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

PROTOCOL NO.: 0881A-101696 (B1801201)

PROTOCOL TITLE: A Multicenter, Open-Label, Randomized, Pilot Study to Evaluate the Efficacy and Safety of the Combination of Etanercept (ETN) and Methotrexate and of Etanercept (ETN) Alone in Patients With Active Plaque Psoriasis Despite Methotrexate Therapy

Study Centers: Eight (8) centers took part in study and enrolled subjects; 2 each in Sweden, Norway, Finland and Denmark.

Study Initiation and Final Completion Dates: 15 March 2005 to 21 August 2006

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To evaluate the efficacy of combined Etanercept (ETN) and methotrexate (MTX) treatment and of ETN treatment alone as measured by the proportion of subjects whose active psoriatic disease was judged to be "Cleared" or "Almost cleared" on the Physicians Global Assessment of psoriasis (PGA) after 24 weeks of treatment.

Secondary Objectives:

To compare ETN + MTX and ETN as measured by:

- Percentage improvement in Psoriasis Area and Severity Index (PASI) and proportion of subjects demonstrating PASI 50, PASI 75 and PASI 90 response;
- Time to clear or almost clear on PGA;
- PGA;
- The Dermatology Life Quality Index (DLQI);
- The European Quality of Life-5 Dimensions (Euro QOL 5D) feeling thermometer;
- The proportion of subjects who discontinue due to adverse events (AEs);
- Subject Global Assessment of psoriasis (psoriasis, itching, joint pain and tiredness);

- Change in topicals;
- Pharmacoeconomic analysis.

METHODS

Study Design: This was a 24 week, open, randomized, parallel-group, multicenter, outpatient pilot study of ETN + MTX and ETN alone in subjects with active plaque psoriasis despite MTX therapy. Subjects enrolled in this study had to have active plaque psoriasis involving ≥10% of the body surface area (BSA) and/or a minimal screening PASI score of 8 and must have received MTX at a minimum dose of 7.5 mg/week for the last 3 months before enrollment. Subjects were informed about the study in due time before enrollment and the randomization was performed at the Baseline Visit. Additional clinical visits were performed at 2, 4, 8, 12, 18 and 24 weeks.

Subjects were randomly assigned to 1 of the 2 study groups: ETN alone and ETN + MTX. The study schedule is presented in Table 1.

Table 1. Study Schedule

Study Schedule Visit	Screening	Baseline						
Week[a]	-2 to 0[b]	0	2	4	8	12	18	24[c]
Signed informed consent	X							
Inclusion / exclusion criteria	X	X						
Randomization		X						
Medical history	X							
Physical examination	X							X
Vital signs	X					X		X
Body weight and height	X							
Adverse events	X	X	X	X	X	X	X	X
Prior DMARDs / corticosteroids		X						
Dose of MTX		X	X	X	X	X	X	X
Prior topicals		X						
Changes in topicals			X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X
Chest radiograph[d]	X							
PGA	X	X	X	X	X	X	X	X
Subject Global Assessment of Psoriasis		X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X
Euro QOL 5D Feeling Thermometer		X			X	X		X
HCRU& work productivity		X			X	X		X
Chemistry/hematology/ urinalysis	X	X[e]		X	X	X	X	X
Urine Pregnancy test		X[f]						
Dispense medication		X		X	X	X	X	

DMARDs = Disease modifying anti-rheumatic drugs; DLQI = Dermatology Life Quality Index; EuroQol EQ-5D = European Quality of Life-5 Dimensions; HCRU = Health Care Resource Utilization; MTX = methotrexate; PGA = Physician Global Assessment of Psoriasis; PASI = Psoriasis Area and Severity Index.

a. Visits were scheduled up to 4 days before or after any prescheduled visit.
b. Screening and baseline visits were permitted on the same day.
c. For subjects who prematurely withdrew from the study, final visit procedures were performed at the time of premature withdrawal.
d. Any chest x-ray performed within the last year of screening was acceptable.
e. Not repeated if done at Screening.
f. For women of childbearing potential only. Pregnancy testing was repeated if done >2 weeks from Baseline Visit.

Number of Subjects (Planned and Analyzed): A total of 60 subjects were planned for the study and 59 subjects (18 in Denmark, 17 in Finland, 16 in Norway, 8 in Sweden) were enrolled and treated.

Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥18 years of age with active plaque psoriasis involving ≥10% of the BSA and/or a minimal screening PASI score of 8 and who had received MTX ≥7.5 mg/week for the preceding 3 months.

Main Exclusion Criteria: Subjects with predominantly guttate, erythrodermic, or pustular psoriasis; or skin conditions other than psoriasis were excluded from the study.

Study Treatment: Subjects were randomized to 1 of 2 treatment groups and received treatment for 24 weeks.

ETN alone: ETN was injected subcutaneously, 50 mg twice weekly during the first 12 weeks, thereafter 25 mg twice weekly. During the first 4 weeks, MTX treatment was to be tapered and discontinued.

