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

PROTOCOL NO.: 0881A3-405-EU (B1801007)

PROTOCOL TITLE: An Open-Label, Multicentre, Supplementary and Extension Study of Etanercept in Subjects With Ankylosing Spondylitis (AS)

Study Centers: This was a multicenter trial conducted in Denmark, Finland, Sweden, and the UK.

Study Initiation Date and Final Completion Date: November 2006 to October 2008

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To evaluate the health care resource utilization (HCRU) and work status in subjects with AS by comparing study evaluations with the Baseline evaluations in a previous study (A Randomized, Double-Blind Study Evaluating the Safety and Efficacy of Etanercept and Sulphasalazine in Subjects With Ankylosing Spondylitis [NCT00247962]).

Secondary Objectives:

- To evaluate the HCRU in subjects receiving 2 strategies of treatment for ankylosing spondylitis (AS):
    - Strategy A: Start with disease-modifying anti-inflammatory drugs (sulphasalazine [SSZ]) followed by anti-Tumor Necrosis Factor (TNF) (etanercept);
    - Strategy B: Start and continue anti-TNF therapy (etanercept).
- To assess the new "Haywood" quality of life instrument (UK only) in relation to other key clinical and patient outcome measures;
- Evaluate the relationship between European Quality of Life-5 Dimensionand Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) in subjects receiving etanercept;
- To assess the direct and indirect cost of therapy in subjects with AS;
- To assess the change in clinical efficacy with treatment with etanercept.

METHODS

Study Design: This was a Phase 4, open-label, multicenter, supplementary and extension study to a previous study in subjects with AS. Baseline was considered to be the Baseline done in the previous study and Visit 1(Week 0) in this study was the last visit (Week 16) in the previous study.

Subjects were treated for approximately 36 weeks with etanercept 50 mg subcutaneously once weekly (QW). A follow-up telephone call was required approximately 15 days after the completion of study treatment to assess adverse events (AEs). Table 1 summarizes the visit procedures in the study.

Table 1. Study Visit Procedure

Study Week[a]	0	12	24	36	38
Visit Number	**1[b]**	**2**	**3**	**4[c]**	**5[d]**
Informed consent[e]	X				
Inclusion/exclusion criteria	X				
Concomitant medications	X[f]	X	X	X	
Physical examination	X[f]				
Vital signs	X[f]	X	X	X	
Joint assessment[g]	X[f]	X	X	X	
Physician global assessment[g,h]	X[f]	X	X	X	
BASMI[g]	X[f]	X	X	X	
Occiput-to-wall distance[g]	X[f]	X	X	X	
Chest expansion[g]	X[f]	X	X	X	
Patient global assessment[h]	X[f]	X	X	X	
Nocturnal and total back pain	X[f]	X	X	X	
BASFI	X[f]	X	X	X	
BASDAI	X[f]	X	X	X	
European quality of life-5 dimension	X[f]	X	X	X	
36-item short-form health survey (SF-36)	X[f]	X	X	X	
Hospital anxiety and depression scale (HADS)	X[f]			X	
Ankylosing spondylitis quality of life (ASQoL) - Haywood questionnaire[i]	X[f]	X	X	X	
Health care resource utilization (HCRU) and work productivity	X	X	X	X	
Urinalysis[j]	X				
Chemistry and haematology[j]	X				
C-reactive protein[j]	X				
Adverse events	X[f]	X	X	X	X
Drug accountability	X[j]	X	X	X	
Dispense diary card	X	X	X		
Dispense test article	X	X	X		

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index.

a. A ±4 day window was permitted for Visits 1 through 4 (Week 0-36).
b. Visit 1 for this study was also the last visit for the previous study.
c. For early termination, final visit procedures were performed at the time of withdrawal or discontinuation.
d. Follow-up telephone call to access new and ongoing adverse events, approximately 15 days after Visit 4 or early discontinuation.
e. Informed consent was discussed and obtained before Visit 1.
f. Results for these evaluations were recorded in the previous study and were also used in this extension study.
g. It was recommended that the same qualified medical personnel, at each of the visits indicated, completed these assessments.
h. Patient and physicians global assessments of peripheral joint arthritis activity were done only if applicable.
i. Only to be used in the United Kingdom.
j. Taken in accordance to the previous study protocol. Not taken according to this study.

