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

PROTOCOL NO.: 0881A6-409

PROTOCOL TITLE: A Randomised, Open-Label Preliminary Study to Assess the Effects of Etanercept 50 mg Once Weekly for 24 Weeks and Etanercept 50 mg Twice Weekly for 12 Weeks Reducing to Etanercept 50 mg Once Weekly for 12 weeks on Nail and Skin Symptoms in Patients With Nail Psoriasis and Plaque Psoriasis

Study Centers: A total of 25 centers participated in study including 14 in Italy, 5 in France, 3 in Greece, 2 in the United Kingdom, and 1 in Austria.

Study Initiation Date and Final Completion Date: 21 September 2007 to 03 August 2009

Phase of Development: Phase 3b/4

Study Objectives:

Primary Objective:

- To estimate the Nail Psoriasis Severity Index (NAPSI) in the target fingernail for both treatment regimens over 24 weeks

Secondary Objective:

- To estimate the overall NAPSI for both treatment regimens over 24 weeks
- To estimate the proportion of subjects achieving a 50% and 75% improvement in NAPSI in the target fingernail and overall NAPSI at 12 and 24 weeks
- To estimate the Psoriasis Area and Severity Index (PASI) scores over 24 weeks
- To estimate the proportion of subjects achieving a 50% and 75% improvement in PASI scores at 12 and 24 weeks
- To estimate the Physician Global Assessment (PGA) of psoriasis over 24 weeks
- To estimate the proportion of subjects achieving a status on the PGA of psoriasis of clear or almost clear over 24 weeks
- To estimate the proportion of subjects achieving a status on the PGA of psoriasis of mild or better over 24 weeks

- To estimate subjects Dermatology Life Quality Index (DLQI) over 24 weeks
- To estimate Physician and Patient Assessment of Nail Psoriasis Activity Visual Analogue Scale (VAS) over 24 weeks
- To evaluate the safety and tolerability of the treatment regimens over 24 weeks
- To explore the utility of a novel fingernail grading assessment tool (Physician fingernail grading assessment) over 24 weeks

METHODS

Study Design: This was a multicenter, multinational, randomized, open-label study in moderate to severe psoriasis subjects with fingernail involvement. In Group 1, subjects were randomly assigned to receive etanercept 50 mg twice weekly for 12 weeks reducing thereafter to etanercept 50 mg once weekly up to 24 weeks. In Group 2, subjects were randomly assigned to receive etanercept 50 mg once weekly for the full 24-week treatment period. Randomized subjects were allocated to either treatment group in a 1:1 ratio.

Treatment response was assessed over 24 weeks with visits at Screening (within 6 weeks of Baseline), Baseline, Weeks 2, 6, 12, 18, 24, and 26 (the latter as 2-week follow-up and End-of-Study Visit). A sub-set of subjects at specified sites had fingernail photographs taken at Baseline, Week 12, and Week 24 to provide qualitative evaluation.

Subjects participated in the study for approximately 32 weeks. This included up to 6 weeks of screening, 24 weeks of treatment, and 2 weeks of follow up. The study flowchart is presented in Table 1.

Table 1. Study Flowchart

Study Week	Screening[a] -6 to 0	Baseline 0	Week 2	Week 6	Week 12	Week 18	Week 24 or Early Termination	Week 26 (2 Week Follow-Up)
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[b]**	**8**
Visit Window (Days)		**±4 Days**	**±2 Days**	**±4 Days**	**±4 Days**	**±4 Days**	**±4 Days**	**±2 Days**
Informed consent	X							
Randomisation		X						
Adverse event collection[c]	X	X	X	X	X	X	X	X
Medical history	X	X[d]						
Physical exam (including vital signs)[e]	X	X			X		X	
Hematology / serum biochemistry[f]	X		X		X		X	
Pregnancy test[g]	X	X						
Chest X ray[h]	X							
TB testing[i]	X							
Prior medications / therapies	X							
Concomitant medications		X	X	X	X	X	X	X
Physical Global Assessment of Psoriasis (PGA)	X	X	X	X	X	X	X	
Nail Psoriasis Severity Index (NAPSI)[j]	X	X			X		X	
Physician and Patient Assessment of Nail Psoriasis Activity VAS	X	X	X	X	X	X	X	
Psoriasis Severity and Area Index (PASI)	X	X	X		X		X	
Dermatology Life Quality Index (DLQI)	X	X	X		X		X	
Physician Fingernail Grading Assessment	X	X			X		X	
Finger nail photographs[k]		X			X		X	
Drug dispensation		X		X	X	X		
Drug accountability			X	X	X	X	X	
Telephone follow up								X
Diary Card		X	X	X	X	X		

TB = tuberculosis; VAS = visual analogue scale.

Table 1. Study Flowchart

a. If Screening and Baseline visits occurred on the same day. If time between Screening and Baseline was 14 days or less then tests and procedures were not repeated at Baseline, except for the urine pregnancy test.
b. Subjects who prematurely withdraw or discontinue with the study, final visit procedures were performed at the time of discontinuation/withdrawal.
c. Adverse events were reported from the time of signing the informed consent.
d. At Baseline, only an update of prior therapies for psoriasis was performed.
e. Only at Screening body weight (kg) and height (cm) were measured.
f. Fasting (at least 8 hours) blood draw required.
g. Serum HCG at Screening and urine HCG at Baseline for women of child bearing potential only.
h. Waived if within 52 weeks and report was available and in subjects source documents.
i. Required at Screening. If TB testing was positive, appropriate prophylactic treatment, according to local regulations, were given.
j. Overall NAPSI and target fingernail NAPSI were both performed. Target nail was defined as the nail with the highest nail score (matrix+bed scores) at Baseline. The target fingernail was chosen by the Investigator if more than 1 fingernail had the same score.
k. A subset of subjects at specified sites had fingernail photographs taken at Baseline, Week 12, and Week 24 to provide qualitative evaluation.

