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

PROTOCOL NO.: 0881X1-4535 (B1801021)

PROTOCOL TITLE: Randomized Open-Label Study Comparing 2 Different Strategies for Management of Subjects With Plaque Psoriasis Who Have Responded to Etanercept Treatment

Study Centers: A total of 44 centers took part in the study and enrolled subjects; 10 in France, 7 in Germany, 4 in Hungary, 6 in Spain, 8 in Turkey, 1 in the United Arab Emirates, 2 in the United Kingdom (UK), and 3 each in Greece and Italy.

Study Initiation and Final Completion Dates: 27 January 2010 to 23 April 2013

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

- To describe the effect on subjects in whom psoriasis (PSO) has responded to initial treatment with etanercept (ETN) of 2 different strategies for managing a good response or complete response (Physician Global Assessment of PSO [PGA] = 1 or 0) over a 52-week time period.

Secondary Objectives:

- To compare the efficacy of the 2 different strategies by reference to quality of life (QoL) measure over the duration of the study;
- To explore the time course of severity following treatment modification;
- To explore the degree of subject satisfaction with the 2 different options for management following successful initial treatment.

METHODS

Study Design: This was a Phase 4, multi-center, open-label, randomized, study in PSO subjects who have responded to initial treatment with ETN. Subjects were randomized to the 2 groups outlined below, after stratification by subjects who were "on other acceptable systemic therapy for psoriasis" and subjects who were "not on any other acceptable systemic therapy for psoriasis".

- Subjects randomized to "stop arm" stopped their ETN treatment on entry into the study and could be retreated with ETN 50 mg once weekly after medical review and agreement between the subject and the Investigator.

- Subjects randomized to "maintenance arm" continued on treatment with ETN at the lower dose of 25 mg once weekly, but had the option to have their drug treatment increased to 50 mg once weekly after medical review and agreement between the subject and the Investigator.

Subjects participated in the study for approximately 60 weeks. This included up to 4 weeks screening, 52 weeks treatment, and 4 weeks follow-up. The schedule of assessments and procedures is presented in Table 1.

Table 1. Scheduled Study Procedures

Study Week[a]	**-4 Scr**[b]	**0 Baseline**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**ET**	**FU**[c]	**SRV**[d]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**99**	**16**	**17-n**
Informed consent	X																	
Medical history & PSO history	X																	
Inclusion/exclusion criteria	X	X																
Physical examination[e] (including weight and height)	X														X	X		
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pregnancy test[g]	X	X																
Blood analysis and urinalysis	X	X			X			X							X	X		X
ESR and HS-CRP[h]	X	X			X			X							X	X		X
Randomization		X																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior / concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
SGA[i] (on weekly basis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
BSA assessment[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PGA[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PASI[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
EQ-5D		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PSSQ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
WPAI: PSO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Subject pharmacoeconomic questionnaire		X			X			X			X				X	X		
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Subject diary dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
TB testing[k]	X																	
Drug dispensation, if required		X	X	X	X	X	X	X	X	X	X	X	X	X				X
Phone call																	X	

Table 1. Scheduled Study Procedures

AE = adverse event; BSA = body surface area; DLQI = dermatology life quality index; EQ-5D = EuroQol-5Dimensions; ESR = erythrocyte sedimentation rate; ET = early termination visit; FU = follow-up visit; Hs-CRP = high sensitivity C-reactive protein; n = visit number; PASI = psoriasis area and severity index; PGA = physician global assessment of psoriasis; PSO = psoriasis; PSSQ = patient psoriasis satisfaction questionnaire; SAE = serious adverse event; Scr = screening; SGA = subject global assessment; SRV = subject requested visit; TB = tuberculosis; WPAI- PSO = work productivity assessment improvement psoriasis.

