 2005 to 29 March 2008

Phase of Development: Phase 3b/4

Study Objectives: The primary objective of the study was to compare the efficacy of 2 different etanercept treatment regimens in treating the skin manifestations of psoriasis subjects with psoriatic arthritis (PsA) over 12 weeks. The study hypothesis was that etanercept 50 mg administered twice weekly (BIW) would demonstrate superior clinical efficacy, as determined by the proportion of subjects achieving a Physician Global Assessment (PGA) of psoriasis of clear or almost clear at 12 weeks, compared with etanercept 50 mg administered once weekly (QW).

The secondary objectives were:

1. To compare the efficacy of 2 different treatment regimens of etanercept in treating the skin manifestations over 24 weeks

2. To compare the efficacy of 2 different treatment regimens of etanercept on joint disease over 12 and 24 weeks

3. To compare the impact of 2 different treatment regimens of etanercept on quality of life and pharmacoeconomic outcomes over 12 and 24 weeks

4. To evaluate the time course of treatment response to 2 different treatment regimens of etanercept

5. To evaluate the safety and tolerability of 2 different treatment regimens of etanercept.

METHODS

Study Design: This was a randomized, multicenter outpatient study conducted in subjects with PsA. The study consisted of a 12-week double-blind treatment period followed by a 12-week open-label treatment period and a follow-up phone call.

Subjects were randomly assigned to 1 of 2 etanercept treatment regimens in a 1:1 ratio:

- 50 mg etanercept administered BIW for 12 weeks in Period 1 followed by 50 mg etanercept administered QW for 12 weeks in Period 2.

- 50 mg etanercept administered QW and matching placebo administered QW for 12 weeks in Period 1 followed by etanercept at a dose of 50 mg administered QW for 12 weeks in Period 2.

Although all subjects received open-label etanercept during Period 2, they remained blinded to their treatment during Period 1 throughout the study.

Subjects who did not achieve at least an improvement of 1 unit from baseline on the PGA of psoriasis by Week 12 were deemed treatment failures and were withdrawn from the study, unless the Investigator determined that the treatment was providing improvement in joint symptoms. After the 24 week treatment period, there was a 2 week follow-up telephone call to assess for adverse events (AEs). The study flowchart is summarized in Table 1.

Table 1. Study Flowchart

Study Week[a]	Screening[b] -4 to 0	Baseline 0	3	6	12	18	24	26	Early Discontinuation
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[c]**	**99**
Informed consent	X								
Medical history	X								
Inclusion/exclusion criteria	X	X							
Prior medications	X	X							
Concomitant medications			X	X	X	X	X		X
Physical examination	X	X			X		X		X
Vital signs[d]	X	X	X	X	X	X	X		X
Joint assessment (including dactylitis and enthesitis)[e]	X	X[f]			X		X		X
Physician global assessment of arthritis[e]		X			X		X		X
Physician global assessment of psoriasis[e]	X	X[f]	X	X	X	X	X		X
Body surface area involvement of psoriasis[e]	X	X[f]	X	X	X	X	X		X
Psoriasis area and severity index (PASI)[e]		X	X	X	X	X	X		X
Subject assessments[g]		X	X	X	X	X	X		X
Health assessment questionnaire (HAQ)		X	X	X	X	X	X		X
Dermatology life quality index (DLQI)		X	X	X	X	X	X		X
EuroQol-5D (EQ-5D)		X	X	X	X	X	X		X
Hospital anxiety and depression scale (HADS)		X			X		X		X
Subject pharmacoeconomic questionnaire		X			X		X		X
Psoriatic arthritis quality of life (PsAQoL)[h]		X			X		X		X
Pregnancy test[i]	X	X							
Chemistry, haematology, urinalysis	X	X[f]			X		X		X
C-reactive protein		X			X		X		X
Serum rheumatoid factor[j]	X								
Adverse events[k]		X	X	X	X	X	X	X[c]	X
Randomization		X							
Drug accountability			X	X	X	X	X		X
Drug dispensation		X		X	X	X			

a. The visit window for Visits 2 through 7 was ± 4 days (Weeks 0 to 24). If 2 different physicians were conducting assessments for a given visit (for example, 1 assessment by a dermatologist and another assessment by a rheumatologist), the assessments were to be done within 8 days of each other.
b. Screening and baseline visits may have occurred on the same day if subjects did not require a washout of prohibited medications. Women of childbearing potential, however, had to have both serum and urine pregnancy testing.
c. Telephone call to follow-up adverse events, occurring approximately 15 days after Visit 7 or early discontinuation.
d. Included sitting blood pressure and pulse rate; weight and height were recorded only at baseline.
e. It was recommended that the same qualified medical personnel completed these assessments at each visit. Generally, a dermatologist was to complete the psoriasis evaluations and a rheumatologist was to complete the joint and arthritis evaluations. Enthesitis assessment was to be performed only if conducted by a rheumatologist or trained assessor.
f. Waived if first dose within 14 days of screening evaluation. This waiver only applied if all screening procedures were done within 14 days.
g. These assessments were on general health, psoriasis disease activity, itching, arthritis activity, joint pain, fatigue, and morning stiffness.
h. The Psoriatic arthritis quality of life was only be administered on subjects for whom a valid translation of the instrument was available.
i. For women of childbearing potential only (serum test at screening visit, urine at baseline visit).
j. Required if no documentation of negative serum rheumatoid factor within 6 months of screening visit.
k. From the signing of the informed consent form (ICF) to approximately 15 days after Visit 7 or early discontinuation.

Number of Subjects (Planned and Analyzed): The study was planned to enroll approximately 800 subjects. The study actually enrolled 754 subjects: 35 in Argentina, 13 in Australia, 9 in Austria, 7 in Belgium, 11 in Columbia, 51 in Czech Republic, 26 in Denmark, 11 in Finland, 21 in France, 117 in Germany, 3 in Greece, 107 in Hungary, 45 in Italy, 15 in Republic of Korea, 18 in Mexico, 23 in Netherlands, 42 in Poland, 3 in Portugal, 108 in Serbia and Montenegro, 20 in Spain, 4 in Sweden, 12 in Switzerland, 23 in Taiwan, 1 in Turkey, and 29 in the United Kingdom. Two (2) enrolled subjects were not administered study medication and were not included in the safety or efficacy analyses.