Number of Subjects (Planned and Analyzed): The number of subjects planned for this study was 136 (68 per group). A total of 85 subjects were screened and 72 of these subjects were randomly assigned to study drug.

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥18 years of age with active, stable plaque psoriasis defined by body surface area ≥10% at Screening and Baseline, or PASI >10 at Screening and Baseline, or PGA of psoriasis status of moderate or worse (moderate, marked, or severe) at Screening and Baseline or DLQI >10 at Baseline. Subjects with active fingernail psoriasis defined as target fingernail NAPSI ≥2 and overall NAPSI >14 (target nail was defined as the nail with the highest nail score [matrix+bed scores]) at Baseline. The target fingernail was chosen by the Investigator if more than 1 fingernail had the same score. Subjects who experienced failure of at least 1 systemic psoriasis therapy for nail psoriasis and who were eligible to receive biologic therapy for psoriasis in accordance to local guidelines were included.

Exclusion Criteria: Subjects with evidence of skin conditions other than psoriasis; subjects who received psoralen plus ultraviolet radiation, cyclosporine, alefacept, methotrexate, acitretin, or any other systemic anti-psoriasis therapy within 28 days of study drug initiation; and subject who had prior exposure to any tumor necrosis factor-inhibitor or prior exposure to efalizumab were excluded from study.

Study Treatment: Etanercept was supplied by the Sponsor as 50 mg vial containing lyophilized powder with 1 mL of sterile water for reconstitution. Vials were kept under refrigerated conditions at 2°C to 8°C. After reconstitution, the study drug could be injected within 6 hours if kept refrigerated at 2°C to 8°C. After reconstitution, etanercept was not to be frozen.

Subjects were randomized to one of either 2 groups:

- Group 1 received 50 mg etanercept subcutaneous (SC) injections twice weekly for 12 weeks reducing to etanercept 50 mg once weekly to Week 24
- Group 2 received 50 mg etanercept SC injections once weekly for the entire 24 week treatment period

Etanercept was administered at approximately the same time of day (±4 hours). Etanercept was administered twice weekly 3-4 days apart on the same days of the week (eg, Monday and Thursday, Tuesday and Friday, Wednesday and Saturday, or Sunday and Wednesday). Injections were administered in the abdomen, thigh, or upper group and the location of injections was rotated with each dose. If administration of etanercept did not occur on the scheduled day, the missed dose should have been resumed immediately, but not within 1 day prior to the next scheduled dose. Subjects received the etanercept vials in quantities to support dosing for 6 weeks of treatment.

Efficacy, Outcomes Research Endpoints:

Primary Endpoint: Change from Baseline in NAPSI for target fingernail at Week 24

Secondary Endpoints:

- Change from Baseline in overall NAPSI over 24 weeks
- Proportion of subjects achieving NAPSI 50 and NAPSI 75 for target fingernail and overall NAPSI at 12 and 24 weeks
- Change from Baseline in the PASI over 24 weeks
- Proportion of subjects achieving PASI 50 and 75 at 12 and 24 weeks
- Change from Baseline in the PGA of psoriasis over 24 weeks
- Proportion of subjects achieving a status on the PGA of psoriasis of clear or almost clear over 24 weeks
- Proportion of subjects achieving a status on the PGA of psoriasis of mild or better over 24 weeks
- Change from Baseline in the DLQI over 24 weeks
- Change from Baseline in the Physician and Patient Assessment of Nail Psoriasis Activity VAS over 24 weeks
- Change from Baseline using a novel fingernail assessment tool (physician fingernail grading assessment) over 24 weeks

Safety Evaluations: The safety of etanercept was determined using the following assessments: monitoring of adverse events (AEs), withdrawal due to AEs, concomitant medications, laboratory determinations, pregnancy test, vital signs, standard 12-lead electrocardiograms (ECGs), and physical examinations. Safety variables were assessed throughout the course of the study.

Statistical Methods: Statistical analysis considered the following study populations:

Safety population: all subjects who received at least 1 dose of test article.

Modified intent-to-treat (mITT) population: all randomized subjects who received at least 1 dose of test article and providing baseline and postbaseline data. All efficacy analyses were carried out on mITT population.

The change from Baseline in NAPSI score for target finger nail was analyzed using a restricted (or residual) maximum likelihood based repeated measures approach. Analyses included the fixed, categorical effects of group, visit, and group-by-visit interaction, as well

as the continuous, fixed covariates of baseline score and baseline score-by-visit-interaction. An unstructured (co)variance structure was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The test of the change from Baseline versus 0 in each treatment group at each visit was based on least-squares means using a paired t-test and two-sided 95% confidence intervals.

A similar model was used for the change from Baseline in the PASI, the change from Baseline in the PGA of Psoriasis, the change from Baseline in the DLQI, the change from Baseline in the Physician and Patient Assessment of Nail Psoriasis Activity VAS.

