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

PROTOCOL NO.: 0881A8-205-WW (B1801285)

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Etanercept 25 mg Twice Weekly in Subjects With Moderate to Severe Persistent Asthma

Study Centers: Thirty-six (36) centers took part in the study and randomized subjects; 3 in Belgium, 3 in Finland, 4 in France, 1 each in Netherlands and Sweden, 5 in United Kingdom and 19 in United States.

Study Initiation and Final Completion Dates: 16 May 2005 to 10 July 2006

Phase of Development: Phase 2

Study Objectives:

The primary objective was to assess the efficacy and safety of etanercept 25 mg twice weekly in subjects with moderate to severe persistent asthma. The secondary objectives were to assess patient-reported outcomes and pharmacodynamics.

METHODS

Study Design: This was a randomized, parallel, double-blind, placebo-controlled, outpatient, worldwide proof of-concept study. Eligible subjects were randomly assigned to receive subcutaneous (SC) injections of either etanercept or placebo twice weekly. Evaluations were performed at Screening, Baseline, Weeks 2, 4, 8, and 12, and follow-up. The use of placebo as a control was necessary to allow a valid comparison and to provide a quantitative assessment of effect. Subjects participated in this study for up to 20 weeks. This included a screening period of 1 to 4 weeks, a treatment period of 12 weeks, and a follow-up period of 2 to 4 weeks. The study flowchart is given in Table 1.

Table 1. Study Flowchart

Study Procedures	Week -1 to -4	Week 0	Week 2[a]	Week 4[a]	Week 8[a]	Week 12[a]	Early Termination	Week 14[b]
Study Interval	**Screening**	**Baseline**	**----------Treatment Phase----------**					**Follow-Up**
Inclusion/exclusion criteria	X	X						
Informed consent	X							
Demographics	X							
Medical history	X							
Randomization		X						
Medical history update		X						
Chest radiograph test[c]	X							
Serum pregnancy[d]	X					X	X	
Body weight	X					X	X	
Height	X							
Physical examination	X	X				X	X	
Abbreviated physical examination			X	X	X			X
Vital signs	X	X	X	X	X	X	X	X
Adverse events		X----------X						
Blood chemistry, hematology, urinalysis	X	X[e]	X	X	X	X	X	
HBsAg and HCV antibody	X							
Pharmacogenomics blood sample collection[f]		X	X			X	X	
Serum etanercept sample collection		X				X		
Serum anti-etanercept antibody sample collection		X		X		X	X	
Record prior medications	X	X						
Record concomitant medications			X	X	X	X	X	X[g]
Spirometry evaluation (FEV_1, FVC, and FEV_1/FVC)	X	X	X	X	X	X	X	
Reversibility[h]	X----------X							
Methacholine challenge[i]		X				X	X	

Table 1. Study Flowchart

Study Procedures	Week -1 to -4	Week 0	Week 2[a]	Week 4[a]	Week 8[a]	Week 12[a]	Early Termination	Week 14[b]
Study Interval	**Screening**	**Baseline**	**----------Treatment Phase----------**					**Follow-Up**
ACQ		X	X	X	X	X	X	
AQLQ		X		X	X	X	X	
EQ-5D		X		X	X	X	X	
Productivity status		X		X	X	X	X	
Dispense peak flow meter	X							
Dispense diary card	X	X	X	X	X			
Collect/review diary cards: PEFR and use of albuterol (salbutamol)		X	X	X	X	X	X	
Dispense test article		X		X	X			
Complete conclusion of phase form						X	X	
Complete conclusion of subject participation form								X

ACQ = asthma control questionnaire; AQLQ = asthma quality of life questionnaire; EQ-5D = EuroQol 5 dimensions; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PEFR: = peak expiratory flow rate.

a. Study visits following the baseline visit were to occur within a ±3 day window of the appropriate date.
b. Follow-up visit was to be performed 2 to 4 weeks after Week 12 or the early termination visit.
c. Waived if within 1 year and report was available and was included in subject's source documents.
d. Serum pregnancy test for women who were of childbearing age or were ≤1 year postmenopausal.
e. Waived if within 14 days of screening evaluation.
f. Subjects had to sign and date a special consent form for pharmacogenomics blood sampling before any pharmacogenomics blood samples were drawn (optional).
g. To be recorded if subject reported adverse events during the follow-up visit.
h. Reversibility had to be demonstrated once and could occur at the Screening or the Baseline Visit, or at an interim visit during the screening period. Subjects participating in Methacholine Challenge testing (to be performed at the baseline visit) were to have reversibility testing performed prior to the day of the baseline visit.
i. Unless contraindicated by local guidelines.