a. Visit window: The visit window should be ±3 days.
b. Screening period was mandatory. The Screening Visit should occur within 4 weeks ±3 days before the Baseline Visit.
c. FU: a follow-up phone call was performed 4 weeks after the final visit to assess any AEs/SAEs since the previous study visit.
d. Subject requested visit: visit scheduled within 1 week from the subject request to the visit site for (re)treatment at 50 mg etanercept (ETN).
e. Physical exam included weight and height at Screening but only weight at Week 52 or early termination.
f. Vital signs (measured in sitting position): systolic blood pressure, diastolic blood pressure, heart rate.
g. For women of child bearing potential only (serum test at Screening, urine test at Baseline). Pregnancy testing might be repeated during the study at the discretion of the Investigator.
h. The ESR was performed at the Investigative site using an ESR kit supplied by the centralized laboratory. Baseline ESR should be assessed prior to eligibility determination. ESR should be completed the same day as all scheduled visits for which blood sample was required.
i. The subject global assessment must be completed by the subject on weekly basis.
j. It was recommended that the same qualified personnel complete these assessments at each visit.
k. Demonstrates an adequate screening for TB in accordance with local country guidelines, since ETN has been prescribed, tests results and/or radiographic report must be available at site.

Number of Subjects (Planned and Analyzed): It was planned to enroll approximately 298 subjects in the study and approximately 149 subjects were to be randomized per treatment arm. A total of 209 subjects (47 in France, 40 in Germany, 19 in Greece, 34 in Hungary, 10 in Italy, 21 in Spain, 27 in Turkey, 3 in the United Arab Emirates, and 8 in the UK) were enrolled in the study. A total of 174 subjects were analyzed; Stop arm (n=88) and Maintenance arm (n=86). The study enrollment was stopped by the sponsor due to slow enrollment.

Diagnosis and Main Criteria for Inclusion: Males and females of age ≥18 years at the time of consent; previously treated with etanercept for chronic plaque PSO for at least 12 weeks prior to the Screening Visit and received a total weekly dose of 50 mg per week for at least the 6 weeks preceding the day of the Screening Visit; having shown clinical response with a PGA ≤1 at the Screening Visit and PGA ≤1 at the Baseline Visit were included in the study.

Subject having evidence of skin conditions (eg, eczema) other than PSO that would interfere with evaluations of the effect of study medication on PSO; evidence of active or previously known medical history of inflammatory arthritis (eg, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis) and any biologics other than etanercept within the 20 weeks prior to the Screening Visit were excluded from the study.

Study Treatment: ETN was supplied as prefilled syringes containing ETN 25 mg or 50 mg solution. Deterioration in PSO control was determined by the subject and confirmed by the Investigator. Subjects complete the subject global assessment (SGA) on a weekly basis. If the subject considers his/her condition was worse (as defined by a SGA ≥2) on 2 consecutive weeks, they were instructed to contact the Investigator and request a subject requested visit (SRV) within 1 week from the subject phone call in order to check with the physician the possibility to being at 50 mg once weekly (stop arm) retreated or having the dose of etanercept increased to 50 mg once weekly from 25 mg once weekly (maintenance arm). Then, after completion of the PGA, treatment was adjusted based upon a (SGA + PGA)/2 average value ≥2 with taking into account the latest (ie, second) SGA value. Subjects continued to receive 50 mg ETN once weekly, irrespective of the original randomization group, until an adequate response was observed.

An adequate response was defined as a PGA of 0 or 1 for 2 consecutive readings 4 weeks apart. This was assessed at the monthly planned visits and not through SRVs. If an adequate response was recorded, the subject was instructed to revert to the regimen as per their randomization, ie, session of treatment cessation for stop arm, or dose down to 25 mg ETN for maintenance arm. At each study visit, subjects returned all used and unused investigational product.

Efficacy Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint was the average 52-week PGA (measured as the time-normalized area under curve [AUC]).

Secondary Efficacy Endpoint:

- Time-normalized area under the dermatology life quality index (DLQI) versus time curve;
- Subject satisfaction with PSO treatment at baseline, before retreatment with ETN 50 mg weekly, and at the end of retreatment;
- Mean PGA at Week 52.

Safety Evaluations: Safety was assessed throughout the 52 weeks of the study and the 4 weeks end of study follow-up period, by evaluation of adverse events (AEs), laboratory evaluations, vital signs (sitting blood pressure and pulse rate), non-study medications, and hospitalizations.