Number of Subjects (Planned and Analyzed): Approximately 80 subjects were planned for this study. A total of 84 subjects were enrolled in the study (50 in the UK, 19 in Denmark, 10 in Finland and 5 in Sweden).

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 years and above who completed 16 weeks of treatment and had completed the Baseline HCRU questionnaire at Screening in the previous study from participating countries were included in the study.

Exclusion Criteria: Subjects who withdrew from the previous study for safety or any other reason were excluded from the study.

Study Treatment: All subjects received subcutaneous (SC) injections of etanercept 50 mg QW for 36 weeks. Etanercept was administered at approximately the same time of day (±4 hours) and on the same day of the week. Injections were administered in the abdomen, thigh, or upper arm. The location of injections was rotated with each dose.

Efficacy, Health Economics and Outcomes Research Endpoints:

Primary Endpoints:

- HCRU and sick leave, 48 week pre-post comparison of etanercept.

Secondary Endpoints:

- HCRU and sick leave during 48 weeks of treatment, all subjects;
- Change in patient global assessment of disease activity;
- Change in total back pain score;
- Change in BASFI;
- Change in BASDAI – morning stiffness;
- Change in BASMI;
- Change in BASDAI – fatigue;
- Change in ankylosing spondylitis quality of life (ASQoL);
- Change in haywood quality of life questionnaire.

Safety Evaluations: The safety of etanercept was determined using the following assessments: monitoring of AEs and serious adverse events (SAEs).

Statistical Methods: The modified Intent-to-Treat (mITT) population included all subjects who received at least 1 dose of study drug and had at least 1 post-baseline assessment.

The primary safety analysis population was all subjects who received at least 1 dose of study drug.

The primary efficacy and health economics population was the mITT population.

Two treatment groups were assessed in this study based on the treatment the subject received in the previous study:

- etanercept (ETN), which is the group of subjects who received etanercept in the previous study (ETN) and etanercept in this study;
- etanercept (SSZ), which is the group of subjects who received sulphasalazine in the previous study and etanercept in this study.

For the health economic continuous variables (including ASQol and Haywood total score) and for the efficacy analysis continuous variables (including the patient global assessment, the total pain, the BASFI and the BASDAI) descriptive statistics (mean, minimum, maximum, and 95% confidence interval) were computed for the raw data, for the changes from Baseline.

For the etanercept (ETN) group HCRU and sick leave was analyzed pre-post treatment initiation. For comparison reasons the 52 week data that was collected before treatment was adjusted to 48 weeks so that the comparison was made for an equal length of time.

Safety was analyzed descriptively in the study.

RESULTS

Subject Disposition and Demography: Of the 84 subjects enrolled, 79 (94%) subjects completed the study (Table 2). A total of 84 subjects were assigned to etanercept. The safety population included 84 subjects.

Table 2. Disposition of Subjects

Conclusion Status Reason	Etanercept (Total) n (%)
Subjects enrolled	84 (100)
Subjects completed	79 (94)
Discontinued	5 (6)
Adverse event	3 (3.6)
Subject request	1 (1.2)
Lost to follow-up	1 (1.2)

n = number of subjects.

A summary of the subject demography is presented in Table 3.

Table 3. Demographic and Baseline Characteristics of the Safety Population

Characteristic	50 mg Etanercept (Total) (N=84)
Age, years	
Mean	42.70
Standard deviation	10.49
Minimum	24
Maximum	65
Median	41
Sex, n (%)	
Female	13 (15.48)
Male	71 (84.52)
Ethnic origin, n (%)	
Other	3 (3.57)
White	81 (96.43)

N = total number of subjects; n = number of subjects meeting specified criteria.

