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

PROTOCOL NO.: 0881A6-410 (B1801011)

PROTOCOL TITLE: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Pilot Study Evaluating the Efficacy and the Safety of Etanercept (ETN) in Patients With Moderate to Severe Plaque Psoriasis After Cessation of Cyclosporine Therapy - SCORE - Sustained Cyclosporine Outcome Replacing Etanercept

Study Centers: A total of 22 centers took part in the study and enrolled subjects; 11 in Italy, 5 in Germany, 4 in Spain and 1 each in Greece and Malta.

Study Initiation and Final Completion Dates: 01 October 2007 to 17 November 2009

Phase of Development: Phase 4

Study Objectives: The aim of this study was to demonstrate the sustained efficacy and safety of etanercept (ETN) as a replacement therapy for cyclosporine (Cs) in subjects with moderate to severe plaque psoriasis who had achieved an adequate response to Cs.

METHODS

Study Design: This was a double-blind, placebo-controlled, randomized, multicenter, multinational pilot study designed to evaluate ETN as replacement therapy for Cs in subjects with moderate-to-severe psoriasis eligible for systemic therapy. The expected total study duration was 115 weeks, with the approximate duration of subject participation up to 38 weeks. Subjects were assessed at regular visits by a trained or qualified dermatologist. In addition, all subjects were evaluated at a follow-up visit, conducted approximately 2 weeks after the Week 30 or early termination visit. The study procedures are presented in Table 1.

Table 1. Study Procedures

Weeks	**-6 to 0 Screening[a]**	**0 Baseline[a]**	**2**	**4**	**6 or PASI 50 Achievement**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**30 or ET**	**32 FUp**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13[b]**	**14**
Visit Window (Days)		**±4**	**±2**	**±2**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±2**
Informed consent	X													
Complete medical history	X													
Full physical examination and dermatological examination[c]	X	X												
Risk factors for renal toxicities (renal inflammation, abnormal cyclosporine adsorption - Mg^{2+})	X													
Renal function (serum creatinine taken after at least 8-hours fast or at least in two occasions)	X	X	X	X	X	X		X						
Chest X-ray[d]	X													
Blood pressure and pulse rate	X	X	X	X	X	X	X	X						
Malignancy screening	X	X												
Blood draw for serum chemistry, hematology and urinalysis[e]	X	X	X	X	X	X	X	X			X		X	
Pregnancy test[f]	X	X												
TB testing[g]	X													
Adverse events[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medications	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment of Psoriasis (PGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Surface Area (BSA)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dermatology Life Quality Index (DLQI)		X	X	X	X	X	X	X	X	X	X	X	X	
Randomization[j]					X									
Drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	
Drug dispensation (Cyclosporine)		X	X	X	X	X	X							
Drug dispensation (Etanercept)					X		X		X	X	X	X		
Diary card		X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Procedures

ET = end of therapy; FUp = follow-up; Mg2+ = magnesium; PASI = Psoriasis Area and Severity Index; TB = tuberculosis.

a. Screening and Baseline visits could not occur on the same day. If the time between Screening and Baseline was 14 days or less, the tests and procedures were not repeated at Baseline.
b. For subjects who prematurely withdraw or discontinued from the study, final visit procedures were performed at the time of withdrawal or discontinuation.
c. Only at Screening body weight (kg) and height (cm) measured. Dermatological examination was performed only at Screening.
d. Waived if within 52 weeks and report was available and in subjects' source documents.
e. Fasting (at least 8 hours) blood draw required.
f. Serum beta-Human Chorionic Gonadotropin (β-HCG) at Screening and urine β-HCG at Baseline for women of childbearing potential only. If urine test was positive, serum pregnancy test was also repeated at Baseline.
g. Required at Screening. If TB testing was positive, appropriate prophylactic treatment, according to local regulations, were to be given.
h. Adverse events were reported from the time of signing the informed consent.
i. Prior medications only at Screening. All prior treatments taken within 28 days of informed consent form signature was recorded. All prior systemic therapies or phototherapies for psoriasis was also recorded.
j. Subjects were randomized to receive etanercept or placebo in combination with cyclosporine tapered as soon as they achieved PASI 50 improvement. The PASI 50 achievement was described in literature to be reached between Week 4 and 8 of Cs treatment. Subjects not achieving PASI 50 at Week 6 were not randomized and discontinued from the study.

Number of Subjects (Planned and Analyzed): One hundred subjects were planned for randomization in the study, in order to achieve 80 completers, and were grouped as follows: 40 in the ETN group and 40 in the control group. A total of 192 subjects were screened, 153 subjects (60 in Italy, 53 in Germany, 23 in Spain, 10 in Greece and 7 in Malta) were enrolled and 120 were randomized for the study. All the 120 subjects received the treatments; of which 62 subjects were assigned to Arm A (subjects randomized to placebo after initial course of Cs) and 58 were assigned to Arm B (subjects randomized to ETN after initial course of Cs).

Diagnosis and Main Criteria for Inclusion: Males or females between 18 and 70 years of age at the screening visit, with active and stable plaque psoriasis with ≥10 of the body surface area (BSA) or ≥10 Psoriasis Area and Severity Index (PASI).

Exclusion Criteria: Subject having evidence of skin conditions other than psoriasis; Psoralen plus psoralen + ultraviolet A (PUVA), Cs, acitretin, alefacept, anakinra, or any other systemic anti-psoriasis therapy or disease-modifying antirheumatic drugs (DMARD) with 28 days of screening; ultraviolet B (UVB) therapy, topical steroids, topical Vitamin A or D analog preparations, or anthralin within 14 days of screening; prior exposure to any tumor necrosis factor-inhibitor. Prior exposure to efalizumab; corticosteroid dose of prednisone >10 mg/day were excluded.

Study Treatment: Subjects were started on treatment with Cs in capsules (50 mg) at the starting dose of 5 mg/kg/day until they achieved PASI 50 or Week 6, whichever occurred earlier. At the time PASI 50 was achieved, subjects were randomized (in a 1:1 ratio) to receive placebo or ETN 50 mg in a sterile lyophilized powder for subcutaneous injection once weekly, to assist in tapering subjects off Cs by 1 mg/kg every 2 weeks, over 6 weeks. Placebo vials had the same formulation except for the active ingredient. Cs were administered at 2 mg/kg/day along with placebo (since Week 12 / Visit 8). Cs were discontinued and subjects were maintained on ETN/placebo blinded therapy for an additional 18 weeks. Subjects not achieving PASI 50 at Week 6 were terminated from the study.