Statistical Methods:

Analysis Populations: There were 3 populations analyzed:

- Modified Intent-to-Treat (mITT) population was the primary efficacy population and corresponded to all randomized subjects who had a baseline PGA and at least 1 postbaseline PGA.
- Per-protocol (PP) population was defined as all mITT subjects with no major protocol deviations. Major deviations from the protocol leading to exclusion from the per-protocol population were identified prior to database lock and regardless of the assigned regimen arm.
- Safety Population was based on all randomized subjects who had taken at least 1 dose of investigational product.

All efficacy endpoints were planned to be analyzed for the mITT population. In addition, the primary endpoint was also planned to be analyzed for the PP population if the PP population represented <80% of mITT population.

The average 52-week PGA (measured as the time-normalized AUC), was planned to be analyzed with an analysis of covariance model with stratification factor (Subjects on other acceptable systemic therapy for psoriasis Yes/No [defined as permitted concomitant systemic therapies methotrexate, acitretin, other oral retinoids, fumarates]), baseline PGA (0 or 1) and treatment as fixed effects. For subjects who discontinued the study before Week 52, the final PGA score was carried forward to the remaining time points before calculating the 52-week AUC.

Due to enrollment difficulties and failure to meet projected enrollment goals, the study was underpowered for any inferential statistical interpretation. Only a descriptive analysis (no p-values) of efficacy, health outcomes, and safety endpoints was performed.

RESULTS

Subject Disposition and Demography: A total of 209 subjects were screened, 174 subjects were randomized, and 136 subjects completed the study. The most frequent reasons for premature discontinuation were "subject request" (5.7%), "unsatisfactory response-efficacy" and "AEs" (each 5.2%). A total of 171 subjects constituted the safety population and 170 subjects constituted the mITT population. The subject disposition and subject analyzed is summarized in Table 2.

Table 2. Subject Disposition and Subject Analyzed – All Randomized Subjects

	Stop Arm n (%)	Maintenance Arm n (%)	Total n (%)
Number of subjects screened			209
Number of subjects randomized	88 (100.0)	86 (100.0)	174 (100.0)
Study completed	64 (72.7)	72 (83.7)	136 (78.2)
Discontinued[a]	24 (27.3)	14 (16.3)	38 (21.8)
Unsatisfactory response - efficacy	6 (6.8)	3 (3.5)	9 (5.2)
Adverse events	4 (4.5)	5 (5.8)	9 (5.2)
Subject request	8 (9.1)	2 (2.3)	10 (5.7)
Investigator request	1 (1.1)	0	1 (0.6)
Sponsor's decision	0	0	0
Protocol violation	2 (2.3)	4 (4.7)	6 (3.4)
Lost to follow up	2 (2.3)	0	2 (1.1)
Other event	1 (1.1)	0	1 (0.6)
Number of subjects in safety population	87 (98.9)	84 (97.7)	171 (98.3)
Number of subjects in mITT population	86 (97.7)	84 (97.7)	170 (97.7)

mITT = modified intent-to-treat; n = number of subject.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

The demographic characteristics among the treatment groups were similar. The mean (standard deviation [SD]) age overall was 49.08 (13.962) years, 111 subjects (64.9%) were male, and 60 subjects (35.1%) were female (Table 3).

Table 3. Demographic Characteristics – Safety Population

	Stop Arm (N=87)	Maintenance Arm (N=84)	Total (N=171)
Age (year)			
Mean	50.39	47.71	49.08
Standard deviation	14.103	13.766	13.962
Minimum	18.5	19.9	18.5
Maximum	86.2	80.1	86.2
Median	49.54	49.48	49.54
Sex			
Male, n (%)	58 (66.7)	53 (63.1)	111 (64.9)
Female, n (%)	29 (33.3)	31 (36.9)	60 (35.1)

N = total number of subjects in treatment group; n = number of subjects with specified criteria.

Efficacy Results:

Primary Efficacy Endpoint Result:

The mean (SD) average 52-week PGA was numerically higher in the Stop arm (1.64 [0.746]) compared to the Maintenance arm (1.33 [0.763]). Summary of PGA results are presented in Table 4.