Diagnosis and Main Criteria for Inclusion: Subjects aged 18 years and older with active psoriatic arthritis along with stable, plaque psoriasis involving more than 10% of the body surface area were included in the study. Subjects with evidence of skin conditions other than psoriasis that would interfere with skin examinations, or undergoing systemic anti-psoriasis therapy or disease-modifying antirheumatic drug (DMARD) within 28 days of study drug initiation, or with prior exposure to any tumor necrosis factor (TNF) inhibitor, including etanercept, were not included in the study.

Study Treatment: Etanercept 50 mg and placebo were supplied in vials as sterile lyophilized powder. The diluent for rehydration of etanercept/placebo was sterile water for injection provided in pre-filled syringes. Study drug was administered by subcutaneous injection. Site personnel instructed the subject (or designee) on proper sterile technique and on the reconstitution and administration of etanercept. At the baseline visit, the first dose of etanercept was to be reconstituted and administered by site personnel while the subject (or designee) observed.

Group A received etanercept 50 mg BIW (1 injection of etanercept 50 mg twice weekly) for 12 weeks (Period 1) followed by etanercept 50 mg QW (1 injection of etanercept 50 mg once weekly) for 12 weeks (Period 2). Group B received etanercept 50 mg QW for the full 24 weeks (1 injection of etanercept 50 mg once weekly and 1 injection of placebo once weekly for 12 weeks in Period 1 and 1 injection of etanercept 50 mg once weekly for 12 weeks in Period 2). The injectable test article was to be administered at approximately the same time of day (± 4 hours) and on the same day of the week. Injections were to be administered in the abdomen, thigh, or upper arm and the location was to be rotated with each dose.

Efficacy Endpoints:

Primary endpoint: Proportion of subjects achieving a status on the PGA of psoriasis of clear or almost clear at Week 12

Secondary efficacy endpoints:

- Proportion of subjects achieving a 50% and 75% improvement or greater from baseline in Psoriasis Area and Severity Index (PASI) score at Weeks 12 and 24
- Proportion of subjects achieving a status on the PGA of psoriasis of clear, almost clear, or mild at Weeks 12 and 24

- Proportion of subjects achieving a status on the PGA of psoriasis of clear or almost clear at Week 24
- Change from baseline by visit in the PGA of psoriasis over 12 and 24 weeks
- Change from baseline by visit in the PASI over 12 and 24 weeks
- Change from baseline by visit in the % body surface area (BSA) involvement of psoriasis
- Change from baseline by visit in the Subject Assessments (General Health, Psoriasis Activity, Itching, Joint Pain, Arthritis Activity, Fatigue, and Morning Stiffness)
- Change from baseline by visit in the PGA of Arthritis
- Proportion of subjects achieving American College of Rheumatology (ACR) 20, 50 and 70 responses at Week 12 and 24
- Proportion of subjects achieving Psoriatic Arthritis Response Criteria (PsARC) at Week 12 and 24

Safety Evaluations: Safety was assessed by evaluation of AEs, vital sign measurements, physical examination findings, and results of laboratory testing. Safety data were collected up to approximately 15 days (or date of telephone follow-up call) after the 24 weeks of treatment.

Statistical Methods: The modified intend-to treat (mITT) population included all subjects who took at least 1 dose of test article and had at least 1 post baseline efficacy evaluation. The mITT population was the primary population for efficacy analyses.

All randomized subjects with documented use of at least 1 dose of double-blind test article were included in the safety population. Subjects who were dispensed test article but had no documented use of at least 1 dose were not included in the safety population.

This study was designed to test the superiority of etanercept given 50 mg BIW compared with etanercept given 50 mg QW based on the primary endpoint of the proportion of subjects achieving a status of clear or almost clear on the PGA of psoriasis at Week 12. The null hypothesis of no difference between the 2 groups was tested using the Mantel-Haenszel chi-square test, stratified by geographic region, using a 2-sided test at α=0.05. Other endpoints that measured the proportions of subjects were compared using the Mantel-Haenszel chi-square test. Continuous and ordinal endpoints, eg, change from baseline in global assessments, were analyzed using analysis of covariance (ANCOVA) stratified by geographic region with baseline value as covariate when baseline value was applicable or using analysis of variance (ANOVA) when baseline value was not applicable.

The primary efficacy analyses used the last observation carried forward (LOCF) approach for missing data imputation; observed cases (OC) results were also summarized for each visit including only those subjects contributing data at each time point.

RESULTS

Subject Disposition and Demography: A total of 754 subjects were enrolled and 752 subjects were treated. Of these, 379 subjects received etanercept 50 mg BIW in Period 1 and etanercept 50 mg QW in Period 2 (50 mg BIW/QW group) and 373 subjects received etanercept 50 mg QW in Periods 1 and 2 (50 mg QW group). All 752 treated subjects were included in the mITT and safety populations. Two subjects were enrolled but were not administered study medication and are not included in the efficacy or safety analyses.

Nearly all subjects in the etanercept 50 mg BIW/QW and 50 mg QW groups completed the study (92.3% and 92.5%, respectively). The most common reasons for discontinuation from the study were AE (3.2%), subject request (1.6%), and unsatisfactory response (1.3%). Subject disposition is summarized in Table 2.

Table 2. Subject Disposition

Conclusion Status Reason[a]	Overall p-Value	Treatment 50 mg BIW/QW (N=379) n (%)	Treatment 50 mg QW (N=373) n (%)	Total (N=752) n (%)
Total treated		379 (100)	373 (100)	752 (100)
Completed	1.000	350 (92.3)	345 (92.5)	695 (92.4)
Discontinued	1.000	29 (7.7)	28 (7.5)	57 (7.6)
Adverse event	0.535	14 (3.7)	10 (2.7)	24 (3.2)
Lost to follow-up	1.000	2 (0.5)	2 (0.5)	4 (0.5)
Protocol violation	1.000	4 (1.1)	3 (0.8)	7 (0.9)
Subject request	0.575	5 (1.3)	7 (1.9)	12 (1.6)
Unsatisfactory response-efficacy	0.543	4 (1.1)	6 (1.6)	10 (1.3)

Overall p-value: Fisher exact test p-value (2-tail).
BIW = twice weekly; N = total number of subjects; n = number of subjects meeting criteria; QW = once weekly.
a. Total discontinued was the sum of individual reasons because they are mutually exclusive by subject.

The study population included healthy subjects 18 years of age or older. Subjects had a mean age of 46.52 years. Most subjects were men (62.9%) and most were white (88.8%). A summary of the subject demography is presented in Table 3.