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint: Evaluation of change in the PASI score from randomization to Week 24 (Week 18 of ETN monotherapy/placebo).

Secondary Efficacy Endpoints:

- PASI area under the curve (AUC) between randomization and Week 24;
- Change in the Physician Global Assessment of Psoriasis (PGA) score from randomization to Week 24;
- Percentage relapse (loss of 50% improvement in PASI) and time to relapse during the 24 weeks after randomization;
- Percentage improvement in PASI score from randomization to Week 24;

- Change in the Dermatology Life Quality Index (DLQI) from randomization to Week 24.

Safety Endpoints:

- Percentage Adverse Events (AEs);
- Rebound effects (worsening of psoriasis to 125% of the baseline PASI or appearance of psoriasis variants, such as erythrodermic or pustular psoriasis within 12 weeks of discontinuation of therapy).

Safety Evaluations: All subjects who received at least 1 dose of the test article were evaluated for safety. The variables assessed were physical examination/vital signs, hematology and chemistry profiles, urinalysis, premature withdrawal, AEs and serious AEs (SAEs) during the study.

During the treatment with Cs, in particular, medical evaluations were performed every 2 weeks for the first 12 weeks; blood pressure, renal function (serum creatinine), serum lipid and magnesium (Mg^{2+}) were addressed.

The percentage of AEs and rebound effects (worsening of psoriasis to 125% of the baseline PASI or appearance of psoriasis variants such as erythrodermic or pustular psoriasis within 12 weeks of discontinuation of therapy) were assessed before randomization, in the combination period of (ETN/placebo and Cs, 6-week taper) and during the 18 weeks after randomization.

Statistical Methods:

Study populations included:

- Intent-To-Treat (ITT) population, which included all randomized subjects.
- Per-Protocol (PP) analysis population, restricted to those subjects taking the drugs according to the protocol for the entire study duration and without major violations.

All statistical tests were 2-sided, with a significance level of 0.05.

A linear mixed model with an auto-regressive correlation structure, with treatment groups and visits as fixed factors, was used to analyze the changes over 24 weeks of treatment from randomization to Visit 13 (end of therapy) in the continuous efficacy variables (PASI score, percentage improvement of PASI score, PASI AUC, PGA score, DLQI score). Comparison of the 2 arms at each visit were also reported using the appropriate contrasts.

Time to first relapse was estimated using the Kaplan-Meier method, median survival time were shown and comparisons between arms were tested with a log-rank tests.

Safety analysis was performed on the safety population, including all subjects who received at least 1 dose of the study medication.

Treatment-emergent AEs (TEAEs) were defined as events reported during the treatment-emergent period that was not present before treatment or an event that was present before treatment but became more severe during the treatment-emergent period. The terms used by the Investigators to report AEs were classified using the Medical Dictionary for Regulatory Activities.

RESULTS

Subject Disposition and Demography: A total of 192 subjects were screened for the study, 153 were enrolled at Baseline as they met all inclusion/exclusion criteria (39 subjects were screening failures and did not undergo the Baseline assessment) and 120 subjects (62 to Arm A and 58 to Arm B) were randomly assigned to test article after response to Cs monotherapy. Thirty-three subjects were not randomized because they did not reach PASI 50 or because of AEs. These subjects represent the ITT population. No subjects were excluded from the ITT population. The safety population also includes 120 subjects.

Overall, 57 (47.5%) subjects completed the study regularly (completion of the whole blinded treatment with placebo/ETN): 19 (30.6%) subjects in Arm A and 38 (65.5%) subjects in Arm B.

The PP analysis was performed on the subset of subjects completing the blinded treatment (24 weeks of treatment after randomization) with no major protocol violations. The PP population consists of 57 subjects (19 subjects in Arm A and 38 subjects in arm B). The disposition and subjects analyzed is presented in Table 2.

Table 2. Subject Disposition and Subject Analyzed

	Arm A	Arm B	Total
Subjects screened		192	
Assigned to treatment	62	58	120
Completed	19 (30.6)	38 (65.5)	57 (47.5)
Discontinued	43 (69.4)	20 (34.5)	63 (52.5)
Adverse event	4 (6.5)	3 (5.2)	7 (5.8)
Investigator request	3 (4.8)	2 (3.4)	5 (4.2)
Subject request or withdrawal of consent	18 (29.0)	9 (15.5)	27 (22.5)
Lost to follow-up	2 (3.2)	2 (3.4)	4 (3.3)
Other	16 (25.8)	4 (6.9)	20 (16.7)
Lack of efficacy	10	2	12
Worsening of conditions	1	0	1
Sponsor request following protocol violation	3	0	3
Mistake in drug assignment	0	1	1
PASI-score not 50% of Baseline score at randomization	1	0	1
Poor compliance	1	0	1
Heroin addiction	0	1	1
Analyzed for efficacy			
ITT population		120	
PP population		57	
Analyzed for safety		120	

ITT = intent-to-treat study population; PASI = Psoriasis Area & Severity Index; PP = per-protocol study population.

The demographic and baseline characteristics of subjects are presented in Table 3. The study population consisted of male and female subjects aged 31 to 58 years, with a mean age of 41.5 years in Arm A; and a range of 36 to 48 years, with a mean age of 41.8 years in Arm B.