Number of Subjects (Planned and Analyzed): Approximately 120 subjects (60 in each treatment group) were planned to be enrolled in the study. A total of 132 subjects were randomized (68 in etanercept group and 64 in the placebo group).

Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female subjects aged 18-70 years who were on a high-dose inhaled corticosteroid, diagnosed with moderate to severe persistent asthma for at least 1 year, who demonstrated reversibility of at least 9% actual with inhaled salbutamol during screening period and forced expiratory volume in 1 second (FEV_1) 50% to 80% predicted demonstrable at least 6 hours after short-acting β_2 agonist or 12 hours after long-acting β_2 agonist at Screening or Baseline were included in the study.

Exclusion Criteria: Subjects with previous treatment with etanercept and who were diagnosed with significant concurrent medical conditions at the time of Screening including concurrent chronic obstructive pulmonary disease, presence of active infection or any underlying diseases that could predispose subjects to infections were excluded from the study.

Study Treatment: Test article was supplied as either placebo or etanercept 25 mg in a sterile lyophilized powder for SC injection twice weekly for 12 weeks. All subjects received the test article in a double-blind fashion. A twice weekly dose regimen could begin on any day of the week, and doses were to be separated by 3 or 4 days. Test article was not to be administered consecutively in the same location. Instead, alternate sites (arms, thighs, abdomen, left/right) were to be used with each injection.

Efficacy Endpoints:

The primary efficacy endpoint was FEV_1 % predicted. The primary comparison of interest between treatment groups was the mean change in FEV_1 % predicted from Baseline to Week 12.

Secondary efficacy endpoints included the following:

- Morning (AM) peak expiratory flow rate (PEFR) (L/min), before bronchodilator administration upon awakening,
- Evening (PM) PEFR (L/min), around 8 PM before bronchodilator administration, if applicable,
- FEV_1 % predicted at Weeks 2, 4, and 8,
- FEV_1 actual at Weeks 2, 4, and 8,
- Forced vital capacity (FVC) % predicted and FEV_1/FVC at Weeks 2, 4, 8 and 12,
- Asthma control questionnaire (ACQ),

- Asthma exacerbations defined as 1) an unscheduled visit requiring de novo systemic corticosteroids, or increase in oral corticosteroids, 2) emergency room visit, or 3) hospitalization.

Safety Evaluations: Safety was monitored by means of physical examination, vital signs, hematology and chemistry, urinalysis, anti-etanercept antibody, premature withdrawals, adverse events (AEs), and serious adverse events (SAEs) during the study.

Statistical Methods: Three (3) population sets were used in analysis:

- The intent-to-treat (ITT) population was defined as all subjects who were randomly assigned to test article.
- Per-protocol analysis set (PAAS) excluded subjects who had major protocol violations.
- Safety analysis set included subjects who received at least 1 dose of test article were included in the safety analyses.

The primary efficacy analysis of interest was the comparison of changes in FEV_1 % predicted from Baseline to Week 12 between the etanercept group and the placebo group, using the analysis of covariance (ANCOVA) model with treatment group as factor and FEV_1 % predicted Baseline value as a covariate variable. The changes in FEV_1 % predicted from Baseline to other study time points were also compared. Basic summary statistics were reported by study time points and treatment groups. Other secondary continuous endpoints were analyzed similarly.

The primary efficacy analysis population was the ITT population. For the ITT population, missing data or data of subjects who withdrew were handled by the last-observation-carried-forward (LOCF) method. Efficacy analyses were also performed for PPAS population.