ETN + MTX: ETN was injected subcutaneously, 50 mg twice weekly during the first 12 weeks, thereafter 25 mg twice weekly. Subjects continued oral MTX tablets at the individual subject's dose (7.5 mg per week minimum).

Efficacy Endpoints:

Primary Endpoint: The proportion of subjects who were cleared or almost cleared on the PGA at 24 weeks.

Secondary Endpoints:

- Percentage improvement in PASI at 2, 4, 8, 12, 16 and 24 weeks;
- Proportion of subjects demonstrating ≥50% improvement in PASI at 24 weeks;
- Proportion of subjects demonstrating ≥75% improvement in PASI at 24 weeks;
- Proportion of subjects demonstrating ≥90% improvement in PASI at 24 weeks;
- Time to clear or almost clear on PGA;
- Subject global assessments;
- The DLQI;
- The Euro QOL 5D Feeling Thermometer;
- The proportion of subjects who discontinued due to adverse effects;
- Change in topicals;

- Pharmacoeconomic endpoints (Health Care Resource Utilization [HCRU] & work productivity versus [vs] Baseline);

- Subject's Visual Analog Scale (VAS) (0-100 mm) for assessments of fatigue, pruritus, and joint pain.

Safety Evaluations: Safety was assessed by evaluation of AEs, vital signs, physical examination, results of blood chemistry, haematology and urinanalysis.

Statistical Methods: The following population sets were analyzed:

Full Analysis Sets (FAS): Included all randomized subjects who had taken at least 1 dose of study medication and had at least 1 observation post randomization on the outcome variables.

Per Protocol Analysis Set (PPAS): Included all randomized subjects who met all of the inclusion criteria, had no major protocol deviations and also had measurement on the actual visit.

For the primary efficacy variables a 2-sided 95% confidence interval (CI) for the difference between treatments in the proportion of subjects who were "Cleared" or "Almost cleared" at Week 24 was calculated and p-values for test of equality between the treatments are given. In addition, 95% CIs for corresponding proportions for each treatment were calculated.

The binary secondary efficacy variables were analyzed in the same manner as the primary efficacy variable. For time to "Cleared" or "Almost cleared" was estimated for each treatment group using Kaplan-Meier estimates and corresponding Log-rank test were used to test for equality between treatments.

Safety was analyzed with descriptive statistics.

RESULTS

Subject Disposition and Demography: In total 60 subjects were included in the study, however, 1 subject was never randomized due to a positive tuberculosis screening test. Thus, 59 subjects were randomized and treated. In total, 51 subjects completed the study and 8 discontinued the study prematurely. Subject disposition is summarized in Table 2.

Table 2. Subject Disposition

Population	Treatment Group			
	ETN		ETN + MTX	
Number included, n (%)	28	(100.0)	31	(100.0)
Disposition				
n (%) of subjects who:				
Completed	23	(82.1)	28	(90.3)
Withdrew	5	(17.9)	3	(9.7)
Reason for withdrawal				
Serious adverse event	3		0	
Lack of subject compliance	0		1	
Principal Investigator's decision	0		1	
Lack of efficacy	2		1	
Number analyzed for safety	28		31	
Number analyzed for efficacy, FAS	28		31	
Number analyzed for efficacy, PPAS	23		26	

ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects with specified criteria; PPAS = per protocol analysis set.

Subject demographics are summarized in Table 3.

Table 3. Subject Demographics

	Treatment		Total
	ETN	ETN + MTX	
Age (years)			
n	28	31	59
Mean	47.3	48.7	48.1
Median	45.5	49.0	47.0
SD	11.2	11.2	11.1
Min	23	24	23
Max	72	69	72
Gender			
n	28	31	59
Males	17 (60.7)	26 (83.9)	43 (72.9)
Females	11 (39.3)	5 (16.1)	16 (27.1)

ETN = etanercept; Max = maximum; Min = minimum; MTX = methotrexate; n = number of subjects; SD = standard deviation.

Efficacy Results:

Proportion "Cleared" or "Almost Cleared" on PGA at Week 24: The proportion of subjects cleared or almost cleared on PGA at Week 24 for FAS is presented in Table 4 and for FAS last observation carried forward is presented in Table 5.

Table 4. Proportion "Cleared" or "Almost Cleared" on PGA at Week 24 in FAS Population

	Treatment	
	ETN	**ETN + MTX**
n	27	30
Missing observations	1	1
Point estimate (%)	37.0	66.7
95% CI	18.8, 55.3	49.8, 83.5
Difference between ETN + MTX and ETN	29.6	
95% CI	4.8, 54.5	
p-Value	0.0253	

CI = confidence interval; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Table 5. Primary Efficacy Variable in FAS LOCF Population

	Treatment	
	ETN	**ETN + MTX**
n	28	31
Missing observations	0	0
Point estimate (%)	35.7	67.7
95% CI	18.0, 53.5	51.3, 84.2
Difference between ETN + MTX and ETN	32.0	
95% CI	7.8, 56.2	
p-Value	0.0139	

CI = confidence interval; ETN = etanercept; FAS = full analysis set; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects.