Table 4. Summary of Physician Global Assessment of Psoriasis (PGA) – mITT Population

	Stop Arm (N=86)	Maintenance Arm (N=84)	Total (N=170)
Average 52-week PGA			
Mean	1.64	1.33	1.49
Standard deviation	0.746	0.763	0.767
Minimum	0.1	0.0	0.0
Maximum	3.4	3.4	3.4
Median	1.64	1.14	1.41
Final Visit (LOCF)			
N	86	84	170
Mean	1.8	1.5	1.7
Standard deviation	1.10	1.06	1.09
Minimum	0	0	0
Maximum	5	4	5
Median	2.0	1.0	2.0

LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects in treatment group; PGA = Physician Global Assessment of Psoriasis.

Secondary Efficacy Endpoint Result:

The Maintenance arm scored lower (better) on health related QoL measures (Dermatology Life Quality Index; DLQI). The summary of DLQI in mITT population is presented in Table 5.

Table 5. Summary of Dermatology Life Quality Index (DLQI) – mITT Population

	Stop Arm (N=86)	Maintenance Arm (N=84)	Total (N=170)
Average 52-week DLQI			
N	86	84	170
Mean	4.07	2.96	3.52
Standard deviation	4.210	3.237	3.792
Minimum	0	0	0
Maximum	22.2	15.2	22.2
Median	3.0	1.82	2.20
Final Visit (LOCF)			
N	86	84	170
Mean	4.9	3.6	4.2
Standard deviation	6.36	4.99	5.74
Minimum	0	0	0
Maximum	26	27	27
Median	2.0	2.0	2.0

DLQI = Dermatology life quality index; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects in treatment group.

A numerically higher proportion of subjects in the Maintenance arm were satisfied with the effect of their psoriasis treatment (Patient Psoriasis Satisfaction Questionnaire; PSSQ), the PSSQ by cycle (prior and end of each re-treatment) for overall appearance of skin in mITT population is summarized in Table 6.

Table 6. Summary of Patient Psoriasis Satisfaction Questionnaire (PSSQ) – mITT Population

	Stop Arm (N=86)	Maintenance Arm (N=84)	Total (N=170)
Baseline			
n	70	71	141
Subjects satisfied	66 (94.3%)	67 (94.4%)	133 (94.3%)
Subjects unsatisfied	4 (5.7%)	4 (5.6%)	8 (5.7%)
Prior to Re-treatment, Cycle 1			
n	32	13	45
Subjects satisfied	15 (46.9%)	5 (38.5%)	20 (44.4%)
Subjects unsatisfied	17 (53.1%)	8 (61.5%)	25 (55.6%)
End of Re-treatment, Cycle 1			
n	37	14	51
Subjects satisfied	31 (83.8%)	12 (85.7%)	43 (84.3%)
Subjects unsatisfied	6 (16.2%)	2 (14.3%)	8 (15.7%)
Prior to Re-treatment, Cycle 2			
n	8	1	9
Subjects satisfied	5 (62.5%)	1 (100%)	6 (66.7%)
Subjects unsatisfied	3 (37.5%)	0	3 (33.3%)
End of Re-treatment, Cycle 2			
n	11	4	15
Subjects satisfied	10 (90.9%)	2 (50.0%)	12 (80.0%)
Subjects unsatisfied	1 (9.1%)	2 (50.0%)	3 (20.0%)

mITT = modified intent-to-treat; N = total number of subjects in treatment group; n = number of subjects in the specified criteria.

Safety Results:

Treatment-Emergent Adverse Events (TEAE): A total of 129 subjects (75.4%) experienced at least 1 TEAE (including infections) during the study, 63 subjects (72.4%) in the Stop arm and 66 subjects (78.6%) in the Maintenance arm.

Treatment-emergent nonserious AEs in ≥2% of subjects (all causality) is presented in Table 7. The most frequently reported treatment-emergent nonserious AEs (preferred term) were nasopharyngitis in 32 (18.7%) subjects, 10 (11.5%) subjects in the Stop arm and 22 (26.2%) subjects in the Maintenance arm.