The 2-sided Fisher exact test was used to compare the 2 treatment groups for discrete safety endpoints. Continuous safety endpoints were compared using the 1-way ANCOVA model.

Baseline demographic data and other characteristics between the 2 treatment groups were compared using the t-test or Fisher exact test as appropriate.

RESULTS

Subject Disposition and Demography: A total of 132 subjects were enrolled in this study (68 were randomly assigned to the etanercept treatment group and 64 were randomly assigned to the placebo group), and 131 subjects received at least 1 dose of test article (68 in the etanercept group and 63 in the placebo group).

AEs were the most common reason for withdrawal with 11 subjects who were withdrawn because of AEs (Table 2). There were no significant differences between the treatment groups.

Table 2. Number (%) of Subjects Who Withdrew From the Study

Conclusion Status Reason[a]	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Completed	0.141	55 (80.9)	57 (90.5)	112 (85.5)
Discontinued	0.141	13 (19.1)	6 (9.5)	19 (14.5)
Adverse event	0.210	8 (11.8)	3 (4.8)	11 (8.4)
Discontinuation of study by Sponsor[c]	1.000	2 (2.9)	1 (1.6)	3 (2.3)
Protocol violation	0.497	2 (2.9)	0	2 (1.5)
Unsatisfactory response-efficacy	0.608	1 (1.5)	2 (3.2)	3 (2.3)

BIW = twice weekly, N = number of subjects per treatment group.
a. The total number who discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. Fisher's exact test p-value (2-tail).
c. Upon further review, this reason for discontinuation was considered to be 'protocol violation'.

The demographic characteristics are presented in Table 3.

Table 3. Demographic Characteristics

Characteristic	p-Value	Etanercept 25 mg BIW N=68	Placebo N=63
Age (years)			
N		68	63
Mean	0.213[a]	45.94	48.67
Standard deviation		12.61	12.29
Minimum		18.00	20.00
Maximum		70.00	69.00
Median		47.50	51.00
Sex	1.000[b]		
Female		46 (67.65)	42 (66.67)
Male		22 (32.35)	21 (33.33)
Ethnic origin	0.578[b]		
Asian		2 (2.94)	
Black or African American		7 (10.29)	7 (11.11)
Other		2 (2.94)	4 (6.35)
White		57 (83.82)	52 (82.54)

BIW = twice weekly, N = number of subjects per treatment group.
a. One-way analysis of variance with treatment as factor.
b. The p-value for Mantel-Haenszel chi-square.

Efficacy Results: The results from the analysis of the change in FEV_1 % predicted (ITT population; LOCF analysis) from Baseline to Week 12 are presented in Table 4. At Week 12, the change from Baseline in FEV1 % predicted was 2.8 for the etanercept group versus 1.9 for the placebo group (p=0.5098). Additionally, there were no statistically significant differences between etanercept and placebo for any of the secondary endpoints.

Table 4. FEV_1 % Predicted: ITT Population (LOCF Data)

						Adjusted Change		Adjusted Treatment Difference	
Week on Therapy	**Therapy**	**N**	**Raw Mean (SD)**	**Change From Baseline (SD)**	**p-Value Within Groups[a]**	**Mean**	**StdErr**	**Mean (Std Err)**	**p-Value Between Groups[b]**
Baseline	Etanercept 25 mg	68	66.0 (12.9)						
	Placebo	64	64.6 (11.7)						
Week 2	Etanercept 25 mg	68	67.8 (14.5)	1.8 (10.4)	0.1557	1.9	1.2	0.5 (1.7)	0.7534
	Placebo	64	66.1 (14.4)	1.4 (8.6)	0.1856	1.4	1.2		
Week 4	Etanercept 25 mg	68	68.3 (13.7)	2.3 (9.5)	0.0475	2.4	1.2	0.8 (1.7)	0.6260
	Placebo	64	66.3 (15.3)	1.7 (9.8)	0.1775	1.6	1.2		
Week 8	Etanercept 25 mg	68	69.7 (13.3)	3.7 (11.8)	0.0127	3.8	1.3	1.8 (1.9)	0.3527
	Placebo	64	66.8 (15.8)	2.2 (10.9)	0.1143	2.0	1.4		
Week 12	Etanercept 25 mg	68	68.8 (14.7)	2.8 (12.8)	0.0763	3.0	1.3	1.2 (1.9)	0.5098
	Placebo	64	66.5 (13.4)	1.9 (9.2)	0.1018	1.7	1.3		