Percentage Improvement From Baseline in PASI: The Percentage improvement from Baseline in PASI to Week 2, 4, 8, 12, 18 and 24 in FAS is presented in Table 6.

Table 6. Percentage Improvement From Baseline in PASI to Week 2, 4, 8, 12, 18 and 24 in FAS

	Treatment	
	ETN	**ETN + MTX**
Week 2		
n	28	31
Missing observations	0	0
Point estimate (%)	13.5	14.4
95% CI	5.2, 21.8	7.9, 20.9
Difference between ETN + MTX and ETN	0.9	
95% CI for the difference	-9.3, 11.1	
p-Value	0.9081	
Week 4		
n	28	30
Missing observations	0	1
Point estimate (%)	31.0	30.6
95% CI	19.9, 42.1	19.3, 41.8
Difference between ETN + MTX and ETN	-0.4	
95% CI for the difference	-15.9, 15.1	
p-Value	0.9283	
Week 8		
n	25	30
Missing observations	3	1
Point estimate (%)	46.7	54.8
95% CI	33.8, 59.6	41.7, 67.8
Difference between ETN + MTX and ETN	8.1	
95% CI for the difference	-10.0, 26.1	
p-Value	0.3809	
Week 12		
n	26	29
Missing observations	2	2
Point estimate (%)	47.9	66.7
95% CI	30.0, 65.8	56.3, 77.1
Difference between ETN + MTX and ETN	18.8	
95% CI for the difference	-0.9, 38.5	
p-Value	0.0672	
Week 18		
n	23	28
Missing observations	3	3
Point estimate (%)	62.8	79.9
95% CI	48.3, 77.2	73.7, 86.1
Difference between ETN + MTX and ETN	17.1	
95% CI for the difference	2.8, 31.4	
p-Value	0.0227	
Week 24		
n	27	30
Missing observations	1	1
Point estimate (%)	51.3	76.4
95% CI	31.4 71.2	67.8 85.0
Difference between ETN + MTX and ETN	25.1	
95% CI for the difference	4.7, 45.5	
p-Value	0.0192	

CI = confidence interval; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects; PASI = Psoriasis Area and Severity Index.

PASI 50: The proportion of subjects demonstrating ≥50% improvement in PASI at Week 24 in FAS is presented in Table 7.

Table 7. PASI 50 at Week 24 in FAS Population

	Treatment	
	ETN	**ETN + MTX**
Week 24		
n	27	30
Missing observations	1	1
Point estimate (%)	66.7	83.3
95% CI	48.9, 84.4	70.0, 96.7
Difference between ETN + MTX and ETN	16.7	
95% CI	-5.6, 38.9	
p-Value	0.1444	

CI = confidence interval; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects; PASI = Psoriasis Area and Severity Index.

PASI 75: The proportion of subjects demonstrating ≥75% improvement in PASI at Week 24 in FAS is presented in Table 8.

Table 8. PASI 75 at Week 24 in FAS Population

	Treatment	
	ETN	**ETN+MTX**
Week 24		
n	27	30
Missing observations	1	1
Point estimate (%)	37.0	70.0
95% CI	18.8, 55.3	53.6, 86.4
Difference between ETN + MTX and ETN	33.0	
95% CI	8.5, 57.5	
p-Value	0.0126	

CI = confidence interval; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects; PASI = Psoriasis Area and Severity Index.

PASI 90: The proportion of subjects demonstrating ≥90% improvement in PASI at Week 24 in FAS is presented in Table 9.

Table 9. PASI 90 at Week 24 in FAS Population

	Treatment	
	ETN	**ETN + MTX**
Week 24		
n	27	30
Missing observations	1	1
Point estimate (%)	18.5	40.0
95% CI	3.9, 33.2	22.5, 57.5
Difference between ETN + MTX and ETN	21.5	
95% CI	-1.4, 44.3	
p-Value	0.0767	

CI = confidence interval; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects; PASI = Psoriasis Area and Severity Index.

Time to "Cleared" or "Almost Cleared" on PGA: The Median time to "Cleared" or "Almost cleared" in days and log-rank test of time to "Cleared" or "Almost cleared" on PGA in FAS population is presented in Table 10.

Table 10. Median Time to "Cleared" or "Almost Cleared" in Days and Log-Rank Test of Time to "Cleared" or "Almost Cleared" on PGA in FAS Population

	Treatment	
	ETN	**ETN + MTX**
Median time to "cleared" or "almost cleared" in days	126	56.5
95% CI for median time	60[a]	56, 85
Log-Rank Test		
χ^2-value	Degrees of freedom	p-value
1.3651	1	0.2427

CI = confidence interval; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; PGA = Physicians Global Assessment.
a. Values above 130 days were censored.