Table 3. Demographic and Baseline Characteristics of Safety Population

Characteristic	p-Value	Treatment		
		50 mg BIW/QW (N=379)	50 mg QW (N=373)	Total (N=752)
Age (years)				
N		379	373	752
Mean	0.328[a]	46.11	46.93	46.52
Standard deviation		11.39	11.41	11.4
Minimum		18	21	18
Maximum		82	77	82
Median		46	48	47
Sex, n (%)	0.498[b]			
Female		136 (35.88)	143 (38.34)	279 (37.10)
Male		243 (64.12)	230 (61.66)	473 (62.90)
Race, n (%)	0.742[b]			
Aboriginal		1 (0.26)	0	1 (0.13)
Arabic		1 (0.26)	2 (0.54)	3 (0.40)
Asian		23 (6.07)	20 (5.36)	43 (5.72)
Other		21 (5.54)	16 (4.29)	37 (4.92)
White		333 (87.86)	335 (89.81)	668 (88.83)
Baseline height (cm)				
N		369	367	736
Mean	0.164[a]	172.40	171.40	171.90
Standard deviation		9.86	9.66	9.77
Minimum		149	146	146
Maximum		203	200	203
Median		172	172	172
Missing		10	6	16
Baseline weight (kg)				
N		371	369	740
Mean	0.171[a]	81.95	83.75	82.85
Standard deviation		17.07	18.65	17.88
Minimum		47	42	42
Maximum		195	182	195
Median		80	83	81
Missing		8	4	12
Body mass index				
N		368	367	735
Mean	0.026[a]	27.53	28.42	27.98
Standard deviation		5.08	5.7	5.42
Minimum		16.1	15.8	15.8
Maximum		55.5	63.0	63.0
Median		26.9	27.5	27.2
Missing		11	6	17

BIW = twice weekly; N = number of subjects; n = number of subjects meeting criteria; QW = once weekly.
a. One (1)-way analysis of variance with treatment as factor.
b. Fisher exact test p-value (2-tail).

Efficacy Results: The primary efficacy endpoint was the comparison between subjects in the etanercept 50 mg BIW/QW group and the etanercept 50 mg QW group for the proportion of subjects achieving a status of clear or almost clear on the PGA of psoriasis at Week 12. At Week 12, a significantly greater proportion of subjects in the etanercept 50 mg BIW/QW group compared with the 50 mg QW group had a PGA of psoriasis status of clear or almost

clear in the LOCF analysis (46.44% versus 31.90%, p<0.001). The results of the OC analysis were similar to the results of the LOCF analysis. A summary of the proportion of subjects with a status of clear of almost clear on the PGA of psoriasis status at Week 12 is presented in Table 4.

Table 4. Proportion of Subjects With a Psoriasis Status of Clear or Almost Clear at Week 12

Time on Therapy	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	p-Value (Cochran-Mantel -Haenszel Test)
Week 12			
LOCF	176/379 (46.44%)	119/373(31.90%)	<0.001
Observed cases	173/367 (47.14%)	118/363(32.51%)	<0.001

BIW = twice weekly; LOCF = last observation carried forward; N = total number of subjects; n= number of subjects meeting criteria; QW = once weekly.

Secondary Endpoints:

Proportion of Subjects Achieving a 50% or 75% or Greater Improvement From Baseline in Psoriasis Area and Severity Index Score at Weeks 12 and 24: At Week 12, a significantly greater proportion of subjects in the etanercept 50 mg BIW/QW group compared with the 50 mg QW group achieved ≥50% and ≥75% improvements in PASI scores. The proportion of subjects achieving a ≥75% improvement in PASI score at Week 24 was significantly greater in the etanercept 50 mg BIW/QW group compared with the 50 mg QW group, whereas, a similar proportion of subjects in both groups had a ≥50% improvement at Week 24. The proportion of subjects achieving a 50% or 75% or greater improvement from baseline in PASI score at Weeks 12 and 24 is presented by treatment group in Table 5.

Table 5. Proportion of Subjects Achieving a 50% and 75% Improvement or Greater From Baseline in Psoriasis Area Severity Index Score at Weeks 12 and 24 - LOCF Analysis

	Time on Therapy	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	p-Value (Cochran-Mantel -Haenszel Test)
≥50% Improvement	Week 12	302/377 (80.11%)	274/371 (73.85%)	0.049
	Week 24	325/377 (86.21%)	306/371 (82.48%)	0.185
≥75% Improvement	Week 12	207/377 (54.91%)	135/371 (36.39%)	<0.001
	Week 24	265/377 (70.29%)	231/371 (62.26%)	0.026

BIW = twice weekly; LOCF = last observation carried forward; n = number of subjects meeting criteria; N = total number of subjects; QW = once weekly.

Proportion of Subjects Achieving a Status of Clear, Almost Clear, or Mild on the Physician Global Assessment of Psoriasis at Weeks 12 and 24: The proportion of subjects achieving a status of clear, almost clear, or mild on the PGA of psoriasis was significantly greater in the etanercept 50 mg BIW/QW group compared with the 50 mg QW group at Week 12 in the LOCF analysis. The proportions were similar for both treatment groups at Week 24. A summary of the proportion of subjects achieving a status of clear, almost clear, or mild on the PGA at Weeks 12 and 24 is presented in Table 6.

Table 6. Proportion of Subjects Achieving a Status of Clear, Almost Clear, or Mild on the Physician Global Assessment at Weeks 12 and 24 - LOCF Analysis

Time on Therapy	Population	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	p-Value (Cochran-Mantel -Haenszel Test)
Week 12	LOCF	296/379 (78.10%)	266/373 (71.31%)	0.041
Week 24	LOCF	302/379 (79.68%)	295/373 (79.09%)	0.934

ANCOVA Model: Change = baseline score + therapy + pooled-center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; n = number of subjects meeting criteria; N = total number of subjects; QW = once weekly.

Proportion of Subjects Achieving a Status of Clear or Almost Clear on the PGA of Psoriasis at Week 24: The proportion of subjects who achieved a status of clear or almost clear on the PGA of psoriasis was not significantly different between etanercept groups at Week 24 in the LOCF analysis. The summary of subjects achieving a status of clear or almost clear on the PGA of psoriasis at Week 24 is presented in Table 7.

Table 7. Proportion of Subjects Achieving a Status of Clear or Almost Clear on the Physician Global Assessment at Week 24 - LOCF Analysis

Time on Therapy	Population	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	p-Value (Cochran-Mantel -Haenszel Test)
Week 24	LOCF	214/379 (56.46%)	187/373 (50.13%)	0.104

ANCOVA Model: Change = baseline score + therapy + pooled-center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; n = number of subjects meeting criteria; N = total number of subjects; QW = once weekly.