Proportions were analyzed using a generalized linear models for correlated data using generalized estimating equations with group and visit as fixed factors and interactions group*visit in the model. This model was used for the proportion of subjects achieving NAPSI 50 and NAPSI 75 for target fingernail and overall NAPSI, the proportion of subjects achieving PASI 50 and 75 at 12 and 24 weeks, the proportion of subjects achieving a status on the PGA of psoriasis of clear or almost clear, the proportion of subjects achieving a status on the PGA of psoriasis of mild or better over 24 weeks. These analyses have been performed on the observed data without any method of substitution of dropout or missing data.

The paired t-test was used to test for significant changes over time in the laboratory determinations. For the vital signs, changes from Baseline were summarized and mean changes were analyzed using paired t-test. The paired t-test was used to test for significant changes over time in the vital signs, weight, and ECGs.

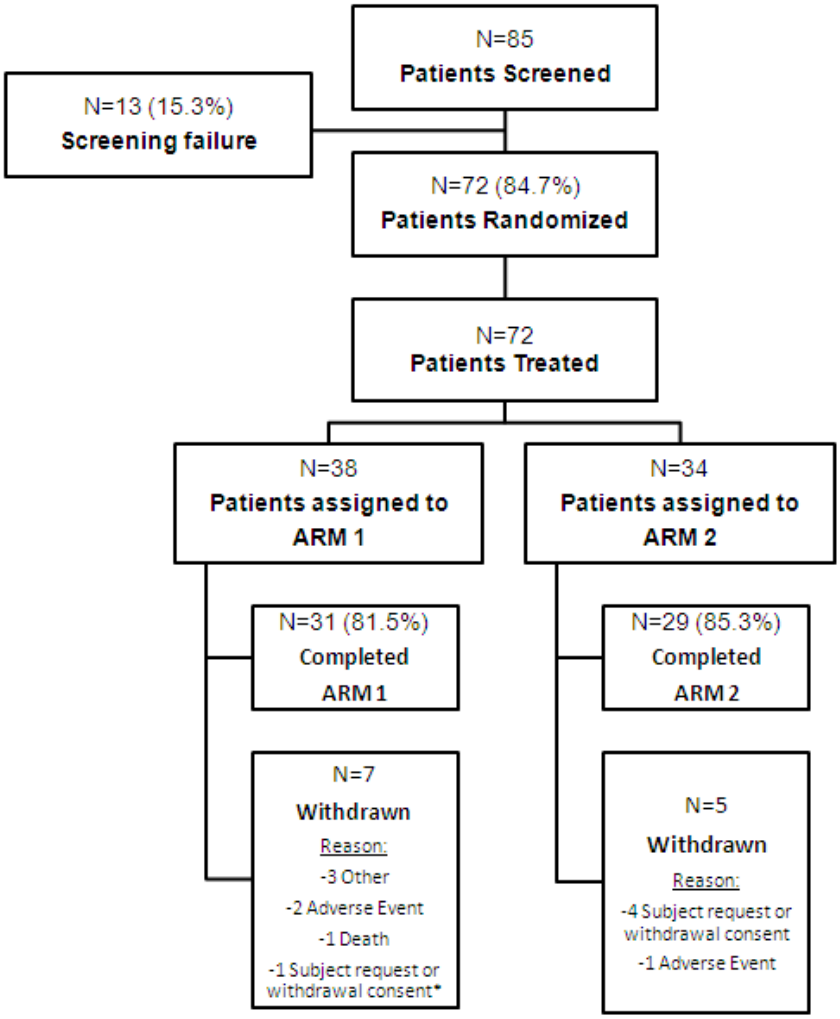
RESULTS

Subject Disposition and Demography: The safety population included 72 subjects. Three (3) subjects were excluded from the mITT population (for withdrawal of consent and unavailability of data for primary variable; 1 subject for AE [acute myocardial infarction] with no postbaseline data for primary variable; 1 subject because of no postbaseline data for primary variable). A total of 69 subjects were included in the mITT population.

A total of 85 subjects were screened and 72 of these subjects were randomly assigned to study drug (Figure 1), including:

- Thirty eight (38) subjects in Group 1, ie, who received 50 mg etanercept as SC injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24)
- Thirty four (34) subjects in Group 2, ie, who received 50 mg etanercept as SC injections once weekly for the entire 24-week treatment period

Figure 1. Disposition of Subjects



N = total number of subjects.

For the mITT population, the demographic and other baseline characteristics were similar in the 2 groups. No relevant differences were observed in demographic characteristics between the safety and mITT populations. A summary of the subject demography and baseline characteristics in mITT population is presented in Table 2.

Table 2. Demographic and Baseline Characteristics, mITT Population

Parameters	Group 1 N=36	Group 2 N=33	Total N=69
Age (years)			
N	36	33	69
Mean	46.28	45.36	45.84
SD	13.511	9.188	11.572
Median	46.50	42.00	44.00
Q1; Q3	36.50; 56.50	39.00; 52.00	39.00; 53.00
Min; max	21.00; 73.00	32.00; 66.00	21.00: 73.00
Sex n (%)			
Male	26 (72.2%)	24 (72.7%)	50 (72.5%)
Female	10 (27.8%)	9 (27.3%)	19 (27.5%)
Race			
Other	1 (2.8%)	0 (0.0%)	1 (1.4%)
White	35 (97.2%)	33 (100.0%)	68 (98.6%)
Height (cm)			
N	36	33	69
Mean	170.78	171.39	171.07
SD	9.580	9.630	9.538
Median	172.50	172.00	172.00
Q1; Q3	162.50; 178.0	164.00; 179.0	163.00; 178.0
Min; max	150.00; 190.0	152.00; 190.0	150.00; 190.0
Weight (kg)			
N	36	33	69
Mean	81.13	82.38	81.73
SD	18.710	18.371	18.423
Median	78.50	82.00	79.00
Q1; Q3	69.00; 91.5	70.00; 90.0	70.00; 90.0
Min; max	48.00: 130.0	52.00: 135.0	48.00: 135.0
BMI (kg/m^2)			
N	36	33	69
Mean	27.58	27.91	27.74
SD	4.614	5.192	4.866
Median	27.31	27.43	27.34
Q1; Q3	24.65; 30.75	23.94; 30.36	24.45; 30.47
Min; max	18.75; 39.18	18.83; 44.08	18.75; 44.08