Subject's Global Assessments:

Psoriasis: The subject's global assessment of psoriasis at Baseline, Week 12 and 24 is presented in Table 11 and analysis of subject's global assessment of psoriasis is presented in Table 12.

Table 11. Subject's Global Assessment of Psoriasis at Baseline, Week 12 and 24 in FAS Population

Treatment		Baseline		Week 12		Week 24	
		n	%	n	%	n	%
ETN	Missing	0	0.0	0	0.0	1	3.8
	0 (Good)	0	0.0	2	7.7	2	7.7
	1	1	3.6	5	19.2	8	30.8
	2	3	10.7	10	38.5	6	23.1
	3	11	39.3	8	30.8	5	19.2
	4	11	39.3	0	0.0	3	11.5
	5 (Severe)	2	7.1	1	3.8	1	3.8
ETN + MTX	Missing	0	0.0	0	0.0	0	0.0
	0 (Good)	0	0.0	9	31.0	10	34.5
	1	4	12.9	11	37.9	9	31.0
	2	6	19.4	5	17.2	5	17.2
	3	10	32.3	2	6.9	5	17.2
	4	7	22.6	2	6.9	0	0.0
	5 (Severe)	4	12.9	0	0.0	0	0.0

ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Table 12. Analysis of Subjects Global Assessment of Psoriasis at Week 12 and 24 in FAS Population

Week 12		
χ^2-value	Degrees of freedom	p-value
6.5060	1	0.0108
Week 24		
χ^2-value	Degrees of freedom	p-value
6.3682	1	0.0116

FAS = full analysis set.

Pruritus: The subject's global assessment of pruritus at Baseline, Week 12 and 24 is presented in Table 13 and analysis of subject's global assessment of pruritus is presented in Table 14.

Table 13. Subject's Global Assessment of Pruritus at Baseline, Week 12 and 24 in FAS Population

Treatment		Baseline		Week 12		Week 24	
		n	%	n	%	n	%
ETN	Missing	0	0.0	0	0.0	1	3.8
	0 (No pruritus)	1	3.6	4	15.4	5	19.2
	1	4	14.3	5	19.2	6	23.1
	2	4	14.3	9	34.6	6	23.1
	3	7	25.0	4	15.4	5	19.2
	4	7	25.0	4	15.4	1	3.8
	5 (Severe pruritus)	5	17.9	0	0.0	2	7.7
ETN + MTX	Missing	0	0.0	0	0.0	0	0.0
	0 (No pruritus)	1	3.2	10	34.5	9	31.0
	1	8	25.8	12	41.4	12	41.4
	2	9	29.0	3	10.3	4	13.8
	3	5	16.1	3	10.3	4	13.8
	4	3	9.7	1	3.4	0	0.0
	5 (Severe pruritus)	5	16.1	0	0.0	0	0.0

ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Table 14. Analysis of Subjects Global Assessment of Pruritus at Week 12 and 24 in FAS Population

Week 12		
χ^2-value	Degrees of freedom	p-Value
6.4052	1	0.0114
Week 24		
χ^2-value	Degrees of freedom	p-Value
1.7952	1	0.1803

FAS = full analysis set.

Joint Pain: The subject's global assessment of joint pain at Baseline, Week 12 and 24 is presented in Table 15 and analysis of subject's global assessment of joint pain is presented in Table 16.

Table 15. Subject's Global Assessment of Joint Pain at Baseline, Week 12 and 24 in FAS Population

Treatment		Baseline		Week 12		Week 24	
		n	%	n	%	n	%
ETN	Missing	0	0.0	0	0.0	1	3.8
	0 (No pain)	11	39.3	9	34.6	11	42.3
	1	2	7.1	5	19.2	4	15.4
	2	6	21.4	4	15.4	3	11.5
	3	7	25.0	5	19.2	4	15.4
	4	1	3.6	3	11.5	1	3.8
	5 (Severe pain)	1	3.6	0	0.0	2	7.7
ETN + MTX	Missing	0	0.0	0	0.0	0	0.0
	0 (No pain)	8	25.8	13	44.8	13	44.8
	1	5	16.1	2	6.9	4	13.8
	2	6	19.4	9	31.0	9	31.0
	3	7	22.6	3	10.3	1	3.4
	4	3	9.7	2	6.9	2	6.9
	5 (Severe pain)	2	6.5	0	0.0	0	0.0

ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Table 16. Analysis of Subjects Global Assessment of Joint Pain at Week 12 and 24 in FAS Population

Week 12		
χ^2-value	Degrees of freedom	p-Value
1.7521	1	0.1856
Week 24		
χ^2-value	Degrees of freedom	p-Value
3.8303	1	0.0503

FAS = full analysis set.

Fatigue: The subject's global assessment of fatigue at Baseline, Week 12 and 24 is presented in Table 17 and analysis of subject's global assessment of fatigue is presented in Table 18.