Change From Baseline by Visit on the PGA of Psoriasis Over 12 and 24 Weeks: At Week 12, the percent change from baseline in the PGA of psoriasis was significantly greater in the etanercept 50 mg BIW/QW group compared with the 50 mg QW group in the LOCF analysis. At Week 24, the change from baseline was similar between etanercept groups. The summary of change from baseline by visit on the PGA of psoriasis is presented in Table 8.

Table 8. Mean and Percent Change (Improvement) From Baseline by Visit in the Physician Global Assessment of Psoriasis - LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW Mean Score (Percent of Change From Baseline)	Etanercept 50 mg QW Mean Score (Percent of Change From Baseline)	p-Value From ANCOVA
Baseline	3.60 (0.00) (N=379)	3.61 (0.00) (N=373)	0.769
Week 3	2.90 (19.17) (N=377)	3.06 (15.24) (N=372)	0.002
Week 6	2.32 (35.56) (N=379)	2.57 (28.81) (N=373)	<0.001
Week 12	1.73 (51.94) (N=379)	2.01 (44.60) (N=373)	<0.001
Week 18	1.63 (54.72) (N=379)	1.78 (50.69) (N=373)	0.056
Week 24	1.55 (56.94) (N=379)	1.62 (55.12) (N=373)	0.420

ANCOVA Model: Change = baseline score + therapy + pooled-center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; N = number of subjects; QW = once weekly.

Change From Baseline by Visit in the Psoriasis Area and Severity Index Score Over 12 and 24 Weeks: At Week 12, the change from baseline in the mean PASI score was significantly greater in the etanercept 50 mg BIW/QW group compared with the 50 mg QW group in the LOCF analysis. At Week 24, the change from baseline was similar between etanercept groups. The summary of change from baseline by visit in the PASI score is presented in Table 9.

Table 9. Mean and Percent Change (Improvement) From Baseline by Visit in the Psoriasis Area and Severity Index Score - LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW Mean Score (Percent of Change From Baseline)	Etanercept 50 mg QW Mean Score (Percent of Change From Baseline)	p-Value From ANCOVA
Baseline	19.84 (0.00) (N=377)	19.01 (0.00) (N=371)	0.292
Week 3	14.11 (28.99) (N=375)	14.38 (24.47) (N=369)	0.024
Week 6	9.39 (52.67) (N=377)	10.34 (45.61) (N=371)	0.003
Week 12	5.81 (70.72) (N=377)	7.16 (62.34) (N=371)	<0.001
Week 18	5.08 (74.40) (N=377)	5.67 (70.23)(N=371)	0.088
Week 24	4.40 (77.77) (N=377)	4.99 (73.75) (N=371)	0.110

ANCOVA Model: Chane = baseline score + therapy + pooled-center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; N = number of subjects; QW = once weekly.

Change From Baseline by Visit in the Percent Body Surface Area Involvement of Psoriasis: The mean and percent reduction from baseline in percent BSA involvement of psoriasis was significantly different between etanercept groups at all study visits in the LOCF analysis. In the etanercept 50 mg BIW/QW and 50 mg QW groups, the percent reductions were 58.40% and 46.01%, respectively, at Week 12, and 73.00% and 64.60%, respectively, at Week 24. The summary of change from baseline by visit in the %BSA involvement of psoriasis is presented in Table 10.

Table 10. Mean and Percent Change (Improvement) From Baseline by Visit in the Body Surface Area Involvement LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW Mean Score (Percent of Change From Baseline)	Etanercept 50 mg QW Mean Score (Percent of Change From Baseline)	p-Value From ANCOVA
Baseline	31.30 (0.00) (N=379)	30.34 (0.00) (N=373)	0.538
Week 3	26.69 (14.89) (N=377)	27.60 (9.12) (N=372)	0.001
Week 6	20.13 (35.65) (N=379)	22.08 (27.22) (N=373)	0.002
Week 12	13.01 (58.40) (N=379)	16.38 (46.01) (N=373)	<0.001
Week 18	10.51 (66.42) (N=379)	12.90 (57.48) (N=373)	0.003
Week 24	8.44 (73.00) (N=379)	10.74 (64.60) (N=373)	0.003

ANCOVA Model: Change = baseline score + therapy + pooled-center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; N = number of subjects; QW = once weekly.

Change From Baseline by Visit in the Subject Assessments (Fatigue, General Health, Itching, Joint Pain, Arthritis Activity, Psoriasis Activity, and Morning Stiffness): There were no

significant differences between etanercept groups except for the global assessment of psoriasis at Weeks 6 and 12 and the assessment of itching at Week 12. The summary of change from baseline by visit in the subject assessments is presented in Table 11.