Efficacy, Health Economics and Outcomes Research Results:

HCRU and Sick Leave, 48 Week Pre-Post Comparison of Etanercept (ETN): For the etanercept (ETN) group HCRU and sick leave was analyzed pre-post treatment initiation. For all variables HCRU and sick leave was reduced during treatment compared to the period before treatment. The difference in the percentage of subjects who had at least 1 visit to a physiotherapist during 48 weeks of treatment was significantly lower for the year in treatment with etanercept compared to the year before treatment (for all subjects p=0.005 43.8% versus. 18.6%) as shown in Table 4.

Table 4. 48 Week Pre-Post Comparison of HCRU and Sick Leave for the Etanercept (ETN) Treatment Group

	48 Week Completers Start With ETN in the Previous Study (N=55)	p-Value: Pre-Post Comparison (Completers)	All Subjects who Started With ETN in the Previous Study (N=59)	p-Value: Pre-Post Comparison (All)
Healthcare Resource Use				
Admissions to hospital, n				
48 weeks before treatment (adjusted from 52 to 48 weeks)	6		6	
During 48 weeks of treatment	3	0.489	4	0.743
Therapeutic warm bath sessions, n				
48 weeks before treatment (adjusted from 52 to 48 weeks)	8		8	
During 48 weeks of treatment	4	0.359	4	0.362
Physiotherapist visits, n				
48 weeks before treatment (adjusted from 52 to 48 weeks)	25		26	
During 48 weeks of treatment	11	0.008	11	0.005
Out-patient visits to a physician, n				
48 weeks before treatment (adjusted from 52 to 48 weeks)	36		40	
During 48 weeks of treatment	28	0.17	30	0.091
Work Productivity				
On sick leave during the past 12 months, n				
48 weeks before treatment (adjusted from 52 to 48 weeks)	26		27	
During 48 weeks of treatment	20	0.331	23	0.576

HCRU = Health Care Resource Utilization; N = total number of subjects; n = number of subjects meeting specified criteria.

HCRU and Sick Leave During 48 Weeks of Treatment, All Subjects: For the total period of 48 weeks treatment, HCRU was generally less frequent for the etanercept (ETN) group compared to the etanercept (SSZ) group. Significantly fewer subjects in the etanercept (ETN) group had therapeutic warm bath sessions when analyzing the 48 week period as a whole (Table 5).

Table 5. HCRU During 48 Weeks of Treatment, Etanercept (ETN) vs. Etanercept (SSZ), All Subjects and Completers

	Start With ETN in the Previous Study, 1 Year Completers (N=54)	Start With SSZ in the Previous Study, 1 Year Completers (N=25)	p-Value, Completers (ETN Starters as Compared to SSZ Starters)	Start With ETN in the Previous Study, All Subjects (N=59)	Start With SSZ in the Previous Study, All Subjects (N=25)	p-Value, All Subjects (ETN Starters as Compared to SSZ Starters)
Healthcare Resource use During 48 Weeks of Treatment						
Admissions to hospital, n (%)	3 (5.6)	2 (8)	0.649	4 (6.8)	2 (8)	1.0
Inpatient days per subject, mean (range)	5.83 (0.5-12)	2.75 (0.5-5)	0.784	6.13 (0.5-12)	2.75 (0.5-5)	0.628
Therapeutic warm bath sessions, No. (%)	4 (7.4)	4 (16)	0.254	4 (6.8)	4 (16)	0.23
Therapeutic warm bath sessions per subject, mean (range)	6.13 (0.5-15)	14 (5-26)	0.06	6.13 (0.5-15)	14 (5-26)	0.045
Physiotherapist visits, No. (%)	11 (20.4)	6 (24)	0.772	11 (18.6)	6 (24)	0.567
Physiotherapist visits per subject, mean (range)	11.41 (0.5-30)	16.58 (0.5-43)	0.434	11.41 (0.5-30)	16.58 (0.5-43)	0.361
Out-patient visits to a physician, No. (%)	28 (51.9)	10 (40)	0.346	30 (50.8)	10 (40)	0.475
Out-patient visits per subject, mean (range)	2.05 (0.5-10)	2.4 (0-6)	0.811	2.08 (0.5-10)	2.4 (0-6)	0.816
Work Productivity						
Employed subjects at the time of the study	n=45	n=13				
On sick leave during the past 12 months, n (%)	20 (37)	10 (40)	0.808	23 (39)	10 (40)	1.0
Days on sick leave for each employed subject, mean (range)	42 (0.5-232)	40.05 (2-252)	0.969	37.67 (0.5-232)	40.05 (2-252)	0.906

ETN = etanercept; HCRU = Health Care Resource Utilization; N = total number of subjects; n = number of subjects meeting specified criteria; SSZ = sulfasalazine; vs = versus.