Table 3. Demographic and Baseline Characteristics

Variable[a]	Arm A N=62	Arm B N=58
Age; Mean (SD)	41.50 (12.97)	41.78 (9.86)
Sex		
Male	45 (72.58)	38 (65.52)
Female	17 (27.42)	20 (34.48)
Race		
Other	1 (1.61)	1 (1.72)
White	60 (96.77)	57 (98.28)
Asian	1 (1.61)	0 (0.00)
Height (cm); Mean (SD)	172.82 (9.56)	172.64 (9.16)
Weight (kg); Mean (SD)	80.25 (16.42)	82.68 (15.95)
BMI (Kg/m^2); Mean (SD)	26.76 (4.44)	27.63 (4.31)
Diastolic blood pressure (mmHg); Mean (SD)	76.90 (8.22)	76.71 (9.34)
Heart rate (beats/min); Mean (SD)	73.17 (10.15)	74.00 (10.14)
PASI score (0–72); Mean (SD)	19.35 (6.98)	20.19 (7.76)
Psoriasis body surface area assessment; Mean (SD)	33.26 (16.20)	32.90 (18.36)
Static global assessment of psoriasis; Mean (SD)	4.07 (0.73)	4.25 (0.85)

BMI = body mass index; N = number of subject; PASI = Psoriasis Area & Severity Index; SD = standard deviation.

a. Continuous variables are reported as mean (SD) and categorical variables were reported as frequency (percentage).

Efficacy Results:

Primary Endpoint: The mean change in PASI score from randomization to Week 24 findings are presented in Table 4. There was a significant change in PASI score from Randomization during Visits 6 to 8 and 11 to 13 for Arm A and during Visits 6 to 11 for Arm B. After 24 weeks from randomization, the mean PASI score had increased by 3.7 (standard error [SE] 0.9) in the Arm A ($p<0.001$ for change from Baseline), while the PASI score did not significantly change in the Arm B (mean change -1.1 [SE 0.9]; $p=0.23$). The mean change difference between the arms was 4.8 (1.3), and was statistically significant ($p<0.001$).

Table 4. Change From Randomization in PASI Score Over 24 Weeks, Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
	Visit 3		**Visit 4**		**Visit 5**	
n	29	32	25	23	8	3
Mean (SE)	5.6 (0.7)	6.1 (0.7)	5.2 (0.8)	5.1 (0.8)	5.2 (1.0)	3.4 (1.5)
Mean change (SE)[a]	-0.5 (1.0)	-	-0.5 (1.0)	-1.0 (0.9)	-0.5 (1.1)	-2.7 (1.6)
95% CI mean change (SE)	(-2.5; 1.6)	-	(-2.3; 1.4)	(-2.8; 0.9)	(-2.7; 1.7)	(-5.8; 0.5)
p-value	0.645	-	0.623	0.295	0.679	0.095
	Visit 6		**Visit 7**		**Visit 8**	
n	59	56	56	55	52	55
Mean (SE)	3.0 (0.6)	2.5 (0.6)	2.6 (0.6)	1.9 (0.6)	2.4 (0.6)	1.8 (0.6)
Mean change (SE)[a]	-2.6 (0.7)	-3.6 (0.7)	-3.0 (0.8)	-4.2 (0.8)	-3.2 (0.8)	-4.3 (0.8)
95% CI mean change (SE)	(-4.0; -1.2)	(-5.0; -2.2)	(-4.5; -1.5)	(-5.7; -2.7)	(-4.8; -1.6)	(-5.9; -2.8)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Visit 9		**Visit 10**		**Visit 11**	
n	45	49	29	45	21	40
Mean (SE)	5.1 (0.6)	2.8 (0.6)	7.0 (0.7)	4.1 (0.6)	8.5 (0.7)	4.3 (0.6)
Mean change (SE)[a]	-0.5 (0.9)	-3.3 (0.8)	1.4 (0.9)	-2.0 (0.9)	2.9 (1.0)	-1.8 (0.9)
95% CI mean change (SE)	(-2.2; 1.2)	(-5.0; -1.7)	(-0.4; 3.2)	(-3.7; -0.3)	(1.0; 4.8)	(-3.5; -0.0)
p-value	0.568	<0.001	0.129	0.021	0.003	0.046
	Visit 12		**Visit 13**			
n	19	38	54	51	-	-
Mean (SE)	9.1 (0.7)	4.4 (0.6)	9.3 (0.6)	5.0 (0.6)	-	-
Mean change (SE)[a]	3.5 (1.0)	-1.7 (0.9)	3.7 (0.9)	-1.1 (0.9)	-	-
95% CI mean change (SE)	(1.6; 5.5)	(-3.5; 0.0)	(1.9; 5.5)	(-2.8; 0.7)	-	-
p-value	<0.001	0.055	<0.001	0.233	-	-

CI = confidence interval; N = total number of subjects per treatment arm; n = number of subjects analyzed in each evaluation visit; SE = standard error.
a. Mean change from Baseline.

Secondary Endpoints: In Arm A, the mean change in the PASI AUC scores from randomization (Table 5), was significant during Visits 7, 8 and 10 to 13; in Arm B the PASI AUC scores remained comparable to randomization values throughout, but were significantly different during Visits 7 to 9. Twenty-four weeks after randomization, the AUC was 83.5 (5.3) in Arm A and 27.7 (5.5) in Arm B. The mean difference in AUC between the arms was 55.8 (7.7), and was statistically significant ($p<0.001$).

Table 5. Change From Randomization in PASI Area Under the Curve (AUC) Score Over 24 Weeks, Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
	Visit 6		**Visit 7**		**Visit 8**	
n	59	56	55	55	52	55
Mean (SE)	20.7 (5.2)	20.7 (5.4)	7.0 (5.3)	5.0 (5.4)	6.7 (5.3)	4.4 (5.4)
Mean change (SE)[a]	0.0 (7.5)	-	-13.7 (2.0)	-15.7 (2.0)	-14.0 (2.8)	-16.3 (2.7)
95% CI mean change (SE)	(-14.7; 14.7)	-	(-17.6, -9.9)	(-19.5, -11.8)	(-19.4, -8.6)	(-21.7, -10.9)
p-value	0.999	-	< 0.001	< 0.001	< 0.001	< 0.001
	Visit 9		**Visit 10**		**Visit 11**	
n	45	49	29	45	21	40
Mean (SE)	17.5 (5.4)	10.8 (5.4)	33.6 (5.6)	17.5 (5.5)	54.8 (5.8)	24.3 (5.5)
Mean change (SE)[a]	-3.2 (3.4)	-9.9 (3.4)	12.9 (4.1)	-3.2 (3.9)	34.1 (4.7)	3.6 (4.3)
95% CI mean change (SE)	(-9.9, 3.5)	(-16.5, -3.3)	(4.8, 20.9)	(-10.8, 4.4)	(24.8, 43.4)	(-4.9, 12)
p-value	0.347	0.003	0.002	0.408	< 0.001	0.408
	Visit 12		**Visit 13**			
n	19	38	54	50	-	-
Mean (SE)	76.6 (5.8)	29.1 (5.6)	83.5 (5.3)	27.7 (5.5)	-	-
Mean change (SE)[a]	55.9 (5.0)	8.4 (4.7)	62.8 (4.7)	7.0 (4.9)	-	-
95% CI mean change (SE)	(46.2, 65.7)	(-0.7, 17.5)	(53.5, 72.0)	(-2.5, 16.5)	-	-
p-value	<0.001	0.072	< 0.001	0.151	-	-

CI = confidence interval; N = total number of subjects per treatment arm; n = number of subjects analyzed in each evaluation visit; SE = standard error.

a. Mean change from Baseline.