Table 11. Mean and Percent Change (Improvement) From Baseline by Visit in the Subject Assessments of General Health, Psoriasis Activity, Itching, Joint Disease, Arthritis Activity, Fatigue, and Morning Stiffness - LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW Mean Score (Percent Change From Baseline)	Etanercept 50 mg QW Mean Score (Percent Change From Baseline)	p-Value From ANCOVA
Assessment of fatigue			
Baseline	55.87 (0.00)(N=373)	54.73 (0.00)(N=369)	0.551
Week 3	42.58 (24.13)(N=368)	42.52 (21.88)(N=365)	0.724
Week 6	37.31 (33.34)(N=371)	39.49 (27.86)(N=369)	0.138
Week 12	33.53(40.08)(N=371)	36.41 (33.49)(N=369)	0.077
Week 18	31.73 (43.29)(N=371)	33.25 (39.27)(N=369)	0.295
Week 24	30.87 (44.85)(N=371)	31.42 (42.59)(N=369)	0.615
Assessment of general health			
Baseline	51.32 (0.00)(N=373)	51.94 (0.00)(N=369)	0.783
Week 3	38.42 (25.44)(N=368)	38.38 (26.33)(N=365)	0.797
Week 6	34.08 (33.70)(N=371)	35.02 (32.58)(N=369)	0.612
Week 12	30.05 (41.54)(N=371)	32.17 (38.04)(N=369)	0.203
Week 18	28.91 (43.75)(N=371)	30.17 (41.91)(N=369)	0.461
Week 24	26.73 (48.00)(N=371)	28.41 (45.28)(N=369)	0.340
Assessment of itching			
Baseline	57.63 (0.00)(N=372)	58.98 (0.00)(N=369)	0.567
Week 3	41.04 (28.86)(N=367)	43.95 (25.15)(N=365)	0.197
Week 6	31.31 (45.54)(N=370)	35.21 (40.30)(N=369)	0.057
Week 12	23.57 (59.00)(N=370)	30.10 (48.97)(N=369)	0.001
Week 18	24.03 (58.20)(N=370)	26.94 (54.32)(N=369)	0.163
Week 24	22.55 (60.78)(N=370)	25.90 (56.09)(N=369)	0.098
Assessment of joint pain			
Baseline	63.17 (0.00)(N=373)	61.90 (0.00)(N=368)	0.500
Week 3	37.65 (40.46)(N=368)	37.79 (38.80)(N=364)	0.748
Week 6	32.26 (48.84)(N=371)	33.06 (46.59)(N=368)	0.528
Week 12	27.92 (55.72)(N=371)	30.45 (50.79)(N=368)	0.132
Week 18	28.33 (55.07)(N=371)	27.78 (55.12)(N=368)	0.880
Week 24	27.03 (57.14)(N=371)	25.38 (58.98)(N=368)	0.439
Global assessment of arthritis activity			
Baseline	63.91 (0.00)(N=373)	61.71 (0.00)(N=368)	0.243
Week 3	38.86 (39.27)(N=367)	38.32 (37.58)(N=363)	0.909
Week 6	32.43 (49.30)(N=371)	32.65 (47.09)(N=368)	0.676
Week 12	27.91 (56.38)(N=371)	28.52 (53.78)(N=368)	0.533
Week 18	27.52 (56.97)(N=371)	26.84 (56.49)(N=368)	0.955
Week 24	26.89 (57.96)(N=371)	25.10 (59.33)(N=368)	0.484
Global assessment of psoriasis activity			
Baseline	66.16 (0.00)(N=373)	64.51 (0.00)(N=368)	0.389
Week 3	41.70 (37.04)(N=368)	42.40 (34.07)(N=362)	0.514
Week 6	33.61 (49.18)(N=371)	36.57 (43.31)(N=368)	0.049
Week 12	26.08 (60.57)(N=371)	32.17 (50.13)(N=368)	<0.001
Week 18	27.02 (59.13)(N=371)	29.69 (53.98)(N=368)	0.107
Week 24	25.37 (61.65)(N=371)	27.83 (56.84)(N=368)	0.156
Total duration of stiffness			
Baseline	143.50 (0.00)(N=365)	140.96 (0.00)(N=362)	0.860

Table 11. Mean and Percent Change (Improvement) From Baseline by Visit in the Subject Assessments of General Health, Psoriasis Activity, Itching, Joint Disease, Arthritis Activity, Fatigue, and Morning Stiffness - LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW Mean Score (Percent Change From Baseline)	Etanercept 50 mg QW Mean Score (Percent Change From Baseline)	p-Value From ANCOVA
Week 3	83.91 (43.12)(N=350)	74.07 (48.37)(N=354)	0.570
Week 6	68.65 (52.50)(N=359)	61.84 (56.44)(N=359)	0.653
Week 12	53.59 (62.80)(N=363)	49.10 (65.26)(N=361)	0.738
Week 18	50.94 (64.63)(N=363)	37.91 (73.18)(N=361)	0.302
Week 24	51.81 (64.03)(N=363)	44.24 (68.70)(N=361)	0.566

ANCOVA Model: Change = baseline score + therapy + pooled center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; N = number of subjects; QW = once weekly.

Change From Baseline in the PGA of Arthritis: At Weeks 12 and 24, the reductions from baseline on the PGA of arthritis were similar in both etanercept groups. The change from baseline by visit in the PGA of arthritis is presented in Table 12.

Table 12. Mean and Percent Change (Improvement) From Baseline by Visit in the Physician's Global Assessment of Arthritis - LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW Mean Score (Percent Change From Baseline)	Etanercept 50 mg QW Mean Score (Percent Change From Baseline)	p-Value From ANCOVA
Baseline	50.61 (0.00)(N=361)	49.89 (0.00)(N=351)	0.651
Week 12	18.66 (63.03)(N=349)	18.99 (61.98)(N=344)	0.823
Week 24	13.54 (73.29)(N=355)	13.17 (73.69)(N=347)	0.760

ANCOVA Model: Change = baseline score + therapy + pooled center.
ANCOVA = analysis of covariance; BIW = twice weekly; LOCF = last observation carried forward; N = number of subjects; QW = once weekly.

Proportion of Subjects Achieving ACR 20, 50, and 70 Responses at Weeks 12 and 24: The proportion of subjects achieving ACR 20, 50, and 70 responses, excluding subjects with no painful or swollen joints at baseline, at Weeks 12 and 24 was similar in both etanercept groups. The summary of proportion of subjects achieving ACR 20, 50, and 70 responses at Weeks 12 and 24 is presented in Table 13.

Table 13. Proportion of Subjects Achieving an ACR 20, 50, and 70 Response at Weeks 12 and 24 Excluding Subjects Who Had No Painful or Swollen Joints at Baseline - LOCF Analysis

	Time on Therapy	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	p-Value (Cochran-Mantel -Haenszel Test)
ACR 20	Week 12	239/360 (66.39%)	219/360 (60.83%)	0.139
	Week 24	249/361 (68.98%)	258/360 (71.67%)	0.379
ACR 50	Week 12	161/360 (44.72%)	146/360 (40.56%)	0.287
	Week 24	187/361 (51.80%)	193/360 (53.61%)	0.594
ACR 70	Week 12	73/360 (20.28%)	79/360 (21.94%)	0.531
	Week 24	125/361 (34.63%)	132/360 (36.67%)	0.530

This table does not include subjects who reported zero painful joints or swollen joints at baseline.
ACR = American college of rheumatology; BIW = twice weekly; LOCF = last observation carried forward; N = total number of subjects; n = number of subjects meeting criteria; QW = once weekly.

Proportion of Subjects Achieving Psoriatic Arthritis Response Criteria at Weeks 12 and 24:
The proportion of subjects achieving PsARC criteria was similar in both etanercept groups at Weeks 12 and 24 in the LOCF analysis. Between 76% and 81% of subjects in both etanercept groups had a PsARC response at Weeks 12 and 24. The summary of proportion of subjects achieving PsARC at weeks 12 and 24 is presented in Table 14.

Table 14. Proportion of Subjects Achieving Psoriatic Arthritis Response Criteria at Weeks 12 and 24 - LOCF Analysis

Time on Therapy	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	p-Value (Cochran-Mantel -Haenszel Test)
Week 12[a]	284/371(76.55%)	282/371(76.01%)	0.938
Week 24[a]	303/372(81.45%)	299/372(80.38%)	0.791

BIW = twice weekly; LOCF = last observation carried forward; N = total number of subjects; n = number of subjects meeting criteria; QW = once weekly.
a. Responders had improvements in 2 out of 4 of the following assessments (1 of which had to be swollen or tender joints: ≥1 unit on the PGA of arthritis, ≥20% on the Subject Global Assessment, and ≥30% improvement in tender and swollen joint counts.