Table 17. Subject's Global Assessment of Fatigue at Baseline, Week 12 and 24 in FAS Population

Treatment		Baseline		Week 12		Week 24	
		n	%	n	%	n	%
ETN	Missing	0	0.0	0	0.0	1	3.8
	0 (No fatigue)	1	3.6	5	19.2	5	19.2
	1	8	28.6	9	34.6	8	30.8
	2	8	28.6	7	26.9	4	15.4
	3	6	21.4	5	19.2	5	19.2
	4	3	10.7	0	0.0	1	3.8
	5 (Very fatigue)	2	7.1	0	0.0	2	7.7
ETN + MTX	Missing	0	0.0	0	0.0	0	0.0
	0 (No fatigue)	3	9.7	13	44.8	10	34.5
	1	8	25.8	2	6.9	9	31.0
	2	5	16.1	11	37.9	7	24.1
	3	12	38.7	3	10.3	3	10.3
	4	3	9.7	0	0.0	0	0.0
	5 (Very fatigue)	0	0.0	0	0.0	0	0.0

ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Table 18. Analysis of Subjects Global Assessment of Fatigue at Week 12 and 24 in FAS Population

Week 12		
χ^2-value	Degrees of freedom	p-Value
0.7269	1	0.3939
Week 24		
χ^2-value	Degrees of freedom	p-Value
2.8110	1	0.0936

FAS = full analysis set.

Dermatology Life Quality Index: The DLQI at Week 12 and Week 24 is presented in Table 19.

Table 19. DLQI at Week 12 and 24 in FAS Population

	Treatment	
	ETN	**ETN + MTX**
Week 12		
n	23	28
Missing observations	5	3
Point estimate	5.5	3.0
95% CI	2.7, 8.3	1.7, 4.3
Difference between ETN + MTX and ETN	-2.5	
95% CI for the difference	-5.3, 0.3	
p-Value	0.2189	
Week 24		
n	22	26
Missing observations	6	5
Point estimate	5.8	2.3
95% CI	2.5, 9.2	1.2, 3.3
Difference between ETN + MTX and ETN	-3.5	
95% CI for the difference	-6.7, -0.4	
p-Value	0.0757	

CI = confidence interval; DLQI = The Dermatology Life Quality Index; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

European Quality of Life-5 Dimensions: The Euro QOL-5D at Baseline and Week 12 and 24 is presented in Table 20.

Table 20. Euro QOL-5D Index at Week 12 and 24 in FAS Population

	Treatment	
	ETN	**ETN + MTX**
Week 12		
n	26	29
Missing observations	2	2
Point estimate (%)	0.766	0.776
95% CI	0.669, 0.862	0.699, 0.853
Difference between ETN + MTX and ETN	0.010	
95% CI for the difference	-0.109, 0.130	
p-Value	0.5808	
Week 24		
n	26	29
Missing observations	2	2
Point estimate (%)	0.772	0.802
95% CI	0.655, 0.889	0.735, 0.869
Difference between ETN + MTX and ETN	0.030	
95% CI for the difference	-0.099, 0.158	
p-Value	0.2174	

CI = confidence interval; Euro QOL-5D = European Quality of Life-5 Dimensions; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Visual Analog Scale: The EQ-VAS at Week 12 and 24 is presented in Table 21.

Table 21. EQ-VAS at Week 12 and 24 in FAS Population

	Treatment	
	ETN	**ETN + MTX**
Week 12		
n	26	29
Missing observations	2	2
Point estimate (%)	71.8	77.0
95% CI	63.1, 80.6	70.8, 83.2
Difference between ETN + MTX and ETN	5.1	
95% CI for the difference	-5.2, 15.4	
p-Value	0.1723	
Week 24		
n	27	29
Missing observations	1	2
Point estimate (%)	71.5	77.6
95% CI	62.8, 80.3	70.8, 84.3
Difference between ETN + MTX and ETN	6.0	
95% CI for the difference	-4.7, 16.7	
p-Value	0.1594	

CI = confidence interval; EQ-VAS = European Quality of Life Visual Analog Scale; ETN = etanercept; FAS = full analysis set; MTX = methotrexate; n = number of subjects.

Change in Topical Medication: In the ETN alone group (FAS) 10 subjects started with a topical medication that was not used at Baseline and no subject ceased with a topical used at Baseline. The corresponding figures for ETN + MTX group were 5 subjects and 2 subjects, respectively.

Health Care Resource Utilization:

Number of Days in Hospital the Last 4 Weeks: The summary of HCRU, number of days in hospital the last 4 weeks, at Baseline, Week 8, 12 and 24 is presented in Table 22.