After 24 weeks from randomization, PGA score had increased by 0.9 (0.2) in Arm A ($p<0.001$) and 0.5 (0.2) in Arm B ($p=0.008$). The between-arm mean change difference was of 0.4 (0.2); such a difference was not statistically significant ($p=0.176$) (Table 6).

Table 6. Change From Randomization in PGA Score Over 24 Weeks, Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
	Visit 3		**Visit 4**		**Visit 5**	
n	29	32	25	23	8	3
Mean (SE)	2.3 (0.2)	2.4 (0.2)	2.3 (0.2)	2.3 (0.2)	2.5 (0.2)	2.2 (0.4)
Mean change (SE)[a]	-	-	-0.0 (0.2)	-0.0 (0.2)	0.2 (0.3)	-0.2 (0.4)
95% CI mean change (SE)	-	-	(-0.5;0.4)	(-0.5;0.4)	(-0.3;0.8)	(-1.0;0.6)
p-value	-	-	0.965	0.873	0.447	0.707
Mean difference A - B (SE)	-0.0 (0.2)		0.0 (0.2)		0.3 (0.5)	
95% CI mean difference	(-0.5; 0.4)		(-0.5; 0.5)		(-0.6; 1.2)	
p-value	0.911		0.998		0.452	
Mean change difference A - B (SE)	-	-	0.0 (0.3)		0.4 (0.5)	
95% CI mean change difference	-	-	(-0.6; 0.7)		(-0.6; 1.3)	
p-value	-	-	0.935		0.458	
	Visit 6		**Visit 7**		**Visit 8**	
n	60	56	56	55	52	55
Mean (SE)	2.1 (0.1)	1.8 (0.1)	1.8 (0.1)	1.7 (0.1)	1.9 (0.1)	1.7 (0.1)
Mean change (SE)[a]	-0.2 (0.2)	-0.5 (0.2)	-0.5 (0.2)	-0.7 (0.2)	-0.4 (0.2)	-0.6 (0.2)
95% CI mean change (SE)	(-0.6; 0.1)	(-0.9; -0.2)	(-0.9; -0.1)	(-1.0; -0.3)	(-0.8; -0.0)	(-1.0; -0.3)
p-value	0.178	0.002	0.009	<0.001	0.049	<0.001
Mean difference A - B (SE)	0.3 (0.2)		0.2 (0.2)		0.2 (0.2)	
95% CI mean difference	(-0.1; 0.6)		(-0.2; 0.5)		(-0.1; 0.6)	
p-value	0.114		0.373		0.194	
Mean change difference A - B (SE)	0.3 (0.2)		0.2 (0.3)		0.3 (0.3)	
95% CI mean change difference	(-0.2; 0.8)		(-0.3; 0.7)		(-0.3; 0.8)	
p-value	0.229		0.488		0.345	
	Visit 9		**Visit 10**		**Visit 11**	
n	45	49	29	46	21	40
Mean (SE)	2.7 (0.1)	2.1 (0.1)	2.9 (0.2)	2.4 (0.1)	3.2 (0.2)	2.6 (0.1)
Mean change (SE)[a]	0.4 (0.2)	-0.3 (0.2)	0.6 (0.2)	0.1 (0.2)	0.9 (0.2)	0.2 (0.2)
95% CI mean change (SE)	(-0.0; 0.8)	(-0.6; 0.1)	(0.2; 1.0)	(-0.3; 0.4)	(0.4; 1.3)	(-0.2;0.6)
p-value	0.065	0.183	0.006	0.786	<0.001	0.251
Mean difference A - B (SE)	0.6 (0.2)		0.5 (0.2)		0.6 (0.2)	
95% CI mean difference	(0.2; 1.0)		(0.1; 0.9)		(0.2;1.0)	
p-value	0.001		0.009		0.007	
Mean change difference A - B (SE)	0.6 (0.3)		0.6 (0.3)		0.6 (0.3)	

Table 6. Change From Randomization in PGA Score Over 24 Weeks, Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
95% CI mean change difference	(0.1; 1.2)		(-0.0; 1.1)		(0.0; 1.2)	
p-value	0.024		0.064		0.049	
	Visit 12		**Visit 13**			
n	19	38	55	54	-	-
Mean (SE)	3.2 (0.2)	2.6 (0.1)	3.2 (0.1)	2.9 (0.1)	-	-
Mean change (SE)[a]	0.8 (0.2)	0.3 (0.2)	0.9 (0.2)	0.5 (0.2)	-	-
95% CI mean change (SE)	(0.4; 1.3)	(-0.1; 0.7)	(0.5; 1.3)	(0.1; 0.9)	-	-
p-value	<0.001	0.19	<0.001	0.008	-	-
Mean difference A - B (SE)	0.5 (0.2)		0.4 (0.2)		-	-
95% CI mean difference	(0.1; 1.0)		(0.0; 0.7)		-	-
p-value	0.013		0.041		-	-
Mean change difference A - B (SE)	0.6 (0.3)		0.4 (0.3)		-	-
95% CI mean change difference	(-0.0; 1.2)		(-0.2; 1.0)		-	-
p-value	0.07		0.176		-	-

CI = confidence interval; N = total number of subjects per treatment arm; n = number of subjects analyzed in each evaluation visit; PGA = Physician Global Assessment; SE = standard error.

a. Mean change from Baseline.