The results of the OC analysis were similar to the results of the LOCF analysis for all secondary efficacy endpoints.

Safety Results: Overall, 56.2% and 50.9% of subjects in the etanercept 50 mg QW/BIW and 50 mg QW groups had at least 1 treatment emergent adverse event (TEAE). A summary of TEAEs (all-causality) reported by ≥5% of subjects in either treatment group is provided in Table 15.

Table 15. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (All Causalities) at a ≥5% Incidence in Either Treatment Group

Body System[a] Adverse Event	Overall p-Value	Treatment 50 mg BIW/QW N=379 n (%)	Treatment 50 mg QW N=373 n (%)	Total N=752 n (%)
Any adverse event	0.165	213 (56.2)	190 (50.9)	403 (53.6)
Body as a whole	0.467	112 (29.6)	101 (27.1)	213 (28.3)
Headache	1.000	19 (5.0)	19 (5.1)	38 (5.1)
Injection site reaction	0.263	32 (8.4)	23 (6.2)	55 (7.3)
Cardiovascular system	1.000	24 (6.3)	23 (6.2)	47 (6.3)
Digestive system	1.000	38 (10.0)	37 (9.9)	75 (10.0)
Metabolic and nutritional	0.754	23 (6.1)	20 (5.4)	43 (5.7)
Nervous system	0.428	24 (6.3)	18 (4.8)	42 (5.6)
Respiratory system	0.596	86 (22.7)	78 (20.9)	164 (21.8)
Pharyngitis	0.762	22 (5.8)	24 (6.4)	46 (6.1)
Upper respiratory infection	0.137	50 (13.2)	36 (9.7)	86 (11.4)
Skin and appendages	0.732	45 (11.9)	41 (11.0)	86 (11.4)

Overall p-value: Fisher exact test p-value (2-tail).
AEs and SAEs are not separated out.
AEs = adverse events; BIW = twice weekly; N = total number of subjects; n = number of subjects with adverse events; QW = once weekly; SAEs = serious adverse events.
a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.

Treatment-related TEAEs reported by ≥3% of subjects in either treatment group are summarized in Table 16.

Table 16. Number of Subjects Reporting Treatment Emergent Treatment Related Adverse Events at a ≥3% Incidence in Either Treatment Group

Body System[a] Adverse Event	Treatment 50 mg BIW/QW N=379 n (%)	Treatment 50 mg QW N=373 n (%)	Total N=752 n (%)
Any adverse event	101 (26.6)	86 (23.1)	187 (24.9)
Body as a whole	54 (14.2)	54 (14.5)	108 (14.4)
Asthenia	4 (1.1)	12 (3.2)	16 (2.1)
Injection site reaction	31 (8.2)	23 (6.2)	54 (7.2)
Digestive system	14 (3.7)	14 (3.8)	28 (3.7)
Respiratory system	37 (9.8)	30 (8.0)	67 (8.9)
Pharyngitis	12 (3.2)	10 (2.7)	22 (2.9)
Upper respiratory infection	18 (4.7)	13 (3.5)	31 (4.1)
Skin and appendages	19 (5.0)	22 (5.9)	41 (5.5)

AEs and SAEs are not separated out.
AEs = adverse events; BIW = twice weekly; N = total number of subjects; n = number of subjects with adverse events; QW = once weekly; SAEs = serious adverse events.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.

The treatment emergent serious adverse events (SAEs) are summarized in Table 17.

Table 17. Treatment Emergent Serious Adverse Events

Body System[a] Adverse Event	Overall p-Value	Treatment 50 mg BIW/QW N=379 n (%)	Treatment 50 mg QW N=373 n (%)	Total N=752 n (%)
Any adverse event	0.550	15 (4.0)	11 (2.9)	26 (3.5)
Body as a whole	1.000	4 (1.1)	4 (1.1)	8 (1.1)
Abdominal pain	1.000	1 (0.3)[b]	0	1 (0.1)
Abscess	0.496	0	1 (0.3)[c]	1 (0.1)
Accidental injury	1.000	1 (0.3)[d]	1 (0.3)[b]	2 (0.3)
Fever	1.000	1 (0.3)[c]	0	1 (0.1)
Infection	0.622	1 (0.3)[e]	2 (0.5)[b, e]	3 (0.4)
Cardiovascular system	1.000	3 (0.8)	2 (0.5)	5 (0.7)
Cerebral ischemia	1.000	1 (0.3)[d]	1 (0.3)[b]	2 (0.3)
Cerebrovascular accident	1.000	1 (0.3)[d]	1 (0.3)[d]	2 (0.3)
Myocardial ischemia	1.000	1 (0.3)[c]	0	1 (0.1)
Digestive system	1.000	2 (0.5)	2 (0.5)	4 (0.5)
Gastrointestinal hemorrhage	0.496	0	1 (0.3)[d]	1 (0.1)
Large intestine perforation	1.000	1 (0.3)[d]	0	1 (0.1)
Melena	0.496	0	1 (0.3)[d]	1 (0.1)
Nausea	1.000	1 (0.3)[b]	0	1 (0.1)
Stomach ulcer hemorrhage	0.496	0	1 (0.3)[d]	1 (0.1)
Vomiting	1.000	1 (0.3)[b]	1 (0.3)[d]	2 (0.3)
Hemic and lymphatic system	1.000	1 (0.3)	0	1 (0.1)
Anemia	1.000	1 (0.3)[d]	0	1 (0.1)
Nervous system	0.249	3 (0.8)	0	3 (0.4)
Abnormal gait	1.000	1 (0.3)[d]	0	1 (0.1)
Depression	1.000	1 (0.3)[d]	0	1 (0.1)
Dizziness	1.000	1 (0.3)[d]	0	1 (0.1)
Paresthesia	1.000	1 (0.3)[d]	0	1 (0.1)
Respiratory system	1.000	1 (0.3)	0	1 (0.1)
Chronic obstructive airways disease	1.000	1 (0.3)[c]	0	1 (0.1)
Skin and appendages	0.686	4 (1.1)	2 (0.5)	6 (0.8)
Psoriasis	1.000	2 (0.5)[c, d]	1 (0.3)[c]	3 (0.4)
Skin carcinoma	1.000	2 (0.5)[b, c]	1 (0.3)[d]	3 (0.4)
Urogenital system	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Breast carcinoma	1.000	1 (0.3)[d]	0	1 (0.1)
Kidney pain	0.496	0	1 (0.3)[b]	1 (0.1)
Adverse event associated w. misc. factors	1.000	1 (0.3)	0	1 (0.1)
Local reaction to procedure	1.000	1 (0.3)[d]	0	1 (0.1)

Overall p-value: Fisher's exact test p-value (2-tail).
BIW = twice weekly; N = total number of subjects; n = number of subjects with adverse events; QW = once weekly.