In Group 1, subjects received 50 mg ETN injections twice weekly for 12 weeks (reducing to ETN 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg ETN injections once weekly for the entire 24 week treatment period.
BMI = body mass index; ETN = etanercept; max = maximum ; min = minimum ;
mITT = modified intent-to-treat ; N = total number of subjects; SD = standard deviation; Q1, Q3 = 1st and 3rd quartile.

Efficacy Outcomes Research Results:

The results of change from Baseline in NAPSI score for target finger nail at Week 24 on mITT population are shown in Table 3. A significant change from Baseline was observed in both groups at Week 12 and Week 24.

Table 3. Change of NAPSI Score for Target Finger Nail Over 24 Weeks of Treatment, mITT Population

Visit	Group 1[a] N=36	Group 2[a] N=33
Week 12		
N	33	31
Mean baseline (SE)	6.18 (0.27)	5.9 (0.28)
Adjusted mean (SE)	3.21 (0.27)	3.04 (0.28)
Adjusted mean change from Baseline (SE)	-2.71 (0.27)	-2.95 (0.28)
95% CI adjusted mean change	(-3.24; -2.18)	(-3.50; -2.40)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	32
Mean baseline (SE)	6.03 (0.27)	5.75 (0.27)
Adjusted mean (SE)	1.60 (0.30)	1.57 (0.31)
Adjusted mean change from Baseline (SE)	-4.32 (0.30)	-4.36 (0.31)
95% CI adjusted mean change	(-4.91; -3.73)	(-4.98; -3.74)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [group visit group*visit baseline baseline*visit].

The change from Baseline in the overall NAPSI score over 24-weeks of treatment in the mITT population is reported in Table 4. A statistically significant change from Baseline was observed in both groups at Week 12 and Week 24. Overall, NAPSI score was calculated as the sum of all finger nail scores, with a possible range of 0 to 64.

Table 4. Change From Baseline in Overall NAPSI Score Over 24 Weeks, mITT Population

Visit	Group 1[a] N=36	Group 2[a] N=33
Week 12		
N	33	31
Mean baseline (SE)	35.82 (2.73)	33 (2.71)
Adjusted mean (SE)	19.79 (1.56)	18.10 (1.61)
Adjusted mean change from Baseline (SE)	-13.58 (1.57)	-15.73 (1.62)
95% CI adjusted mean change	(-16.71; -10.45)	(-18.98; -12.49)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	32
Mean baseline (SE)	34.83 (2.67)	31.44 (2.49)
Adjusted mean (SE)	10.52 (1.91)	10.75 (2.00)
Adjusted mean change from Baseline (SE)	-22.64 (1.90)	-22.63 (1.99)
95% CI adjusted mean change	(-26.44; -18.85)	(-26.61; -18.66)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [group visit group*visit baseline baseline*visit].

The proportion of subjects achieving NAPSI 50 for target fingernail over 24 weeks in the mITT population is presented in Table 5. A statistically significant proportion of subjects achieving NAPSI 50 for target fingernail was observed in both groups at Week 12 and Week 24.

Table 5. Proportion of Subjects Achieving NAPSI 50 for Target Fingernail Over 24 Weeks, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 12		
Proportion (%)	20/33 (60.61)	16/31 (51.61)
p-Value[b]	<0.001	<0.001
Week 24		
Proportion (%)	29/35 (82.86)	26/32 (81.25)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The proportion of subjects achieving NAPSI 75 for target fingernail over 24 weeks in the mITT population is presented in Table 6. A statistically significant proportion of subjects

achieving NAPSI 75 for target fingernail was observed in both groups at Week 12 and Week 24.

Table 6. Proportion of Subjects Achieving NAPSI 75 for Target Fingernail Over 24 Weeks, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 12		
Proportion (%)	6/33 (18.18)	6/31 (19.35)
p-Value[b]	0.007	0.006
Week 24		
Proportion (%)	20/35 (57.14)	22/32 (68.75)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The proportion of subjects achieving NAPSI 50, for the overall NAPSI score over 24 weeks, in the mITT population is presented in Table 7. A statistically significant proportion of subjects achieving NAPSI 50 for the overall NAPSI score was observed in both groups at Week 12 and Week 24.

Table 7. Proportion of Subjects Achieving NAPSI 50 for the Overall NAPSI Score at Weeks 12 and 24, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 12		
Proportion (%)	18/33 (54.55)	15/31 (48.39)
p-Value[b]	<0.001	<0.001
Week 24		
Proportion (%)	24/35 (68.57)	26/32 (81.25)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The proportion of subjects achieving NAPSI 75, for the overall NAPSI score over 24 weeks, in the mITT population is presented in Table 8. A statistically significant proportion of subjects achieving NAPSI 75 for the overall NAPSI score was observed in Group 1 at Week 24 and in Group 2 at Week 12 and Week 24.