The proportion of subjects meeting criteria for relapse was significantly higher in the group of subjects who switched to placebo (44 subjects; 71%) as opposed to the group of subjects who switched to ETN (25 subjects, 43%) (p=0.002). Overall, a relapse (loss of 50% improvement in PASI) occurred in 63.77% of the subjects assigned to Arm A and 36.23 of the subjects in Arm B (p=0.002), suggesting a significant loss of improvement in PASI for Arm A versus Arm B. Furthermore, the time to relapse was also earlier in Arm A compared to Arm B.

Improvements in the PASI score: In Arm A, a 127% worsening in the PASI score was documented from randomization to Week 24 (p <0.001); in Arm B, a small increase in the PASI score from randomization was documented (+12.4%; p = 0.853). Mean change difference between the arms was of 118.2% and was statistically significant (p = 0.004) (Table 7).

Table 7. Change From Randomization Percent Improvement of PASI Over 24 Weeks, Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
	Visit 3		**Visit 4**		**Visit 5**	
n	26	31	24	22	8	3
Mean (SE)	4.0 (25.5)	7.1 (24.0)	-0.6 (24.9)	-9.8 (25.7)	-15.0 (31.2)	-14.0 (46.3)
Mean change (SE)[a]	-	-	-4.6 (30.2)	-16.9 (29.5)	-18.9 (34.7)	-21.1 (47.8)
95% CI mean change (SE)	-	-	(-63.7; 54.6)	(-74.7; 40.9)	(-86.9; 49.0)	(-114.9; 72.7)
p-value	-	-	0.880	0.567	0.585	0.660
Mean difference A - B (SE)	-3.1 (35.0)		9.2 (35.8)		-1.0 (55.8)	
95% CI mean difference	(-71.7; 65.5)		(-60.9; 79.3)		(-110.4; 108.4)	
p-value	0.929		0.797		0.986	
Mean change difference A - B (SE)	-	-	12.3 (42.2)		2.1 (59.1)	
95% CI mean change difference	-	-	(-70.4; 95.0)		(-113.7; 117.9)	
p-value	-	-	0.770		0.971	
	Visit 6		**Visit 7**		**Visit 8**	
n	56	54	53	53	49	53
Mean (SE)	-47.9 (19.5)	-55.6 (20.0)	-56.6 (19.7)	-63.5 (20.0)	-57.4 (20.0)	-65.6 (20.1)
Mean change (SE)[a]	-51.9 (23.2)	-62.7 (21.9)	-60.5 (24.8)	-70.6 (23.5)	-61.4 (26.2)	-72.7 (24.7)
95% CI mean change (SE)	(-97.4; -6.4)	(-105.6; -19.8)	(-109.1; -12.0)	(-116.6; -24.6)	(-112.7; -10.1)	(-121.1; -24.2)
p-value	0.026	0.004	0.015	0.003	0.019	0.003
Mean difference A - B (SE)	7.7 (27.9)		7.0 (28.1)		8.2 (28.4)	
95% CI mean difference	(-47.0; 62.4)		(-48.1; 62.0)		(-47.4; 63.7)	
p-value	0.783		0.804		0.774	
Mean change difference A - B (SE)	10.8 (31.9)		10.1 (34.1)		11.3 (36.0)	
95% CI mean change difference	(-51.8; 73.3)		(-56.8; 76.9)		(-59.3; 81.8)	
p-value	0.735		0.768		0.754	
	Visit 9		**Visit 10**		**Visit 11**	
n	43	47	27	43	19	38
Mean (SE)	11.0 (20.5)	-45.6 (20.4)	96.0 (22.3)	-20.5 (20.8)	125.9 (24.2)	-6.2 (21.3)
Mean change (SE)[a]	7.1 (27.5)	-52.6 (26.0)	92.1 (29.6)	-27.6 (27.1)	121.9 (31.6)	-13.3 (28.1)
95% CI mean change (SE)	(-46.8; 61.0)	(-103.5; -1.7)	(34.1; 150.0)	(-80.7; 25.5)	(59.9; 183.9)	(-68.4;41.8)
p-value	0.797	0.043	0.002	0.309	<0.001	0.636
Mean difference A - B (SE)	56.6 (29.0)		116.5 (30.5)		132.1 (32.2)	
95% CI mean difference	(-0.2; 113.4)		(56.7; 176.3)		(69.0; 195.2)	
p-value	0.052		<0.001		<0.001	
Mean change difference A - B (SE)	59.7 (37.8)		119.6 (40.1)		135.2 (42.3)	

Table 7. Change From Randomization Percent Improvement of PASI Over 24 Weeks, Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
95% CI mean change difference	(-14.4; 133.8)		(41.0; 198.3)		(52.3; 218.1)	
p-value	0.115		0.003		0.001	
	Visit 12		**Visit 13**			
n	17	36	51	49	-	-
Mean (SE)	127.0 (23.9)	-6.4 (21.3)	127.5 (20.3)	12.4 (20.7)	-	-
Mean change (SE)[a]	123.1 (31.9)	-13.5 (28.7)	123.5 (29.8)	5.3 (28.7)	-	-
95% CI mean change (SE)	(60.5; 185.7)	(-69.7; 42.8)	(65.1; 181.9)	(-51.0; 61.6)	-	-
p-value	<0.001	0.639	<0.001	0.853	-	-
Mean difference A - B (SE)	133.4 (32.0)		115.1 (28.9)		-	-
95% CI mean difference	(70.7; 196.2)		(58.4; 171.8)		-	-
p-value	<0.001		<0.001		-	-
Mean change difference A - B (SE)	136.5 (42.9)		118.2 (41.4)		-	-
95% CI mean change difference	(52.4; 220.7)		(37.1; 199.3)		-	-
p-value	0.002		0.004		-	-

CI = confidence interval; N = total number of subjects per treatment arm; n = number of subjects analyzed in each evaluation visit; PASI = Psoriasis Area & Severity Index; SE = standard error.

a. Mean change from Baseline.

After 24 weeks from randomization, the DLQI score had significantly increased (ie, worsened) by 3.2 (1.1) in Arm A (p=0.003) but not in Arm B (increase of 0.5 (1.1); p=0.659). The mean change difference between the arms was of 2.8 (1.5), and did not reach statistical significance (p=0.069) (Table 8).