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.
b. Definitely not related to study treatment.
c. Possibly related to study treatment.
d. Probably not related to study treatment.
e. Probably related to study treatment.

Safety-Related Discontinuations: Sixteen (16, 4.2%) and 10 (2.7%) subjects in the etanercept 50 mg BIW/QW and 50 mg QW groups, respectively, were withdrawn from the

study because of TEAEs. The summary of subjects discontinuing the study due to TEAEs is presented in Table 18.

Table 18. Treatment-Emergent Adverse Events Leading to Discontinuation From the Study

Body System[a] Adverse Event	Overall p-Value	Treatment 50 mg BIW/QW N=379 n (%)	Treatment 50 mg QW N=373 n (%)	Total N=752 n (%)
Any adverse event	0.319	16 (4.2)	10 (2.7)	26 (3.5)
Body as a whole	1.000	3 (0.8)	2 (0.5)	5 (0.7)
Allergic reaction	0.496	0	1 (0.3)	1 (0.1)
Fever	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Infection	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Lab test abnormal	1.000	1 (0.3)	0	1 (0.1)
Cardiovascular system	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Cerebrovascular accident	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Digestive system	1.000	2 (0.5)	2 (0.5)	4 (0.5)
Large intestine perforation	1.000	1 (0.3)	0	1 (0.1)
Liver function tests abnormal	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Stomach ulcer hemorrhage	0.496	0	1 (0.3)	1 (0.1)
Hemic and lymphatic system	0.496	0	1 (0.3)	1 (0.1)
Thrombocytopenia	0.496	0	1 (0.3)	1 (0.1)
Metabolic and nutritional	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Peripheral edema	1.000	1 (0.3)	1 (0.3)	2 (0.3)
Nervous system	1.000	2 (0.5)	1 (0.3)	3 (0.4)
Anxiety	1.000	1 (0.3)	0	1 (0.1)
Facial paralysis	1.000	1 (0.3)	0	1 (0.1)
Myelitis	0.496	0	1 (0.3)	1 (0.1)
Respiratory system	1.000	1 (0.3)	0	1 (0.1)
Chronic obstructive airways disease	1.000	1 (0.3)	0	1 (0.1)
Skin and appendages	1.000	4 (1.1)	3 (0.8)	7 (0.9)
Eczema	1.000	1 (0.3)	0	1 (0.1)
Psoriasis	1.000	2 (0.5)	2 (0.5)	4 (0.5)
Pustular rash	0.496	0	1 (0.3)	1 (0.1)
Skin carcinoma	1.000	1 (0.3)	0	1 (0.1)
Urogenital system	0.499	2 (0.5)	0	2 (0.3)
Breast carcinoma	1.000	1 (0.3)	0	1 (0.1)
Uterine fibroids enlarged	0.487	1 (0.7)	0	1 (0.4)

Overall p-value: Fisher's exact test p-value (2-tail).
BIW = twice weekly; Lab = laboratory; N = total number of subjects; n = number of subjects with adverse events; QW = once weekly.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.

Deaths: No subjects died during the study.

Clinical Laboratory Evaluations: Small changes from baseline were reported for most hematology and chemistry laboratory parameters; however, none were considered to be clinically relevant with the exception of reductions in C-reactive protein (CRP). Mean CRP values were 15.3 mg/L and 16.2 mg/L at baseline in the etanercept 50 mg QW/BIW and

50 mg QW groups, respectively, and 4.9 mg/L and 5.9 mg/L, respectively, at Week 12, and 5.5 mg/L and 5.7 mg/L, respectively, at Week 24.

Grade 3 or 4 laboratory values were reported in 11 (3.0%) of subjects in the etanercept 50 mg BIW/QW group and 4 (1.1%) of subjects in the etanercept 50 mg QW group. The subjects with grade 3 or 4 clinical laboratory values are presented in Table 19.

Table 19. Subjects With Grade 3 or 4 Clinical Laboratory Values During the Study

Category Test+Units	Overall p-Value	Etanercept 50 mg BIW/QW n/N (%)	Etanercept 50 mg QW n/N (%)	Total n/N (%)
Total	0.115	11/372 (3.0)	4/372 (1.1)	15/744 (2.0)
Blood chemistry	0.055	11/372 (3.0)	3/372 (0.8)	14/744 (1.9)
Potassium mmol/L	0.249	3/372 (0.8)	0/372	3/744 (0.4)
Grade 4	0.249	3/372 (0.8)	0/372	3/744 (0.4)
Total bilirubin µmol/L	0.505	6/372 (1.6)	3/372 (0.8)	9/744 (1.2)
Grade 3	0.505	6/372 (1.6)	3/372 (0.8)	9/744 (1.2)
SGOT/AST mU/mL	1.000	2/372 (0.5)	1/372 (0.3)	3/744 (0.4)
Grade 3	1.000	2/372 (0.5)	1/372 (0.3)	3/744 (0.4)
SGPT/ALT mU/mL	1.000	1/372 (0.3)	0/372	1/744 (0.1)
Grade 3	1.000	1/372 (0.3)	0/372	1/744 (0.1)
Hematology	1.000	0/370	1/372 (0.3)	1/742 (0.1)
Platelet count 10^9 /L	1.000	0/369	1/371 (0.3)	1/740 (0.1)
Grade 3	1.000	0/369	1/371 (0.3)	1/740 (0.1)

For each test, only the maximum grade for a subject was counted.
Overall p-value: Fisher's exact test p-value (2-tail).
BIW = twice weekly; N = total number of subjects; n = number of subjects meeting criteria; QW = once weekly; SGOT/AST = serum glutamic oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT = serum glutamic pyruvic transaminase/alanine aminotransferase.

Vital Signs: No within or between group trends were observed with respect to changes in vital sign measurements.