Table 8. Proportion of Subjects Achieving NAPSI 75 for the Overall NAPSI at Weeks 12 and 24, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 12		
Proportion (%)	3/33 (9.09)	6/31 (19.35)
p-Value[b]	0.069	0.006
Week 24		
Proportion (%)	22/35 (62.86)	20/32 (62.50)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The change from Baseline in PASI score over 24-weeks is presented in Table 9.

Table 9. Change From Baseline in Psoriasis Area and Severity Index Score Over 24 Weeks, mITT Population

Visit	Group 1[a] N=36	Group 2[a] N=33
Week 2		
N	36	33
Mean baseline (SE)	19.21 (1.38)	17.13 (1.78)
Adjusted mean (SE)	13.81 (0.86)	13.62 (0.90)
Adjusted mean change from Baseline (SE)	-4.41 (0.86)	-4.60 (0.90)
95% CI adjusted mean change	(-6.13; -2.69)	(-6.39; -2.80)
p-Value[b]	<0.0001	<0.0001
Week 12		
N	33	31
Mean baseline (SE)	19.25 (1.5)	17.24 (1.89)
Adjusted mean (SE)	4.68 (0.65)	4.56 (0.67)
Adjusted mean change from Baseline (SE)	-13.24 (0.67)	-13.44 (0.70)
95% CI adjusted mean change	(-14.58; -11.89)	(-14.84; -12.04)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	32
Mean baseline (SE)	19.34 (1.41)	16.99 (1.83)
Adjusted mean (SE)	3.31 (0.86)	3.83 (0.90)
Adjusted mean change from Baseline (SE)	-14.81 (0.88)	-14.11 (0.92)
95% CI adjusted mean change	(-16.56; -13.05)	(-15.95; -12.28)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [group visit group*visit baseline baseline*visit].

The proportion of subjects achieving PASI 50 at Weeks 2, 12, and 24 in the mITT population is presented in Table 10. A statistically significant proportion of subjects achieving PASI 50 was observed in both groups at Week 2, 12, and 24.

Table 10. Proportion of Subjects Achieving PASI 50 at Weeks 12 and 24, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 2		
Proportion (%)	6/36 (16.67)	6/33 (18.18)
p-Value[b]	0.007	0.007
Week 12		
Proportion (%)	30/33 (90.91)	27/31 (87.10)
p-Value[b]	<0.001	<0.001
Week 24		
Proportion (%)	30/35 (85.71)	27/32 (84.38)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index.
a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12-weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.
b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The proportion of subjects achieving PASI 75 at Weeks 2, 12, and 24 in the mITT population is presented in Table 11. A significant proportion of subjects achieving PASI 75 was observed in both groups at Week 12 and 24.

Table 11. Proportion of Subjects Achieving PASI 75 at Weeks 12 and 24, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 2		
Proportion (%)	2/36 (5.56)	1/33 (3.03)
p-Value	0.146	0.310
Week 12		
Proportion (%)	17/33 (51.52)	18/31 (58.06)
p-Value[b]	<0.001	<0.001
Week 24		
Proportion (%)	27/35 (77.14)	20/32 (62.50)
p-Value	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index.
a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.
b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The change from Baseline in PGA assessment over Week 24 of treatment for the mITT population is presented in Table 12. A statistically significant change from Baseline of PGA was observed in both groups at Week 2, 6, 12, 18, and 24.

Table 12. Change From Baseline in Physician Global Assessment of Psoriasis Over 24 Weeks, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 2		
N	36	33
Mean baseline (SE)	3.08 (0.12)	2.79 (0.14)
Adjusted mean (SE)	2.56 (0.11)	2.58 (0.12)
Adjusted mean change from Baseline (SE)	-0.39 (0.11)	-0.36 (0.12)
95% CI adjusted mean change	(-0.61; -0.16)	(-0.59; -0.13)
p-Value[b]	0.0009	0.0024
Week 6		
N	34	33
Mean baseline (SE)	3.09 (0.12)	2.79 (0.14)
Adjusted mean (SE)	1.81 (0.12)	1.89 (0.13)
Adjusted mean change from Baseline (SE)	-1.12 (0.13)	-1.04 (0.13)
95% CI adjusted mean change	(-1.37; -0.87)	(-1.30; -0.79)
p-Value[b]	<0.0001	<0.0001
Week 12		
N	32	31
Mean baseline (SE)	3.03 (0.12)	2.77 (0.15)
Adjusted mean (SE)	1.31 (0.13)	1.29 (0.13)
Adjusted mean change from Baseline (SE)	-1.55 (0.13)	-1.55 (0.14)
95% CI adjusted mean change	(-1.82; -1.28)	(-1.82; -1.27)
p-Value[b]	<0.0001	<0.0001
Week 18		
N	30	28
Mean baseline (SE)	3.03 (0.12)	2.82 (0.16)
Adjusted mean (SE)	1.34 (0.15)	1.06 (0.16)
Adjusted mean change from Baseline (SE)	-1.47 (0.16)	-1.72 (0.17)
95% CI adjusted mean change	(-1.80; -1.15)	(-2.06; -1.39)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	32
Mean baseline (SE)	3.11 (0.11)	2.78 (0.15)
Adjusted mean (SE)	1.26 (0.20)	1.06 (0.21)
Adjusted mean change from Baseline (SE)	-1.65 (0.20)	-1.84 (0.21)
95% CI adjusted mean change	(-2.05; -1.26)	(-2.25; -1.43)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections once weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [group visit group*visit baseline baseline*visit].