Table 8. Change from Randomization in DLQI Over 24 Weeks - Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
	Visit 3		**Visit 4**		**Visit 5**	
n	28	30	25	22	8	3
Mean (SE)	4.1 (0.9)	4.0 (0.9)	3.0 (0.9)	4.0 (0.9)	1.5 (1.2)	1.9 (1.9)
Mean change (SE)[a]	-	-	-1.1 (1.2)	0.0 (1.2)	-2.6 (1.4)	-2.1 (2.0)
95% CI mean change (SE)	-	-	(-3.4; 1.2)	(-2.3; 2.3)	(-5.3; 0.1)	(-6.0; 1.8)
p-value	-	-	0.345	0.977	0.06	0.286
Mean difference A - B (SE)	0.1 (1.2)	-	-1.1 (1.3)	-	-0.4 (2.2)	-
95% CI mean Difference	(-2.3; 2.5)	-	(-3.6; 1.5)	-	(-4.8; 3.9)	-
p-value	0.956	-	0.41	-	0.844	-
Mean change difference A - B (SE)	-	-	-1.1 (1.6)	-	-0.5 (2.4)	-
95% CI mean Change Difference	-	-	(-4.3; 2.1)	-	(-5.2; 4.2)	-
p-value	-	-	0.494	-	0.834	-
	Visit 6		**Visit 7**		**Visit 8**	
n	58	55	56	54	52	54
Mean (SE)	1.6 (0.6)	1.6 (0.7)	1.7 (0.6)	1.0 (0.7)	2.0 (0.7)	1.0 (0.7)
Mean change (SE)[a]	-2.4 (0.9)	-2.4 (0.9)	-2.3 (0.9)	-3.0 (0.9)	-2.1 (1.0)	-3.0 (1.0)
95% CI mean change (SE)	(-4.2; -0.7)	(-4.1; -0.7)	(-4.2; -0.5)	(-4.8; -1.2)	(-4.0; -0.2)	(-4.9; -1.1)
p-value	0.006	0.006	0.013	0.001	0.034	0.002
Mean difference A - B (SE)	0.0 (0.9)	-	0.7 (0.9)	-	1.0 (0.9)	-
95% CI mean difference	(-1.8; 1.8)	-	(-1.1; 2.5)	-	(-0.9; 2.8)	-
p-value	0.968	-	0.441	-	0.3	-
Mean change difference A - B (SE)	-0.0 (1.3)	-	0.7 (1.3)	-	0.9 (1.4)	-
95% CI mean change difference	(-2.5; 2.4)	-	(-2.0; 3.3)	-	(-1.8; 3.6)	-
p-value	0.981	-	0.624	-	0.511	-
	Visit 9		**Visit 10**		**Visit 11**	
n	44	48	29	44	20	40
Mean (SE)	5.5 (0.7)	2.8 (0.7)	6.2 (0.8)	3.3 (0.7)	6.1 (0.9)	3.6 (0.7)
Mean change (SE)[a]	1.4 (1.0)	-1.2 (1.0)	2.2 (1.1)	-0.7 (1.0)	2.0 (1.2)	-0.4 (1.1)
95% CI mean change (SE)	(-0.6; 3.4)	(-3.1; 0.8)	(-0.0; 4.3)	(-2.8;1.3)	(-0.4; 4.3)	(-2.5; 1.7)
p-value	0.183	0.252	0.053	0.474	0.097	0.716
Mean difference A - B (SE)	2.6 (1.0)	-	3.0 (1.0)	-	2.4 (1.1)	-
95% CI mean difference	(0.7; 4.5)	-	(0.9; 5.0)	-	(0.2; 4.6)	-
p-value	0.008	-	0.005	-	0.031	-
Mean change difference A - B (SE)	2.5 (1.4)	-	2.9 (1.5)	-	2.4 (1.6)	-

Table 8. Change from Randomization in DLQI Over 24 Weeks - Intent-To-Treat Population

	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58	Arm A N=62	Arm B N=58
95% CI Mean Change Difference	(-0.3; 5.4)		(-0.1; 5.9)		(-0.8; 5.5)	
p-value	0.079		0.057		0.139	
	Visit 12		**Visit 13**			
n	19	38	51	51	-	-
Mean (SE)	7.4 (0.9)	3.8 (0.7)	7.3 (0.7)	4.5 (0.7)	-	-
Mean change (SE)[a]	3.4 (1.2)	-0.2 (1.1)	3.2 (1.1)	0.5 (1.1)	-	-
95% CI mean change (SE)	(1.0; 5.7)	(-2.3;2.0)	(1.1; 5.4)	(-1.6; 2.6)	-	-
p-value	0.005	0.878	0.003	0.659	-	-
Mean difference A - B (SE)	3.6 (1.1)		2.8 (1.0)	-	-	-
95% CI mean difference	(1.4; 5.8)		(0.9; 4.7)	-	-	-
p-value	0.001		0.004	-	-	-
Mean change difference A - B (SE)	3.5 (1.6)		2.8 (1.5)	-	-	-
95% CI mean change difference	(0.4; 6.7)		(-0.2; 5.8)	-	-	-
p-value	0.028		0.069	-	-	-

CI = confidence interval; DLQI = Dermatology Life Quality Index; N = total number of subjects per treatment arm; n = number of subjects analyzed in each evaluation visit; SE = standard error.

a. Mean change from Baseline.

Safety Results: Overall, 48 of subjects in the placebo group (77.4%) and 43 in the ETN group (74.1%) experienced at least 1 AE during the study (the statistical difference between groups was not significant: p=0.6748). Three subjects reported SAEs (1 with placebo and 2 with ETN). The number of subjects reporting AEs during the study is summarized in Table 9.

Table 9. Summary of Adverse Events

Number of Subjects (%)[a]	Arm A (N=62)	Arm B (N=58)
Any adverse event	48 (77.4)	43 (74.1)
Treatment-emergent adverse events	22 (35.5)	15 (25.9)
Serious adverse events	1 (1.6)	2 (3.4)
AEs causing discontinuation	4 (6.5)	3 (5.2)
Treatment-related adverse events	23 (37.1)	23 (39.7)

N = total nuber of subjects per treatment arm.

a. Percentages in each column are referred to the corresponding total number of subjects in either the placebo or Etanercept (ETN) group. The sum of items in each column does not correspond to the total number of subjects in that group.