ANCOVA = analysis of covariance, FEV_1 = forced expiratory volume in 1 second, ITT = intent to treat, LOCF = last observation carried forward, N = total number of subjects, SD = standard deviation, StdErr = standard error.

a. p-Value within groups: paired t-test.

b. p-Value between groups: ANCOVA model change = baseline + treatment group.

Safety Results:

Noninfectious SAEs (excluding asthma exacerbations) and serious infections are presented separately below in Table 5 and Table 6 respectively. One (1) subject experienced a noninfectious SAE (anaphylactic reaction in the etanercept group) during the study which was considered probably not related to study drug. A total of 4 (3%) subjects experienced a serious infection SAE during the study (Table 6), 2 were considered probably not related to study drug and 2 were considered possibly related to study drug. There was 1 case of acute diverticulitis and 1 case of meningitis in the etanercept group, and there was 1 case of culture-negative lower respiratory tract infection and 1 case of flu syndrome in the placebo group.

Table 5. Number (%) of Subjects With SAEs, Excluding Asthma Exacerbations, Infections, and Injection Site Reactions

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any SAE	1.000	1 (1.5)	0	1 (0.8)
Body as a whole	1.000	1 (1.5)	0	1 (0.8)
Anaphylactoid reaction	1.000	1 (1.5)	0	1 (0.8)

BIW = twice weekly, N = number of subjects per treatment group, SAE = serious adverse event.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.
b. Fisher's exact test p-value (2-tail).

Table 6. Number (%) of Subjects With Serious Infections

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	1.000	2 (2.9)	2 (3.2)	4 (3.1)
Pulmonary/thoracic	0.481	0	1 (1.6)	1 (0.8)
Other, pulmonary/thoracic	0.481	0	1 (1.6)	1 (0.8)
GI tract	1.000	1 (1.5)	0	1 (0.8)
Other, GI tract	1.000	1 (1.5)	0	1 (0.8)
CNS	1.000	1 (1.5)	0	1 (0.8)
Meningitis	1.000	1 (1.5)	0	1 (0.8)
Respiratory	0.481	0	1 (1.6)	1 (0.8)
Flu syndrome	0.481	0	1 (1.6)	1 (0.8)

BIW = twice weekly, CNS = central nervous system; GI = gastrointestinal, N = number of subjects per treatment group.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.
b. Fisher's exact test p-value (2-tail).

Two (2) subjects in the placebo group experienced asthma exacerbations that were considered SAEs, 1 considered probably not related to study drug and 1 considered possibly related to study drug

Overall, 72 (55%) subjects experienced a noninfectious treatment-emergent adverse events (TEAE) excluding asthma exacerbations and injection site reactions (ISRs) and 64 (49%)

subjects experienced a treatment-emergent infection during the study and 40 (31%) subjects experienced a treatment-emergent asthma exacerbation during the study. The noninfectious TEAEs, excluding asthma exacerbations and ISRs are presented in Table 7 and those which were related to study drug are presented in Table 8. There were no significant differences between the groups in the reporting of any noninfectious TEAEs.