The proportion of subjects achieving a status on the PGA of psoriasis of "mild" or better (ie, PGA ≤2) over 24 weeks in the mITT population is presented in Table 13. A statistically significant change from Baseline of PGA in the proportions of the category "mild" or "better" was observed in both groups at Week 2, 6, 12, 18 and 24.

Table 13. Proportion of Subjects Achieving a Status on the PGA of Psoriasis of Mild or Better over 24 week, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 2		
Proportion (%)	16/36 (44.44)	17/33 (51.52)
p-Value[b]	<0.001	<0.001
Week 6		
Proportion (%)	32/36 (88.89)	26/33 (78.79)
p-Value[b]	<0.001	<0.001
Week 12		
Proportion (%)	29/33 (87.88)	29/31 (93.55)
p-Value[b]	<0.001	<0.001
Week 18		
Proportion (%)	28/31 (90.32)	28/29 (96.55)
p-Value[b]	<0.001	<0.001
Week 24 or early termination		
Proportion (%)	29/35 (82.86)	28/32 (87.50)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index; PGA = Physician Global Assessment.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24-week treatment period.

b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The proportion of subjects achieving a status on the PGA of psoriasis of "clear" or "almost clear" (ie, PGA =0 or 1) over 24-weeks in the mITT population is presented in Table 14. A statistically significant change from Baseline of PGA in the proportions of the category "clear" or "almost clear" was observed in Group 2 at Week 2 and in both groups at Week 6, 12, 18, and 24.

Table 14. Proportion of Subjects Achieving a Status on the PGA of Psoriasis of Clear or Almost Clear Over 24 Week, mITT Population

Time Point	Group 1[a] N=36	Group 2[a] N=33
Week 2		
Proportion (%)	2/36 (5.56)	5/33 (15.15)
p-Value[b]	0.146	0.015
Week 6		
Proportion (%)	10/36 (27.78)	12/33 (36.36)
p-Value[b]	<0.001	<0.001
Week 12		
Proportion (%)	21/33 (63.64)	21/31 (67.74)
p-Value[b]	<0.001	<0.001
Week 18		
Proportion (%)	19/31 (61.29)	22/29 (75.86)
p-Value[b]	<0.001	<0.001
Week 24 or early termination		
Proportion (%)	24/35 (68.57)	24/32 (75.00)
p-Value[b]	<0.001	<0.001

mITT = modified intent-to-treat; N = total number of subjects; NAPSI = Nail Psoriasis Severity Index; PGA = Physician Global Assessment.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Value from generalized linear models for correlated data using generalized estimating equations with treatment and visits as fixed factors. Model for proportion = [group visit group*visit].

The change from Baseline on DLQI over 24 weeks of treatment in the mITT population is presented in Table 15. The changes between visits have been estimated using adjusted means along with the associated SE and 95% CI from the mixed model, as used for primary analysis. A statistically significant change from Baseline of DLQI was observed in both groups at Week 2, 12 and 24.

Table 15. Change From Baseline of Dermatology Life Quality Index Over 24 Weeks, mITT Population

Visit	Group 1[a] (N=36)	Group 2[a] (N=33)
Week 2		
N	36	32
Mean baseline (SE)	10.78 (0.88)	13.31 (1.25)
Adjusted mean (SE)	8.55 (0.57)	9.44 (0.60)
Adjusted mean change from Baseline (SE)	-3.38 (0.57)	-2.49 (0.61)
95% CI adjusted mean change	(-4.51; -2.24)	(-3.70; -1.28)
p-Value[b]	<0.0001	0.0001
Week 12		
N	33	30
Mean baseline (SE)	10.48 (0.85)	13.07 (1.32)
Adjusted mean (SE)	4.80 (0.71)	4.66 (0.74)
Adjusted mean change from Baseline (SE)	-6.64 (0.77)	-6.52 (0.81)
95% CI adjusted mean change	(-8.18; -5.10)	(-8.14; -4.89)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	31
Mean baseline (SE)	10.6 (0.89)	13.03 (1.26)
Adjusted mean (SE)	3.08 (0.69)	2.88 (0.73)
Adjusted mean change from Baseline (SE)	-8.60 (0.69)	-8.74 (0.74)
95% CI adjusted mean change	(-9.98; -7.21)	(-10.21; -7.26)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24-week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [Group visit Group*visit baseline baseline*visit].

The change from Baseline in the the physician and subject assessment of nail psoriasis activity VAS over Week 24 of treatment in the mITT population are presented in Table 16 and Table 17. The changes between visits have been estimated using adjusted means along with the associated SE and 95% CI from the mixed model, as used for primary analysis.