Table 7. Treatment-Emergent Adverse Events in ≥2% of Subjects in any Arm, by System Organ Class and Preferred Term (All Causalities)

System Organ Class and Preferred Term	Stop Arm (N=87) n (%)	Maintenance Arm (N=84) n (%)
Subjects with nonserious adverse event	53 (60.9)	49 (58.3)
Cardiac disorders	2 (2.3)	0
Tachycardia	2 (2.3)	0
Gastrointestinal disorders	5 (5.7)	10 (11.9)
Diarrhoea	1 (1.1)	4 (4.8)
Nausea	2 (2.3)	1 (1.2)
Toothache	2 (2.3)	2 (2.4)
Vomiting	0	4 (4.8)
General disorders and administration site conditions	4 (4.6)	4 (4.8)
Asthenia	2 (2.3)	2 (2.4)
Chest pain	0	2 (2.4)
Influenza like illness	2 (2.3)	0
Infections and infestations	30 (34.5)	37 (44.0)
Acute tonsillitis	1 (1.1)	2 (2.4)
Bronchitis	5 (5.7)	9 (10.7)
Gastroenteritis	2 (2.3)	1 (1.2)
Herpes simplex	3 (3.4)	0
Influenza	4 (4.6)	3 (3.6)
Nasopharyngitis	10 (11.5)	22 (26.2)
Oral herpes	3 (3.4)	0
Pharyngitis	5 (5.7)	3 (3.6)
Rhinitis	1 (1.1)	2 (2.4)
Sinusitis	2 (2.3)	0
Upper respiratory tract infection	4 (4.6)	1 (1.2)
Urinary tract infection	2 (2.3)	1 (1.2)
Wound infection	0	2 (2.4)
Injury, poisoning and procedural complications	7 (8.0)	2 (2.4)
Animal bite	2 (2.3)	0
Limb injury	3 (3.4)	1 (1.2)
Tooth fracture	2 (2.3)	1 (1.2)
Investigations	1 (1.1)	2 (2.4)
Red blood cell sedimentation rate increased	1 (1.1)	2 (2.4)
Musculoskeletal and connective tissue disorders	12 (13.8)	12 (14.3)
Arthralgia	8 (9.2)	6 (7.1)
Back pain	3 (3.4)	4 (4.8)
Pain in extremity	2 (2.3)	2 (2.4)
Nervous system disorders	3 (3.4)	4 (4.8)
Carpal tunnel syndrome	0	2 (2.4)
Headache	3 (3.4)	2 (2.4)
Psychiatric disorders	4 (4.6)	3 (3.6)
Depression	3 (3.4)	2 (2.4)
Insomnia	2 (2.3)	1 (1.2)
Respiratory, thoracic and mediastinal disorders	3 (3.4)	1 (1.2)
Cough	3 (3.4)	1 (1.2)
Skin and subcutaneous tissue disorders	6 (6.9)	1 (1.2)
Pruritus	3 (3.4)	0
Psoriasis	3 (3.4)	1 (1.2)

Table 7. Treatment-Emergent Adverse Events in ≥2% of Subjects in any Arm, by System Organ Class and Preferred Term (All Causalities)

System Organ Class and Preferred Term	Stop Arm (N=87) n (%)	Maintenance Arm (N=84) n (%)
Vascular disorders	4 (4.6)	2 (2.4)
Hypertension	4 (4.6)	2 (2.4)

Subjects were only counted once per treatment for each row.
AEs were collected up to 15 days post last dose or study visit, whichever was the later.
MedDRA (version 15.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in treatment group; n = number of subjects.

The TEAEs (treatment-related) in ≥2% of subjects by system organ class and preferred term is presented in Table 8.