Table 7: Number (%) of Subjects With TEAEs Reported at a Frequency ≥3%, Excluding Asthma Exacerbations, Infections, and Injection Site Reactions (All Causality)

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.222	41 (60.3)	31 (49.2)	72 (55.0)
Body as a whole	0.555	20 (29.4)	15 (23.8)	35 (26.7)
Accidental injury	1.000	3 (4.4)	3 (4.8)	6 (4.6)
Asthenia	0.367	4 (5.9)	1 (1.6)	5 (3.8)
Back pain	0.367	4 (5.9)	1 (1.6)	5 (3.8)
Chest pain	0.245	3 (4.4)	0	3 (2.3)
Fever	1.000	2 (2.9)	2 (3.2)	4 (3.1)
Headache	0.781	8 (11.8)	6 (9.5)	14 (10.7)
Neck pain	0.229	0	2 (3.2)	2 (1.5)
Cardiovascular system	1.000	8 (11.8)	7 (11.1)	15 (11.5)
Hypertension	0.427	2 (2.9)	4 (6.3)	6 (4.6)
Migraine	0.682	4 (5.9)	2 (3.2)	6 (4.6)
Digestive system	1.000	7 (10.3)	7 (11.1)	14 (10.7)
Nausea	1.000	3 (4.4)	3 (4.8)	6 (4.6)
Musculoskeletal system	0.720	5 (7.4)	3 (4.8)	8 (6.1)
Myalgia	0.620	3 (4.4)	1 (1.6)	4 (3.1)
Respiratory system	0.565	8 (11.8)	5 (7.9)	13 (9.9)
Cough increased	0.367	4 (5.9)	1 (1.6)	5 (3.8)
Dyspnea	0.608	1 (1.5)	2 (3.2)	3 (2.3)
Rhinitis	1.000	3 (4.4)	2 (3.2)	5 (3.8)
Wheezing	0.108	0	3 (4.8)	3 (2.3)

BIW = twice weekly, N = number of subjects per treatment group, TEAE = treatment-emergent adverse event.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may have reported ≥2 different adverse events in the same body system.
b. Fisher's exact test p-value (2-tail).

Table 8: Number (%) of Subjects With Treatment-Related TEAEs Reported Excluding Asthma Exacerbations, Infections, and Injection Site Reactions Related to Study Drug

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.222	20 (29.4)	12 (19.0)	32 (24.4)
Body as a whole	0.555	6 (8.8)	4 (6.3)	10 (7.6)
Abdominal Pain	1.000	1 (1.5)	0	1 (0.8)
Asthenia	0.367	1 (1.5)	0	1 (0.8)
Chest pain	0.245	2 (2.9)	0	2 (1.5)
Fever	1.000	2 (2.9)	1 (1.6)	3 (2.3)
Headache	0.781	2 (2.9)	3 (4.8)	5 (3.8)
Injection site hemorrhage	0.497	1 (1.5)	0	1 (0.8)
Cardiovascular system	1.000	2 (2.9)	0	2 (1.5)
Migraine	0.682	1 (1.5)	0	1 (0.8)
Palpitation	1.000	1 (1.5)	0	1 (0.8)
Digestive system	1.000	6 (8.8)	6 (9.5)	12 (9.2)
Abdominal distension	1.000	1 (1.5)	0	1 (0.8)
Chelitis	1.000	1 (1.5)	0	1 (0.8)
Diarrhea	0.481	0	1 (1.6)	1 (0.8)
Liver function tests abnormal	0.481	0	1 (1.6)	1 (0.8)
Nausea	1.000	3 (4.4)	3 (4.8)	6 (4.6)
Nausea and vomiting	1.000	1 (1.5)	0	1 (0.8)
Vomiting	1.000	1 (1.5)	1 (1.6)	2 (1.5)
Hemic and lymphatic system	0.443	4 (5.9)	1 (1.6)	5 (3.8)
Ecchymosis	0.497	1 (1.5)	0	1 (0.8)
Eosinophilia	1.000	1 (1.5)	0	1 (0.8)
Erythrocytes abnormal	0.481	0	1 (1.6)	1 (0.8)
Leukopenia	1.000	1 (1.5)	0	1 (0.8)
Lymphadenopathy	1.000	1 (1.5)	0	1 (0.8)
Neutropenia	0.497	2 (2.9)	0	2 (1.5)
Metabolic and nutritional	0.72	3 (4.4)	1 (1.6)	4 (3.1)
BUN increased	0.481	0	1 (1.6)	1 (0.8)
SGOT increased	1.000	1 (1.5)	0	1 (0.8)
SGPT increased	0.497	2 (2.9)	0	2 (1.5)
Musculoskeletal system	0.72	1 (1.5)	1 (1.6)	2 (1.5)
Myalgia	0.62	1 (1.5)	1 (1.6)	2 (1.5)
Nervous system	1.000	3 (4.4)	2 (3.2)	5 (3.8)
Dizziness	1.000	0	1 (1.6)	1 (0.8)
Emotional lability	1.000	1 (1.5)	0	1 (0.8)
Hostility	1.000	1 (1.5)	0	1 (0.8)
Nervousness	0.481	0	1 (1.6)	1 (0.8)
Sleep disorder	0.497	1 (1.5)	0	1 (0.8)
Vertigo	1.000	1 (1.5)	0	1 (0.8)
Respiratory system	0.565	1 (1.5)	0	1 (0.8)
Cough increased	0.367	1 (1.5)	0	1 (0.8)
Skin and appendages	0.737	3 (4.4)	2 (3.2)	5 (3.8)
Exfoliative dermatitis	0.481	0	1 (1.6)	1 (0.8)
Lichenoid dermatitis	0.481	0	1 (1.6)	1 (0.8)
Pruritic rash	1.000	1 (1.5)	0	1 (0.8)
Pruritus	0.497	2 (2.9)	0	2 (1.5)
Special senses	1.000	0	1 (1.6)	1 (0.8)
Abnormal vision	0.481	0	1 (1.6)	1 (0.8)