A rebound effect (ie, worsening of PASI by 125% vs Baseline) was documented in 4 subjects in the placebo arm and none in the ETN arm (p=0.1196).

Treatment-Emergent Adverse Events: Nonserious treatment-emergent AEs (TEAEs) are presented in Table 10. The most common nonserious TEAEs were headache (21 [33.9%] subjects in Arm A versus [vs] 17 [29.3%] subjects in Arm B), nasopharyngitis (13 [21%] vs 11 [19%]), nausea (13 [21%] vs 7 [12.1%]), abdominal pain (8 [12.9%] vs 8 [13.8%]) and hypertension (9 [14.5%] vs 9 [15.5%]).

Table 10. Summary of Nonserious Treatment-Emergent Adverse Events (All Causality)

System Organ Class and MedDRA Preferred Term	Arm A N=62 n (%)	Arm B N=58 n (%)
Blood and lymphatic system disorders	1 (1.6)	1 (1.7)
Iron deficiency anaemia	0	1 (1.7)
Leukopenia	1 (1.6)	0
Cardiac disorders	1 (1.6)	0
Oedema peripheral	1 (1.6)	0
Congenital, familial and genetic disorders	0	2 (3.4)
Inborn error of bilirubin metabolism	0	1 (1.7)
Odontogenic cyst	0	1 (1.7)
Ear and labyrinth disorders	1 (1.6)	0
Ear pain	1 (1.6)	0
Eye disorders	4 (6.5)	1 (1.7)
Conjunctivitis	2 (3.2)	1 (1.7)
Vision blurred	1 (1.6)	0
Vitreous detachment	1 (1.6)	0
Gastrointestinal disorders	41 (66.1)	29 (50)
Abdominal discomfort	0	1 (1.7)
Abdominal distension	1 (1.6)	0
Abdominal pain	8 (12.9)	8 (13.8)
Anal pruritus	1 (1.6)	0
Diarrhoea	4 (6.5)	0
Diarrhoea infectious	0	1 (1.7)
Dysentery	0	1 (1.7)
Dyspepsia	1 (1.6)	1 (1.7)
Enteritis	1 (1.6)	0
Flatulence	1 (1.6)	0
Gastritis	1 (1.6)	1 (1.7)
Gastroenteritis	1 (1.6)	1 (1.7)
Gastrointestinal disorder	0	1 (1.7)
Gastrooesophageal reflux disease	2 (3.2)	0
Gingival disorder	0	1 (1.7)
Gingival hyperplasia	1 (1.6)	0
Gingival hypertrophy	0	1 (1.7)
Gingivitis	2 (3.2)	1 (1.7)
Haemorrhoids	1 (1.6)	0
Lip dry	1 (1.6)	0
Nausea	13 (21)	7 (12.1)
Paraesthesia oral	0	1 (1.7)
Throat irritation	1 (1.6)	0
Toothache	0	2 (3.4)
Vomiting	1 (1.6)	1 (1.7)
General disorders and administration site conditions	14 (22.6)	15 (25.9)
Asthenia	0	2 (3.4)
Chest pain	0	1 (1.7)
Fatigue	4 (6.5)	5 (8.6)
Feeling hot	2 (3.2)	1 (1.7)
Feeling of body temperature change	2 (3.2)	0
Hyperpyrexia	1 (1.6)	0
Injection site anaesthesia	1 (1.6)	0
Injection site pain	0	1 (1.7)
Injection site pruritus	2 (3.2)	0
Injection site reaction	1 (1.6)	2 (3.4)

Table 10. Summary of Nonserious Treatment-Emergent Adverse Events (All Causality)

System Organ Class and MedDRA Preferred Term	Arm A N=62 n (%)	Arm B N=58 n (%)
Localised oedema	0	1 (1.7)
Malaise	0	1 (1.7)
Pyrexia	1 (1.6)	1 (1.7)
Infections and infestations	24 (38.7)	19 (32.8)
Ascariasis	1 (1.6)	0
Asymptomatic bacteriuria	0	1 (1.7)
Escherichia urinary tract infection	0	1 (1.7)
Influenza	2 (3.2)	3 (5.2)
Nasopharyngitis	13 (21)	11 (19)
Oral herpes	1 (1.6)	0
Pharyngitis	1 (1.6)	1 (1.7)
Rhinitis	0	2 (3.4)
Superinfection	1 (1.6)	0
Tinea cruris	1 (1.6)	0
Tooth abscess	0	2 (3.4)
Urinary tract infection	1 (1.6)	0
Injury, poisoning and procedural complications	2 (3.2)	1 (1.7)
Accidental overdose	2 (3.2)	0
Hand fracture	0	1 (1.7)
Investigations	5 (8.1)	11 (19)
Alanine aminotransferase increased	0	1 (1.7)
Blood cholesterol abnormal	1 (1.6)	0
Blood cholesterol increased	1 (1.6)	0
Blood creatinine increased	2 (3.2)	4 (6.9)
Blood magnesium decreased	0	1 (1.7)
Blood pressure increased	0	1 (1.7)
Blood uric acid increased	0	1 (1.7)
Hepatic enzyme increased	0	3 (5.2)
Transaminases increased	1 (1.6)	0
Metabolism and nutrition disorders	3 (4.8)	2 (3.4)
Diabetes mellitus	1 (1.6)	0
Hypercholesterolaemia	1 (1.6)	0
Hypertriglyceridaemia	1 (1.6)	0
Hyperuricaemia	0	1 (1.7)
Hypomagnesaemia	0	1 (1.7)
Musculoskeletal and connective tissue disorders	13 (21)	17 (29.3)
Arthralgia	3 (4.8)	1 (1.7)
Arthropathy	1 (1.6)	0
Back pain	0	1 (1.7)
Intervertebral disc protrusion	0	1 (1.7)
Joint swelling	0	1 (1.7)
Limb discomfort	0	1 (1.7)
Muscle spasms	3 (4.8)	5 (8.6)
Musculoskeletal pain	0	1 (1.7)
Musculoskeletal stiffness	1 (1.6)	0
Myalgia	1 (1.6)	1 (1.7)
Neck pain	1 (1.6)	0
Pain in extremity	2 (3.2)	5 (8.6)
Sensation of heaviness	1 (1.6)	0
Nervous system disorders	38 (61.3)	31 (53.4)
Burning sensation	1 (1.6)	1 (1.7)