Table 22. Summary of HCRU, Number of Days in Hospital the Last 4 Weeks, at Baseline, Week 8, 12 and 24 in FAS Population

Treatment		Baseline	Week 8	Week 12	Week 24
ETN	n	27	24	26	26
	Missing	1	4	2	2
	Mean	0.0	0.0	0.0	0.2
	SD	0.2	0.0	0.0	0.8
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	1	0	0	4
ETN + MTX	n	30	29	29	28
	Missing	1	2	2	3
	Mean	0.1	0.0	0.0	0.0
	SD	0.4	0.0	0.0	0.0
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	2	0	0	0

ETN = etanercept; FAS = full analysis set; HCRU = Health Care Resource Utilization; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects; Q = question; SD = standard deviation.

Number of Visits to Emergency the Last 4 Weeks: The summary of HCRU, number of visits to emergency the last 4 weeks, at Baseline, Week 8, 12 and 24 is presented in Table 23.

Table 23. Summary of HCRU, Number of Visits to Emergency the Last 4 Weeks, at Baseline, Week 8, 12 and 24 in FAS Population

Treatment		Baseline	Week 8	Week 12	Week 24
ETN	n	26	24	26	26
	Missing	2	4	2	2
	Mean	0.1	0.1	0.0	0.2
	SD	0.3	0.3	0.2	0.6
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	1	1	1	2
ETN + MTX	n	31	29	28	28
	Missing	0	2	3	3
	Mean	0.2	0.1	0.0	0.0
	SD	0.9	0.4	0.0	0.2
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	5	2	0	1

ETN = etanercept; FAS = full analysis set; HCRU = Health Care Resource Utilization; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects; Q = question; SD = standard deviation.

Number of Visits to Dermatologist or Other Physician the Last 4 Weeks: Summary of HCRU, number of visits to Dermatologist or other Physician the last 4 weeks, at Baseline, Week 8, 12 and 24 is presented in Table 24.

Table 24. Summary of HCRU, Number of Visits to Dermatologist or Other Physician the Last 4 Weeks, at Baseline, Week 8, 12 and 24 in FAS Population

Treatment		Baseline	Week 8	Week 12	Week 24
ETN	n	25	24	26	25
	Missing	3	4	2	3
	Mean	0.3	0.2	0.2	0.2
	SD	0.6	0.5	0.5	0.5
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	2	2	2	2
ETN + MTX	n	30	29	29	28
	Missing	1	2	2	3
	Mean	0.5	0.1	0.0	0.1
	SD	1.2	0.3	0.2	0.3
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	1.0	0.0	0.0	0.0
	Max	6	1	1	1

ETN = etanercept; FAS = full analysis set; HCRU = Health Care Resource Utilization; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects; Q = question; SD = standard deviation.

Number of Sick-Leave Days the Last 4 Weeks: The summary of HCRU, number of sick-leave days the last 4 weeks, at Baseline, Week 8, 12 and 24 is presented in Table 25.

Table 25. Summary of HCRU, Number of Sick-Leave Days the Last 4 Weeks, at Baseline, Week 8, 12 and 24 in FAS Population

Treatment		Baseline	Week 8	Week 12	Week 24
ETN	n	28	24	26	27
	Missing	0	4	2	1
	Mean	0.7	0.4	0.1	0.2
	SD	2.0	1.3	0.4	1.2
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	10	6	2	6
ETN + MTX	n	31	29	29	29
	Missing	0	2	2	2
	Mean	0.5	0.4	0.4	0.1
	SD	1.8	1.9	1.9	0.3
	Min	0	0	0	0
	Q1	0.0	0.0	0.0	0.0
	Median	0.0	0.0	0.0	0.0
	Q3	0.0	0.0	0.0	0.0
	Max	10	10	10	1

ETN = etanercept; FAS = full analysis set; HCRU = Health Care Resource Utilization; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects; Q = question; SD = standard deviation.

Work and Extent of Work: The summary of HCRU, work and extent of work at Baseline, Week 8, 12 and 24 is presented in Table 26.

Table 26. Summary of HCRU, Work and Extent of Work at Baseline, Week 8, 12 and 24 in FAS Population

Treatment			Baseline		Week 8		Week 12		Week 24	
			n	%	n	%	n	%	n	%
ETN	Yes	<30 h	2	7.4	1	4.2	1	3.8	1	3.8
		>30 h	17	63.0	18	75.0	19	73.1	17	65.4
	No	0 h	8	29.6	5	20.8	6	23.1	8	30.8
	Missing		1		4		2		2	
ETN + MTX	Yes	<30 h	2	6.5	2	7.1	4	14.3	3	10.3
		>30 h	20	64.5	16	57.1	16	57.1	17	58.6
	No	0 h	9	29.0	10	35.7	8	28.6	9	31.0
	Missing		1		3		3		2	

ETN = etanercept; FAS = full analysis set; HCRU = Health Care Resource Utilization; MTX = methotrexate; n = number of subjects.

Safety Results:

The brief summary of AEs is presented in Table 27.