Table 8: Number (%) of Subjects With Treatment-Related TEAEs Reported Excluding Asthma Exacerbations, Infections, and Injection Site Reactions Related to Study Drug

BIW = twice weekly, BUN = blood urea nitrogen, N = number of subjects per treatment group, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase, TEAE = treatment-emergent adverse event.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.

b. Fisher's exact test p-value (2-tail).

The number (%) of subjects with all causality and treatment-related treatment-emergent infections to study drug are provided in Table 9 and Table 10 respectively.

Table 9. Number (%) of Subjects With Treatment-Emergent Infections (All Causality)

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.296	30 (44.1)	34 (54.0)	64 (48.9)
Urinary tract	1.000	1 (1.5)	1 (1.6)	2 (1.5)
Cystitis	1.000	1 (1.5)	1 (1.6)	2 (1.5)
Pulmonary/thoracic	0.596	7 (10.3)	9 (14.3)	16 (12.2)
Other, pulmonary/thoracic	0.481	0	1 (1.6)	1 (0.8)
Bronchitis	1.000	7 (10.3)	7 (11.1)	14 (10.7)
Pneumonia	0.481	0	1 (1.6)	1 (0.8)
Skin	0.195	1 (1.5)	4 (6.3)	5 (3.8)
Other, skin	0.481	0	1 (1.6)	1 (0.8)
Vaginitis	0.351	1 (1.5)	3 (4.8)	4 (3.1)
GI tract	0.210	5 (7.4)	1 (1.6)	6 (4.6)
Clostridium difficile colitis	0.481	0	1 (1.6)	1 (0.8)
Other, GI tract	0.059	5 (7.4)	0	5 (3.8)
CNS	1.000	1 (1.5)	0	1 (0.8)
Meningitis	1.000	1 (1.5)	0	1 (0.8)
Oropharynx	1.000	21 (30.9)	20 (31.7)	41 (31.3)
Other, oropharynx	1.000	3 (4.4)	3 (4.8)	6 (4.6)
Gingival/dental infections	0.620	3 (4.4)	1 (1.6)	4 (3.1)
Otitis	0.229	0	2 (3.2)	2 (1.5)
Pharyngitis/laryngitis	0.737	4 (5.9)	5 (7.9)	9 (6.9)
Sinusitis	0.534	7 (10.3)	4 (6.3)	11 (8.4)
Upper respiratory infection	0.233	8 (11.8)	13 (20.6)	21 (16.0)
Eye	0.497	2 (2.9)	0	2 (1.5)
Conjunctivitis	0.497	2 (2.9)	0	2 (1.5)
Respiratory	0.737	4 (5.9)	5 (7.9)	9 (6.9)
Flu syndrome	0.737	4 (5.9)	5 (7.9)	9 (6.9)
Other	1.000	1 (1.5)	0	1 (0.8)
Other (not in 1 of the systems)	1.000	1 (1.5)	0	1 (0.8)

BIW = twice weekly, N = number of subjects per treatment group.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.

b. Fisher's exact test p-value (2-tail).