Table 8. Treatment-Emergent Treatment-Related Adverse Events in ≥2% of Subjects in any Arm, by System Organ Class and Preferred Term

System Organ Class Preferred Term	Stop Arm (N=87) n (%)	Maintenance Arm (N=84) n (%)	Total (N=171) n (%)
Subjects with any related adverse event	16 (18.4)	32 (38.1)	48 (28.1)
Infections and infestations	11 (12.6)	22 (26.2)	33 (19.3)
Bronchitis	2 (2.3)	5 (6.0)	7 (4.1)
Nasopharyngitis	3 (3.4)	10 (11.9)	13 (7.6)
Oral herpes	2 (2.3)	0	2 (1.2)
Pharyngitis	3 (3.4)	2 (2.4)	5 (2.9)
Musculoskeletal and connective tissue disorders	2 (2.3)	2 (2.4)	4 (2.3)
Arthralgia	2 (2.3)	2 (2.4)	4 (2.3)
Psychiatric disorders	3 (3.4)	0	3 (1.8)
Insomnia	2 (2.3)	0	2 (1.2)

AEs and SAEs are not separated out. Body system totals are not necessarily the sum of the individual adverse events since a subject could report 2 or more different AEs in the same body system.
AEs were coded using the MedDRA dictionary version 15.1.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in treatment group; n = number of subjects; SAE= serious adverse event.

Treatment Emergent Serious AEs (SAEs): A total of 10 (5.8%) subjects experienced at least 1 serious TEAE, 6 (6.9%) subjects in the Stop arm and 4 (4.8%) subjects in the Maintenance arm. One subject in Maintenance Arm reported SAEs which were not treatment emergent (Table 9).

Table 9. Treatment-Emergent Serious Adverse Events, by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Stop Arm (N=87) n (%)	Maintenance Arm (N=84) n (%)
Subjects with any serious adverse event	6 (6.9)	4 (4.8)
Cardiac disorders	0	1 (1.2)
Angina pectoris	0	1 (1.2)
Gastrointestinal disorders	1 (1.1)	0
Inguinal hernia	1 (1.1)	0
General disorders and administration site conditions	0	1 (1.2)
Pyrexia	0	1 (1.2)
Infections and infestations	0	2 (2.4)
Bacterial pyelonephritis	0	1 (1.2)
Escherichia urinary tract infection	0	1 (1.2)
Furuncle	0	1 (1.2)
Sinusitis	0	1 (1.2)
Injury, poisoning and procedural complications	1 (1.1)	1 (1.2)
Animal bite	1 (1.1)	0
Facial bones fracture	0	1 (1.2)
Nervous system disorders	1 (1.1)	0
Viith nerve paralysis[a]	1 (1.1)	0
Pregnancy, puerperium and perinatal conditions	1 (1.1)	0
Abortion spontaneous	1 (1.1)	0
Pregnancy	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders	1 (1.1)	0
Nasal polyps	1 (1.1)	0
Vascular disorders	1 (1.1)	0
Arterial stenosis	1 (1.1)	0

Subjects were only counted once per treatment for each row. AEs were collected up to 15 days post last dose or study visit, whichever was the later.
MedDRA (version 15.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in treatment group; n = number of subjects.
a. Viith refers to VIIth Nerve.

There were 11 subjects with SAEs that required hospitalization. Of those, only 1 subject experienced events that were considered related to the study drug. These events were due to an *Escherichia coli* infection with symptoms of fever, maxillary sinusitis, pyelonephritis and urinary tract infection. All SAEs resolved.

Safety Related Discontinuations: A total of 24 (14.0%) subjects experienced at least 1 TEAE that led to withdrawal defined as study drug discontinued and/or discontinued from the study, 11 (12.6%) subjects in the Stop arm and 13 (15.5%) subjects in the Maintenance arm. The most frequently reported TEAE (preferred term) leading to withdrawal was nasopharyngitis in overall 4 (2.3%) subjects, 2 (2.3%) subjects in the Stop arm and 2 (2.4%) subjects in the Maintenance arm (Table 10).

Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (Including Infections) Leading to Withdrawal, by System Organ Class and Preferred Term

System Organ Class Preferred Term	Stop Arm (N=87) n (%)	Maintenance Arm (N=84) n (%)	Total (N=171) n (%)
Subject with any adverse event leading to withdrawal	11 (12.6%)	13 (15.5%)	24 (14.0%)
Gastrointestinal disorders	1 (1.1%)	0	1 (0.6%)
Inguinal hernia	(1.1%)	0	1 (0.6%)
General disorders and administration site conditions	0	1 (1.2%)	1 (0.6%)
Inflammation	0	1 (1.2%)	1 (0.6%)
Infections and infestations	5 (5.7%)	9 (10.7%)	14 (8.2%)
Bronchitis	2 (2.3%)	1 (1.2%)	3 (1.8%)
Furuncle	0	1 (1.2%)	1 (0.6%)
Gastroenteritis	1 (1.1%)	0	1 (0.6%)
Nasopharyngitis	2 (2.3%)	2 (2.4%)	4 (2.3%)
Osteomyelitis	0	1 (1.2%)	1 (0.6%)
Pharyngitis	0	1 (1.2%)	1 (0.6%)
Sinusitis	1 (1.1%)	1 (1.2%)	2 (1.2%)
Upper respiratory tract infection	0	1 (1.2%)	1 (0.6%)
Urinary tract infection	1 (1.1%)	0	1 (0.6%)
Viral upper respiratory tract infection	0	1 (1.2%)	1 (0.6%)
Injury, poisoning and procedural complications	1 (1.1%)	0	1 (0.6%)
Animal bite	1 (1.1%)	0	1 (0.6%)
Investigations	0	1 (1.2%)	1 (0.6%)
Platelet count decreased	0	1 (1.2%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	1 (1.1%)	1 (1.2%)	2 (1.2%)
Arthralgia	1 (1.1%)	0	1 (0.6%)
Arthritis	0	1 (1.2%)	1 (0.6%)
Nervous system disorders	0	1 (1.2%)	1 (0.6%)
Carpal tunnel syndrome	0	1 (1.2%)	1 (0.6%)
Pregnancy, puerperium and perinatal conditions	1 (1.1%)	0	1 (0.6%)
Pregnancy	1 (1.1%)	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	0	1 (1.2%)	1 (0.6%)
Bronchitis chronic	0	1 (1.2%)	1 (0.6%)
Skin and subcutaneous tissue disorders	2 (2.3%)	1 (1.2%)	3 (1.8%)
Dermatitis	0	1 (1.2%)	1 (0.6%)
Psoriasis	2 (2.3%)	0	2 (1.2%)

Body system totals are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.
Summary includes subjects that had study drug discontinued and /or discontinued from the study.
AEs were coded using the MedDRA dictionary version 15.1.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in treatment group; n = number of subjects.

Deaths: There were no deaths during the study.

Vital signs, other safety related observations: There were no clinically relevant mean changes of any vital sign and laboratory parameter, nor clinically relevant abnormal findings.

CONCLUSIONS: The study enrollment was stopped by the Sponsor due to slow enrollment; therefore, the study was underpowered for any inferential statistical interpretation. Only a descriptive analysis (no p-values) of efficacy and safety endpoints was performed.

The mean (SD) average 52-week PGA was numerically higher in the Stop arm (1.64 [0.746]) compared to the Maintenance arm (1.33 [0.763]). A numerically higher proportion of subjects in the Maintenance arm were satisfied with the effect of their psoriasis treatment (PSSQ), had lower (better) levels of work related productivity (absenteeism, presenteeism) and activity impairment (work productivity assessment improvement psoriasis), observed lower (better) Psoriasis Area and Severity Index scores, and had scored lower (better) on health related QoL measures (DLQI and EuroQol-5 Dimensions).

Safety analyses confirmed previously reported results on the AEs profile in this subject population under treatment with ETN. The most frequently reported TEAE (preferred term) was nasopharyngitis.

A total of 11 (6.4%) subjects experienced at least 1 SAE. All SAEs (preferred terms) were reported not more than once. Regarding laboratory parameters and vital signs, there were no clinically relevant mean changes during the study compared to baseline for any parameter, nor clinically relevant abnormal findings. In general, as referenced above, there were no clinically relevant differences between the Stop arm and the Maintenance arm. There were no deaths, demyelinating events, opportunistic infections, malignancies or tuberculosis reported during the study.

In conclusion, the study enrollment was terminated early; therefore, the study was underpowered for any inferential statistical interpretation. There were no unexpected new safety findings. The benefit-risk ratio remains in favor of ETN treatment.