CONCLUSIONS: The purpose of this study was to compare the efficacy and safety of etanercept 50 mg administered BIW for 12 weeks followed by QW for 12 weeks with etanercept 50 mg administered QW for 24 weeks in the treatment of PsA. Safety and efficacy were evaluated in 752 subjects; 379 subjects received etanercept 50 mg BIW/QW and 373 subjects received etanercept 50 mg QW.

Psoriasis symptoms were improved to a greater extent after 12 weeks of etanercept BIW/QW treatment compared with etanercept 50 mg QW treatment; at 24 weeks there was a trend toward greater benefit in subjects who had initiated treatment with a BIW regimen. In contrast, improvements in rheumatoid arthritis (RA) symptoms were generally similar with both treatment regimens at Weeks 12 and 24. The efficacy results are summarized below:

- For the primary efficacy endpoint, the comparison between the etanercept 50 mg BIW/QW and 50 mg QW groups for the proportion of subjects achieving a status of clear or almost clear on the PGA of psoriasis at Week 12, a significantly greater proportion of subjects receiving etanercept 50 mg QW/BIW had a status of clear or almost clear on the PGA of psoriasis at Week 12 (46.44% versus 31.90%, $p<0.001$).

- The secondary efficacy analyses of the PGA of psoriasis included the proportion of subjects achieving a status of clear or almost clear at Week 24, change and percent change from baseline in scores, and the proportion of subjects with a status of clear, almost clear, or mild. The proportion of subjects with a status of clear or almost clear at Week 24 was similar between etanercept groups (56.46% and 50.13%, p=0.104). Other PGA of psoriasis secondary endpoints followed a similar trend to that observed for the proportion of subjects with a PGA status of clear or almost clear. Significant differences in improvement favored the etanercept 50 mg BIW/QW group at Week 12, but at Week 24 the improvements were similar in the etanercept groups.

- Other secondary efficacy endpoints which assessed improvement in psoriasis included the change and percent from baseline in PASI scores and %BSA involvement, and the proportion of subjects achieving a ≥50% or ≥75% improvement in PASI scores. At Week 12, greater reductions in PASI scores were shown in the etanercept 50 mg BIW/QW group compared with the etanercept 50 mg QW group (70.72% versus 62.34%, p<0.001), while improvements were similar at Week 24 (77.77% versus 73.75%, p=0.110). The proportion of subjects achieving an improvement of ≥50% or ≥75% was significantly greater in the etanercept 50 mg BIW/QW group than in the etanercept 50 mg QW group at Week 12 (p=0.049 and p<0.001, respectively) and the proportion of subjects with a ≥75% PASI improvement in score was also statistically significant at Week 24 (p=0.026).

- Reductions in percent BSA involvement were significantly greater in the etanercept 50 mg BIW/QW group than in the etanercept 50 mg QW group at Weeks 12 and 24 (p<0.001 and p=0.003, respectively). At Week 24, reductions in %BSA involvement were 73.00% and 64.60% in the etanercept 50 mg BIW/QW and 50 mg QW groups, respectively (p=0.003).

- In both etanercept groups, the within-group changes from baseline in the PGA of psoriasis, PASI, and percent BSA involvement were statistically significant (p<0.001).

- The secondary efficacy variables which assessed improvement in arthritis symptoms of PsA included the change and percent change from baseline in PGA of arthritis and the proportion of subjects with ACR 20, 50, and 70 responses. There were no statistically significant differences between the etanercept 50 mg BIW/QW and 50 mg QW groups in these assessments of arthritis symptoms of PsA at Week 12 or Week 24. The within-group changes for the PGA of arthritis were significant in both etanercept groups at Weeks 12 and 24 (p<0.001), indicating that all subjects had reductions in arthritis symptoms of PsA.

- The secondary efficacy endpoints that assessed both psoriasis and arthritis symptoms of PsA included the PsARC and Subject Assessments (fatigue, general health, itching, joint pain, arthritis activity, psoriasis activity, and morning stiffness). Approximately 75% of subjects in both etanercept groups achieved a PsARC response at Weeks 12 and 24. On the Subject Assessments, there were no significant differences between etanercept groups at Weeks 12 and 24 except for the percent change on the global assessment of psoriasis at Week 12 (60.57% in the etanercept 50 mg BIW/QW group and 50.13% in the etanercept

50 mg QW group, p<0.001) and the assessment of itching at Week 12 (59.00% in the etanercept 50 mg BIW/QW group and 48.97% in the etanercept 50 mg QW group, p=0.001). The within-group changes from baseline on the Subject Assessments were significant in both etanercept groups at Weeks 12 and 24 (p<0.001).

There were no unexpected safety findings in this study population. The safety results are summarized below:

- Treatment-emergent AEs were reported at a similar incidence in the etanercept 50 mg BIW/QW and 50 mg QW groups (56.2% and 50.9%). The most common TEAEs (≥5% of subjects) were upper respiratory infection, injection site reaction, pharyngitis, and headache.

- Sixteen (16, 4.2%) and 10 (2.7%) subjects in the etanercept 50 mg BIW/QW and 50 mg QW groups, respectively, withdrew from the study because of TEAEs. Events leading to discontinuation in more than 1 subject were psoriasis (4 subjects) and cerebrovascular accident, fever, infection, liver function tests abnormal, and peripheral edema (2 subjects each). SAEs were reported in 15 (4.0%) and 11 (2.9%) subjects in the etanercept 50 mg BIW/QW and 50 mg QW groups, respectively.

- Serious AEs reported in more than 1 subject were skin carcinoma, psoriasis, and infection (3 subjects each) and accidental injury, cerebral ischemia, cerebrovascular accident, and vomiting (2 subjects each). Breast carcinoma was reported in 1 subject. No tuberculosis or other opportunistic infections were reported. No cases of lupus erythematosus, aplastic anemia, or pancytopenia were reported. No deaths were reported during the study.

- Small changes from baseline were reported for most hematology and chemistry laboratory parameters; however, none were considered to be clinically relevant with the exception of reductions in CRP. CRP was reduced approximately 65% in both etanercept groups.

In summary, a treatment regimen of etanercept 50 mg BIW for 12 weeks followed by etanercept 50 mg QW for 12 weeks resulted in more rapid improvement of psoriasis symptoms compared with an etanercept 50 mg QW regimen for 24 weeks. Subjects who received etanercept 50 mg QW for 24 weeks continued to improve with additional treatment; however, after 24 weeks, a modest trend remained toward greater benefit in subjects who had initiated treatment with a BIW regimen. In contrast, improvements in arthritis symptoms of PsA were not affected by increasing to a BIW regimen, with both etanercept groups showing similar efficacy. Safety findings were consistent with previous studies.