Table 10. Number (%) of Subjects With Treatment-Emergent Infections Related to Study Drug

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.296	10 (14.7)	10 (15.9)	20 (15.3)
Pulmonary/thoracic	0.596	4 (5.9)	4 (6.3)	8 (6.1)
Bronchitis	1.000	4 (5.9)	3 (4.8)	7 (5.3)
Pneumonia	0.481	0	1 (1.6)	1 (0.8)
GI tract	0.210	1 (1.5)	0	1 (0.8)
Other, GI tract	0.059	1 (1.5)	0	1 (0.8)
Oropharynx	1.000	5 (7.4)	4 (6.3)	9 (6.9)
Gingival/dental infections	0.620	2 (2.9)	0	2 (1.5)
Otitis	0.229	0	1 (1.6)	1 (0.8)
Pharyngitis/laryngitis	0.737	1 (1.5)	2 (3.2)	3 (2.3)
Sinusitis	0.534	2 (2.9)	1 (1.6)	3 (2.3)
Upper respiratory infection	0.233	1 (1.5)	1 (1.6)	2 (1.5)
Respiratory	0.737	1 (1.5)	2 (3.2)	3 (2.3)
Flu syndrome	0.737	1 (1.5)	2 (3.2)	3 (2.3)

BIW = twice weekly, GI = gastrointestinal, N = number of subjects per treatment group.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.
b. Fisher's exact test p-value (2-tail).

A total of 40 (31%) subjects, 17 (27%) in the placebo group and 23 (34%) in the etanercept group, experienced a treatment-emergent asthma exacerbation during the study as shown in Table 11. Table 12 presents the number (%) of subjects reporting treatment-emergent asthma exacerbations related to study drug.

Table 11. Number (%) of Subjects Reporting Treatment Emergent Asthma Exacerbations

Body System	Overall p-Value	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.450	23 (33.8)	17 (27.0)	40 (30.5)
Asthma exacerbation	0.450	23 (33.8)	17 (27.0)	40 (30.5)

BIW = twice weekly, N = number of subjects per treatment group.

Table 12. Number (%) of Subjects Reporting Treatment-Emergent Asthma Exacerbations Related to Study Drug

Body System[a]	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.450	2 (2.9)	6 (9.5)	8 (6.1)
Asthma exacerbation	0.450	2 (2.9)	6 (9.5)	8 (6.1)

BIW = twice weekly, N = number of subjects per treatment group.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system
b. Fisher's exact test p-value (2-tail).

Nineteen (19) subjects were withdrawn from the study of which 11 were withdrawn because of AEs (Table 2). There were no significant differences between the treatment groups.

The noninfectious AEs (excluding asthma exacerbations) and infectious AEs that led to withdrawal are presented in Table 13 and Table 14, respectively.

Table 13. Number (%) of Subjects Withdrawn Because of Adverse Events, Excluding Asthma Exacerbations, Infections, and Injection Site Reactions

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.682	4 (5.9)	2 (3.2)	6 (4.6)
Body as a whole	1.000	1 (1.5)	0	1 (0.8)
Abdominal pain	1.000	1 (1.5)	0	1 (0.8)
Cardiovascular system	1.000	1 (1.5)	0	1 (0.8)
Migraine	1.000	1 (1.5)	0	1 (0.8)
Digestive system	1.000	1 (1.5)	0	1 (0.8)
Cheilitis	1.000	1 (1.5)	0	1 (0.8)
Hemic and lymphatic system	1.000	1 (1.5)	1 (1.6)	2 (1.5)
Erythrocytes abnormal	0.481	0	1 (1.6)	1 (0.8)
Lymphadenopathy	1.000	1 (1.5)	0	1 (0.8)
Skin and appendages	1.000	1 (1.5)	1 (1.6)	2 (1.5)
Lichenoid dermatitis	0.481	0	1 (1.6)	1 (0.8)
Pruritic rash	1.000	1 (1.5)	0	1 (0.8)

BIW = twice weekly, N = number of subjects per treatment group.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.
b. Fisher's exact test p-value (2-tail).