Table 16. Change From Baseline in the Physician Assessment of Nail Psoriasis Activity Visual Analogue Scale Over 24 Weeks, mITT Population

Visit	Group 1[a] N=36	Group 2[a] N=33
Week 2	35	33
N		
Mean baseline (SE)	62.74 (4.01)	60.79 (3.21)
Adjusted mean (SE)	56.17 (2.40)	57.73 (2.47)
Adjusted mean change from Baseline (SE)	-5.59 (2.40)	-4.03 (2.47)
95% CI adjusted mean change	(-10.37; -0.80)	(-8.96; 0.90)
p-Value[b]	0.0229	0.1075
Week 6		
N	35	33
Mean baseline (SE)	62.74 (4.01)	60.79 (3.21)
Adjusted mean (SE)	43.56 (3.35)	49.17 (3.45)
Adjusted mean change from Baseline (SE)	-18.13 (3.35)	-12.52 (3.45)
95% CI adjusted mean change	(-24.82; -11.44)	(-19.41; -5.63)
p-Value[b]	<0.0001	0.0006
Week 12		
N	33	31
Mean baseline (SE)	62.82 (4.24)	59.84 (3.2)
Adjusted mean (SE)	32.68 (3.51)	33.02 (3.62)
Adjusted mean change from Baseline (SE)	-27.41 (3.51)	-28.34 (3.62)
95% CI adjusted mean change	(-34.43; -20.40)	(-35.57; -21.11)
p-Value[b]	<0.0001	<0.0001
Week 18		
N	31	29
Mean baseline (SE)	63.52 (4.38)	59.31 (3.38)
Adjusted mean (SE)	22.32 (3.03)	22.73 (3.13)
Adjusted mean change from Baseline (SE)	-37.61 (3.15)	-36.58 (3.25)
95% CI adjusted mean change	(-43.93; -31.29)	(-43.09; -30.06)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	34	32
Mean baseline (SE)	62.41 (4.11)	60.81 (3.32)
Adjusted mean (SE)	15.79 (3.58)	19.38 (3.69)
Adjusted mean change from Baseline (SE)	-44.66 (3.72)	-41.03 (3.84)
95% CI adjusted mean change	(-52.11; -37.21)	(-48.70; -33.35)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [Group visit Group*visit baseline baseline*visit].

Table 17. Change From Baseline in the Subject Assessment of Nail Psoriasis Activity Visual Analogue Scale Over 24 Weeks, mITT Population

Visit	Group 1[a] N=36	Group 2[a] N=33
Week 2		
N	36	33
Mean baseline (SE)	70.64 (4.11)	67.76 (3.7)
Adjusted mean (SE)	63.65 (2.85)	62.14 (2.97)
Adjusted mean change from Baseline (SE)	-5.45 (2.84)	-6.96 (2.97)
95% CI adjusted mean change	(-11.13; 0.23)	(-12.88; -1.03)
p-Value[b]	0.0596	0.0221
Week 6		
N	36	33
Mean baseline (SE)	70.64 (4.11)	67.76 (3.7)
Adjusted mean (SE)	50.91 (3.81)	52.16 (3.98)
Adjusted mean change from Baseline (SE)	-18.01 (3.81)	-16.76 (3.98)
95% CI adjusted mean change	(-25.62; -10.40)	(-24.70; -8.82)
p-Value[b]	<0.0001	<0.0001
Week 12		
N	33	31
Mean baseline (SE)	69.97 (4.4)	67.58 (3.76)
Adjusted mean (SE)	37.15 (4.03)	40.23 (4.15)
Adjusted mean change from Baseline (SE)	-30.43 (3.95)	-27.63 (4.10)
95% CI adjusted mean change	(-38.32; -22.55)	(-35.82; -19.44)
p-Value[b]	<0.0001	<0.0001
Week 18		
N	31	29
Mean baseline (SE)	68.52 (4.56)	66.72 (3.84)
Adjusted mean (SE)	26.17 (4.11)	24.54 (4.24)
Adjusted mean change from Baseline (SE)	-40.33 (4.01)	-41.55 (4.17)
95% CI adjusted mean change	(-48.35; -32.31)	(-49.89; -33.21)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	32
Mean baseline (SE)	70.06 (4.18)	66.75 (3.67)
Adjusted mean (SE)	19.63 (4.01)	26.15 (4.20)
Adjusted mean change from Baseline (SE)	-48.89 (3.99)	-41.69 (4.17)
95% CI adjusted mean change	(-56.86; -40.91)	(-50.02; -33.35)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [group visit group*visit baseline baseline*visit].

The adjusted change from Baseline of the physician fingernail grading assessment total score over Week 24 of treatment in the mITT population is presented in Table 18. The changes between visits have been estimated using adjusted means along with the associated SE and 95% CI from the mixed model, as used for primary analysis.

Table 18. Change From Baseline of the Physician Fingernail Grading Assessment Total Score Over 24 Weeks, mITT Population

Visit	Group 1[a] N=36	Group 2[a] N=33
Week 12		
N	33	31
Mean baseline (SE)	19.18 (1.21)	18.71 (1.36)
Adjusted mean (SE)	11.98 (0.95)	10.73 (0.98)
Adjusted mean change from Baseline (SE)	-6.25 (0.97)	-7.83 (1.01)
95% CI adjusted mean change	(-8.20; -4.30)	(-9.85; -5.81)
p-Value[b]	<0.0001	<0.0001
Week 24		
N	35	32
Mean baseline (SE)	19.11 (1.21)	17.81 (1.32)
Adjusted mean (SE)	7.04 (1.02)	6.08 (1.06)
Adjusted mean change from Baseline (SE)	-11.47 (1.03)	-12.21 (1.08)
95% CI adjusted mean change	(-13.54; -9.41)	(-14.37; -10.05)
p-Value[b]	<0.0001	<0.0001

CI = confidence interval; mITT = modified intent-to-treat; N = total number of subjects; SE = standard error.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

b. p-Values are based on mixed model. Adjusted change calculated from mixed model. Model for change = [Group visit Group*visit baseline baseline*visit].