Table 27. Brief Summary of Adverse Events

	ETN		ETN + MTX		Total	
Category of adverse event	n and (%) of subjects who reported at least 1 AE in each category					
	n	%	n	%	n	%
Number of subjects in population	28		31		59	
Any AE	21	75.0	19	61.3	40	67.8
SAEs	4	14.3	1	3.2	5	8.5
Discontinuation of study treatment due to AE	3	13.0	0	0.0	3	5.1
Total Number of AEs						
Total number of reported AEs	51		50		101	
Related to study medication	28		26		54	
Total number of SAEs	5		2		7	
Related to study medication	5		2		7	
Other significant AEs	0		0		0	

AE = adverse events; ETN = etanercept; MTX = methotrexate; n = number of subjects; SAE = serious adverse event.

The incidence of AEs during respective treatment and in total during treatment by system organ class and preferred term in the safety population is presented in Table 28.

Table 28. Incidence of Adverse Events During Respective Treatment and in Total During Treatment by System Organ Class and Preferred Term in Safety Population

MedDRA System Organ Class / Preferred Term for Adverse Event	Treatment						Total		
	ETN			ETN + MTX					
	n	(m)	%	n	(m)	%	n	(m)	%
Number of subjects	28			31			59		
Number of subjects with at least 1 AE	21		75.0	19		61.3	40		67.8
Cardiac disorders	1	(2)	3.6	0	(0)	0.0	1	(2)	1.7
Atrial fibrillation	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Cardiac failure	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Eye disorders	3	(4)	10.7	0	(0)	0.0	3	(4)	5.1
Conjunctivitis	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Eye irritation	1	(2)	3.6	0	(0)	0.0	1	(2)	1.7
Eyelid oedema	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Gastrointestinal disorders	0	(0)	0.0	4	(4)	12.9	4	(4)	6.8
Diarrhoea	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Haematemesis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Nausea	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Oral pain	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
General disorders and administration site conditions	8	(10)	28.6	5	(5)	16.1	13	(15)	22.0
Chest pain	2	(2)	7.1	0	(0)	0.0	2	(2)	3.4
Fatigue	1	(1)	3.6	2	(2)	6.5	3	(3)	5.1
Influenza like illness	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Injection site pain	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Injection site pruritus	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Injection site rash	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Injections site irritation	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Pyrexia	2	(2)	7.1	3	(3)	9.7	5	(5)	8.5
Infections and infestations	7	(8)	25.0	12	(17)	38.7	19	(25)	32.2
Bronchitis	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Campylobacter intestinal infection	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Gastroenteritis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Herpes simplex	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Impetigo	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Infection	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Influenza	0	(0)	0.0	2	(2)	6.5	2	(2)	3.4
Nasopharyngitis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Otitis externa	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Pharyngitis	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Pneumonia	2	(2)	7.1	0	(0)	0.0	2	(2)	3.4
Respiratory tract infection	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Rhinitis	0	(0)	0.0	2	(4)	6.5	2	(4)	3.4
Sinusitis	0	(0)	0.0	2	(2)	6.5	2	(2)	3.4
Tonsillitis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Tooth abcess	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7

Table 28. Incidence of Adverse Events During Respective Treatment and in Total During Treatment by System Organ Class and Preferred Term in Safety Population

MedDRA System Organ Class / Preferred Term for Adverse Event	Treatment						Total		
	ETN			ETN + MTX					
	n	(m)	%	n	(m)	%	n	(m)	%
Upper respiratory tract infection	0	(0)	0.0	2	(3)	6.5	2	(3)	3.4
Injury, poisoning and procedural complications	4	(4)	14.3	1	(1)	3.2	5	(5)	8.5
Accident	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Muscle rupture	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Open wound	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Subcutaneous hematoma	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Tooth injury	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Investigations	5	(6)	17.9	4	(4)	12.9	9	(10)	15.3
Body temperature increased	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Hepatic enzyme increased	5	(5)	17.9	4	(4)	12.9	9	(9)	15.3
Musculoskeletal and connective tissue disorders	1	(1)	3.6	4	(6)	12.9	5	(7)	8.5
Arthralgia	0	(0)	0.0	3	(4)	9.7	3	(4)	5.1
Joint swelling	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Musculoskeletal pain	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Psoriatic arthropathy	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Nervous system disorders	1	(2)	3.6	1	(1)	3.2	2	(3)	3.4
Formacation	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Headache	1	(1)	3.6	1	(1)	3.2	2	(2)	3.4
Renal and urinary disorders	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Calculus ureteric	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Respiratory, thoracic and mediastinal disorders	1	(1)	3.6	4	(4)	12.9	5	(5)	8.5
Cough	1	(1)	3.6	2	(2)	6.5	3	(3)	5.1
Haemptysis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Rhinorrhoea	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Skin and subcutaneous tissue disorders	7	(11)	25.0	5	(5)	16.1	12	(16)	20.3
Blepharitis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Erythema	2	(2)	7.1	0	(0)	0.0	2	(2)	3.4
Hidradenitis	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Pruritus	3	(4)	10.7	2	(2)	6.5	5	(6)	8.5
Psoriasis	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Pustular psoriasis	1	(2)	3.6	0	(0)	0.0	1	(2)	1.7
Skin exfoliation	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Skin fissures	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Swelling face	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Surgical and medical procedures	1	(1)	3.6	1	(1)	3.2	2	(2)	3.4
Dental treatment	0	(0)	0.0	1	(1)	3.2	1	(1)	1.7
Hospitalization	1	(1)	3.6	0	(0)	0.0	1	(1)	1.7
Vascular disorders	0	(0)	0.0	2	(2)	6.5	2	(2)	3.4