Table 14. Number (%) of Subjects Withdrawn Because of Infections

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	1.000	2 (2.9)	1 (1.6)	3 (2.3)
Pulmonary/thoracic	0.481	0	1 (1.6)	1 (0.8)
Pneumonia	0.481	0	1 (1.6)	1 (0.8)
GI tract	1.000	1 (1.5)	0	1 (0.8)
Other, GI tract	1.000	1 (1.5)	0	1 (0.8)
CNS	1.000	1 (1.5)	0	1 (0.8)
Meningitis	1.000	1 (1.5)	0	1 (0.8)

BIW = twice weekly, CNS = central nervous system, GI = gastrointestinal, N = number of subjects per treatment group.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.

b. Fisher's exact test p-value (2-tail).

Overall, 25 (37%) subjects in the etanercept group and 7 (11%) of subjects in the placebo group experienced at least 1 ISR during the study. Two (2) subjects were withdrawn from the study due to ISRs.

Seven subjects (7) presented with medically important infections reported; 2 in the etanercept group (meningitis and acute diverticulitis) and 5 in the placebo group (lower respiratory tract infection, flu syndrome, respiratory flu, urinary infection, and bronchitis and otitis right ear (in 1 subject). There were no significant differences between the groups. A summary of medically important infections (those requiring hospitalization or parenteral antibiotics) is provided in Table 15.

Table 15. Number (%) of Subjects With Infections Requiring Hospitalization or Parenteral Antimicrobials

Body System[a] Adverse Event	Overall p-Value[b]	Etanercept 25 mg BIW N=68	Placebo N=63	Total N=131
Any adverse event	0.260	2 (2.9)	5 (7.9)	7 (5.3)
Urinary tract	0.481	0	1 (1.6)	1 (0.8)
Cystitis	0.481	0	1 (1.6)	1 (0.8)
Pulmonary/thoracic	0.229	0	2 (3.2)	2 (1.5)
Other, pulmonary/thoracic	0.481	0	1 (1.6)	1 (0.8)
Bronchitis	0.481	0	1 (1.6)	1 (0.8)
GI tract	1.000	1 (1.5)	0	1 (0.8)
Other, GI tract	1.000	1 (1.5)	0	1 (0.8)
CNS	1.000	1 (1.5)	0	1 (0.8)
Meningitis	1.000	1 (1.5)	0	1 (0.8)
Oropharynx	0.481	0	1 (1.6)	1 (0.8)
Otitis	0.481	0	1 (1.6)	1 (0.8)
Respiratory	0.229	0	2 (3.2)	2 (1.5)
Flu syndrome	0.229	0	2 (3.2)	2 (1.5)

BIW = twice weekly, CNS = central nervous system, GI = gastrointestinal, N = number of subjects per treatment group.

a. Body system totals are not necessarily the sum of the individual adverse events since a subject might report ≥2 different adverse events in the same body system.

b. Fisher's exact test p-value (2-tail).

There were no deaths during this study.

There were no National Cancer Institute (NCI) grade 4 laboratory abnormalities reported during therapy. There were 4 NCI grade 3 laboratory abnormalities reported in the etanercept group during therapy: low potassium level, high aspartate transaminase (AST) level, low neutrophil count, and low lymphocyte count. The grade 3 AST, neutrophils, and lymphocytes occurred at only 1 time point during the study and returned to normal, whereas the subject with the grade 3 potassium had below normal potassium levels at all-time points measured during treatment.

CONCLUSIONS:

Etanercept 25 mg SC administered twice daily did not demonstrate efficacy in the treatment of subjects with moderate to severe persistent asthma. Etanercept was well tolerated and there were no unexpected safety findings in this population.