Safety Results:

On average (SD), the exposure to etanercept in the safety population was 145.16 (43.01) days in Group 1 and 151.53 (32.92) days in Group 2. Overall, the exposure ranged from 18 to 176 days.

The number of subjects with treatment emergent AEs (TEAEs) reported over the observation period by treatment in the safety population is presented in Table 19.

Table 19. Number (%) of Subjects With Treatment Emergent Adverse Events, Safety Population

System Organ Class/Preferred Term	Group 1[a] N=38	Group 2 N=34
Any event	22 (57.9%)	12 (35.3%)
Blood and lymphatic system disorders	1 (2.6%)	0
Cardiac disorders	1 (2.6%)	0
Eye disorders	0	1 (2.9%)
Gastrointestinal disorders	5 (13.2%)	1 (2.9%)
General disorders and administration site conditions	5 (13.2%)	3 (8.8%)
Hepato-biliary disorders	1 (2.6%)	0
Infections and infestations	7 (18.4%)	7 (20.6%)
Investigations	1 (2.6%)	0
Musculoskeletal, connective tissue and bone disorders	2 (5.3%)	2 (5.9%)
Neoplasms benign and malignant (including cysts and polyps)	1 (2.6%)	0
Nervous system disorders	4 (10.5%)	4 (11.8%)
Respiratory, thoracic and mediastinal disorders	0	1 (2.9%)
Skin & subcutaneous tissue disorders	5 (13.2%)	3 (8.8%)
Vascular disorders	2 (5.3%)	0

N = total number of subjects.

a. In Group 1, subjects received 50 mg etanercept injections twice weekly for 12 weeks (reducing to etanercept 50 mg once weekly to Week 24); in Group 2, subjects received 50 mg etanercept injections once weekly for the entire 24 week treatment period.

There were 22 subjects (57.9%) reporting TEAEs in Group 1 and 12 subjects (35.3%) reporting TEAEs in Group 2. A higher incidence of adverse events occurred in Group 1. Most TEAEs were mild or moderate in severity. Three (3; 7.9%) subjects reported severe TEAEs in Group 1 and 1 in Group 2 (1; 2.9%). Ten (10; 26.3%) subjects in Group 1 and 5 (14.7%) subjects in Group 2 experienced TEAEs considered by the Investigator to be related to study drug.

Serious Adverse Events and Deaths: There were two (5.3%) serious adverse events (death due to lung cancer; myocardial infarction) reported in Group 1 and none in Group 2.

Discontinuations: Four (10.5%) subjects in Group 1 and 1 (2.9%) subject in Group 2 reported TEAEs leading to withdrawal. The TEAEs that led to discontinuation were:

- Myocardial infarction (Group 1)
- Injection site pain (Group 1)
- Toxiderma (Group 1)
- Lung cancer (Group 1)
- Aggravated psoriasis (Group 2)

Other Safety Results: No significant changes in the slopes of the laboratory values curves were found, except weak trends for urea in Group 1 (slope =0.310; p=0.039) and white blood cells in Group 2 (slope =0.165; p=0.035). No subject showed clinically relevant changes, as

per the Investigator's evaluation, in blood pressure and heart rate, except for 1 subject who reported mild hypertension during treatment in Group 1. No significant changes in mean values of blood pressure and heart rate were reported during the study in either study groups. There were no clinically important changes in physical findings.

CONCLUSIONS: The study documented statistically significant efficacy with both regimens which became apparent at the 12th week of therapy and confirmed sustained efficacy over 24 weeks. Safety was good in both groups, with a suggestion of better overall tolerability when starting with an initial low-dose regimen.

The study duration is in line with studies performed with etanercept in psoriasis and nail psoriasis, so it is interesting to note that these results compare favorably with those previously obtained in the subject populations similar in terms of their plaque psoriasis. However, it should be noted that the efficacy assessments derive from an open-label design and reflect a relatively modest number of subjects enrolled in the study. Despite the difficulty in recruiting the original planned number of subjects, any protocol deviations were mostly minor and did not affect the safety of the study subjects, nor the conduct or the conclusions of the study.

The study duration is in line with the labeling instructions for use of etanercept in psoriasis, where at least 12 weeks of therapy should be given before initial evaluation for signs of response, but where 24 weeks may be necessary to give full benefit.

The choice of the NAPSI score as the primary end-point of the study is justified, as this is a well-established parameter for the evaluation of nail psoriasis and is based on typical clinical signs that are easy to evaluate and to quantify.

The treatment with etanercept in this study did not show unexpected toxicity. Local skin reactions were the most frequently observed AEs in this study and this corresponds with data on etanercept in the literature. The possibility of paradoxical aggravation of the psoriasis aggravation has been considered in the past. In this study this was recorded in one case. Larger databases would be necessary to understand whether this may be a drug-related phenomenon in a subpopulation of subjects, or part of the natural history of this characteristically fluctuating condition. It is reassuring that no serious infections and no demyelinating disorders occurred in this study, although again such events have to be continually monitored via pharmacovigilance systems. It is of interest that with the initial 12-week low-dose regimen (50 mg once weekly) there was a suggestion of better tolerability compared to the higher dose regimen (50 mg twice weekly).

In conclusion, the results of this exploratory study showed that nail psoriasis can be treated effectively with etanercept irrespective of the regimen used, with benefit clearly apparent after only 12 weeks of therapy.