Table 10. Summary of Nonserious Treatment-Emergent Adverse Events (All Causality)

System Organ Class and MedDRA Preferred Term	Arm A N=62 n (%)	Arm B N=58 n (%)
Dizziness	1 (1.6)	5 (8.6)
Dysgeusia	0	1 (1.7)
Headache	21 (33.9)	17 (29.3)
Hyperaesthesia	1 (1.6)	0
Insomnia	0	1 (1.7)
Migraine	2 (3.2)	2 (3.4)
Paraesthesia	10 (16.1)	3 (5.2)
Presyncope	1 (1.6)	0
Sensory disturbance	0	1 (1.7)
Vertigo	1 (1.6)	0
Psychiatric disorders	1 (1.6)	3 (5.2)
Anxiety	0	1 (1.7)
Depression	1 (1.6)	1 (1.7)
Somatoform disorder	0	1 (1.7)
Renal and urinary disorders	2 (3.2)	2 (3.4)
Cystitis	2 (3.2)	0
Haematuria	0	1 (1.7)
Renovascular hypertension	0	1 (1.7)
Reproductive system and breast disorders	1 (1.6)	4 (6.9)
Breast pain	0	1 (1.7)
Dysmenorrhoea	0	1 (1.7)
Menstruation irregular	0	1 (1.7)
Postmenopausal haemorrhage	0	1 (1.7)
Prostatitis	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders	6 (9.7)	5 (8.6)
Bronchitis	3 (4.8)	1 (1.7)
Cough	0	1 (1.7)
Oropharyngeal pain	2 (3.2)	1 (1.7)
Upper respiratory tract infection	1 (1.6)	2 (3.4)
Skin and subcutaneous tissue disorders	12 (19.4)	18 (31)
Alopecia	2 (3.2)	0
Alopecia effluvium	0	2 (3.4)
Dermal cyst	0	1 (1.7)
Folliculitis	1 (1.6)	1 (1.7)
Hair disorder	0	1 (1.7)
Herpes simplex	2 (3.2)	0
Hypertrichosis	2 (3.2)	4 (6.9)
Ingrowing nail	1 (1.6)	0
Injection site dermatitis	0	1 (1.7)
Injection site rash	0	1 (1.7)
Pruritus	1 (1.6)	2 (3.4)
Psoriasis	2 (3.2)	3 (5.2)
Rash	1 (1.6)	0
Swelling face	0	1 (1.7)
Urticaria	0	1 (1.7)
Surgical and medical procedures	1 (1.6)	1 (1.7)
Tooth extraction	0	1 (1.7)
Tooth repair	1 (1.6)	0
Vascular disorders	21 (33.9)	14 (24.1)
Deep vein thrombosis	1 (1.6)	0
Essential hypertension	2 (3.2)	1 (1.7)

Table 10. Summary of Nonserious Treatment-Emergent Adverse Events (All Causality)

System Organ Class and MedDRA Preferred Term	Arm A N=62 n (%)	Arm B N=58 n (%)
Hot flush	3 (4.8)	2 (3.4)
Hypertension	9 (14.5)	9 (15.5)
Hypotension	1 (1.6)	0
Lymphoedema	0	1 (1.7)
Migraine with aura	1 (1.6)	0
Secondary hypertension	2 (3.2)	1 (1.7)
Systolic hypertension	1 (1.6)	0
Venous injury	1 (1.6)	0

MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects per treatment arm; n = number of subjects having a particular nonserious treatment-emergent adverse event.

Twenty-three (37.1%) subjects in Arm A and 23 (39.7%) subjects in Arm B experienced AEs which were considered related to the study drug.

SAEs: One subject in the placebo arm (1.6%; benign prostatic hyperplasia) and 2 subjects in the ETN arm (3.4%; tonsillitis and bronchial carcinoma) reported SAEs during the study. These events were considered to be not related to study drug by the Investigator.

Deaths: No deaths occurred during the study.

Discontinuations: Overall, 7 (5.8%) subjects discontinued from the study for AEs. In the placebo arm 4 (6.5%) subjects discontinued study for AEs (Exacerbation of psoriasis, Blood creatinine increased, severe hypertension, chronic prostatitis). In the ETN arm 3 (5.2%) subjects discontinued study for AEs (psoriasis aggravated, blood creatinine increased, inborn error of bilirubin metabolism not otherwise specified.

CONCLUSIONS: This study documented statistically significant differences between ETN and placebo in the maintenance of a clinical response previously achieved with Cs, based on the reduction of the PASI score. The choice of the PASI score as the primary endpoint parameter of the study is justified as this is a well-established parameter for the evaluation of psoriasis and is based on typical clinical signs that are easy to evaluate and to quantify.

These results were obtained over a treatment period of 24 weeks, which is in line with the labeling instructions for use of ETN in psoriasis, where 24 weeks may be necessary to give full benefit.

The treatment with ETN was well tolerated with no relevant differences vs placebo, and with no unexpected toxicity. Local skin reactions, which are frequently observed with ETN, were more frequent than with placebo in this study. Conversely, other adverse effects commonly reported in the literature, in particular infections, were observed less frequently than with placebo.

A relatively modest number of subjects were enrolled in the trial and a substantial number of subjects discontinued the study, especially among those enrolled in the placebo arm. This

outcome is to be placed in relation with the occurrence of relapses in the placebo arm after the completion of Cs tapering phase, and mirrors the efficacy results obtained with ETN.

Protocol deviations were mostly minor and did not affect the safety of the study subjects, nor the conduct or the conclusions of the study.

As a conclusion, ETN can be safely added to other systemic and topical agents to augment efficacy in severe recalcitrant psoriasis. With this exploratory study it was shown that subjects with moderate to severe plaque psoriasis can be treated effectively and safely with ETN as replacement therapy for Cs, thus reducing the risk of threatening adverse effects possibly linked to the use of Cs.