Table 28. Incidence of Adverse Events During Respective Treatment and in Total During Treatment by System Organ Class and Preferred Term in Safety Population

MedDRA System Organ Class / Preferred Term for Adverse Event	Treatment						Total		
	ETN			ETN + MTX					
	n	(m)	%	n	(m)	%	n	(m)	%
Hypertension	0	(0)	0.0	2	(2)	6.5	2	(2)	3.4

Non SAE/SAE results are not separated out.
AE = adverse event; ETN = etanercept; MTX = methotrexate; MedDRA = Medical Dictionary for Regulatory activities; m = number of subjects with specified criteria; n = number of subjects; SAE = serious adverse event.

Treatment-related AEs in the ETN group are presented in Table 29.

Table 29. Adverse Events Related to Study Medication - Safety Population. Treatment Group: ETN

	Total
	Related
Cardiac disorders	2
Atrial fibrillation	1
Cardiac failure	1
General disorders and administration site conditions	7
Chest pain	1
Fatigue	1
Influenza like illness	1
Injection site pain	1
Injection site pruritus	1
Injection site rash	1
Injections site irritation	1
Infections and infestations	6
Bronchitis	1
Herpes simplex	1
Infection	1
Pharyngitis	1
Pneumonia	2
Investigations	3
Body temperature increased	1
Hepatic enzyme increased	2
Respiratory, thoracic and mediastinal disorders	1
Cough	1
Skin and subcutaneous tissue disorders	8
Erythema	1
Pruritus	3
Pustular psoriasis	2
Skin exfoliation	1
Swelling face	1
Surgical and medical procedures	1
Hospitalisation	1

Non SAE/SAE results are not separated out.

Table 29. Adverse Events Related to Study Medication - Safety Population. Treatment Group: ETN

	Total Related

ETN = etanercept; SAE = serious adverse event.

Treatment-related AEs in ETN + MTX group are presented in Table 30.

Table 30. Adverse Events Related to Study Medication - Safety population. Treatment Group: ETN + MTX

	Total Related
Gastro-intestinal disorders	3
Diarrhoea	1
Haematemesis	1
Nausea	1
General disorders and administration site conditions	5
Fatigue	2
Pyrexia	3
Infections and infestations	6
Influenza	1
Nasopharyngitis	1
Respiratory tract infection	1
Sinusitis	1
Upper respiratory tract infection	2
Investigations	4
Hepatic enzyme increased	4
Nervous system disorders	1
Headache	1
Respiratory, thoracic and mediastinal disorders	3
Cough	2
Rhinorrhoea	1
Skin and subcutaneous tissue disorders	4
Hidradenitis	1
Pruritus	2
Skin fissures	1

Non SAE/SAE results are not separated out.
ETN = etanercept; MTX = methotrexate; SAE = serious adverse event.

Serious Adverse Events (SAEs): A total of 5 subjects had at least 1 SAE as summarized in Table 31. In total there were 7 SAEs.

Table 31. Summary of All Subjects who had a Serious Adverse Event

Treatment	Subject Serial Number	Adverse Event (Investigator Text)	Relationship
ETN	1	Infection, hospitalized	Possibly
ETN	2	Pustular psoriasis in hands	Probably
ETN	3	Pneumonia	Probably
ETN	4	Heart insufficiency	Possibly
		Atrial fibrillation	Possibly
ETN + MTX	5	Vomited and vomit had blood in it.	Possibly
		Respiratory infection with high fever for 3 days	Possibly

ETN = etanercept; MTX = methotrexate.

Deaths: No deaths were reported in this study.

Discontinuation due to Adverse Events: Three (3) subjects were discontinued from the study treatment due to an AE and are summarized in Table 32.

Table 32. Discontinuations due to Adverse Events

Treatment	Subject Serial Number	Adverse Event (Investigator Text)	Relationship
ETN	1	Pustular psoriasis in hands	Probably
ETN	2	Pneumonia	Probably
ETN	3	Heart insufficiency	Possibly
		Atrial fibrillation	Possibly

ETN = etanercept.

CONCLUSION: The addition of ETN to the MTX treatment regimen achieved an improved response after 24 weeks, as indicated by a PASI 75 of 70% and PASI 90 of 40%, in subjects who had previously responded inadequately to MTX monotherapy. The study did not give rise to any safety concerns.