Patient Global Assessment of Disease Activity: Patient global assessment of disease activity was measured on a 0 to 100 mm visual analogue scale (VAS), with 0 mm = no disease activity. Mean changes from Week 0 through to Week 38 are shown in the Table 6.

Change in Total Back Pain: Total back pain was measured on a 0 to 100 mm VAS scale, with 0 mm indicating no pain. The mean scores per visit from Week 0 through to Week 38 for all subjects are presented in the Table 7.

Change in BASFI: Assessment of physical function was presented by the BASFI score. The mean change Week 0 through to Week 38 for BASFI VAS (0-100 mm) score, are summarized in Table 8.

Change in BASDAI - Morning Stiffness: The changes in morning stiffness at Week 0 through to Week 38 in subjects are shown in the Table 9.

Change in BASMI Score: Spinal mobility was measured by BASMI occiput-to-wall distance, and chest expansion. The mean changes from Baseline for total BASMI score for the subjects are shown in the Table 10.

Change in BASDAI ‑ Fatigue: The changes from Baseline in fatigue at Week 0 through to Week 38 in subjects are shown in the Table 11.

Change in ASQoL: The ASQoL score improved quicker in the ETN group than in the SSZ group. The improvement in the ETN group was significantly higher than in the SSZ group. The results are presented in the Table 12.

Change in Haywood Questionnaire: The results from the Haywood questionnaire total score, change from Baseline per treatment per visit are summarized in Table 13. The Haywood score improved quicker in the etanercept (ETN) group than in the etanercept (SSZ) group. The improvement in the etanercept (ETN) group was significantly higher than in the etanercept (SSZ) group.

Table 6. Disease Activity Patient Global Assessment - Change From Baseline per Visit and per Treatment

Visit	Treatment	N Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	57	42.84	42	37	26.42	-21	98	(35.83, 49.85)
	Etanercept (SSZ)	25	11.44	10	37	30.51	-55	77	(-1.15, 24.03)
Week 12	Etanercept (ETN)	53	42.58	42	39	26.75	-14	98	(35.21, 49.96)
	Etanercept (SSZ)	22	38.77	37.5	51	34.36	-49	100	(23.54, 54.01)
Week 24	Etanercept (ETN)	54	42.56	44	42	25.56	-11	98	(35.58, 49.53)
	Etanercept (SSZ)	22	39.91	46.5	52	35.66	-47	86	(24.10, 55.72)
Week 38	Etanercept (ETN)	52	46.23	44.5	33	24.24	-19	97	(39.48, 52.98)
	Etanercept (SSZ)	24	36.08	35.5	59.5	36.09	-42	87	(20.85, 51.32)

(ETN) or (SSZ) was the study drug the subject took in study previous study.
CI = confidence interval; ETN = etanercept; IQR = interquartile range; N = number of subjects; SSZ = sulphasalazine.

Table 7. Back Pain Total Back Pain - Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	57	40.04	41	40	29.82	-25	100	(32.12, 47.95)
	Etanercept (SSZ)	24	11.67	8.5	32	32.19	-60	84	(-1.93, 25.26)
Week 12	Etanercept (ETN)	54	41.06	41	43	29.88	-32	100	(32.90, 49.21)
	Etanercept (SSZ)	21	31.33	38	41	32.34	-55	84	(16.61, 46.05)
Week 24	Etanercept (ETN)	53	39.83	42	42	27.89	-23	97	(32.14, 47.52)
	Etanercept (SSZ)	22	39.68	44.5	41	33.63	-51	84	(24.77, 54.59)
Week 38	Etanercept (ETN)	52	41.06	41	36.5	28.52	-36	99	(33.12, 49.00)
	Etanercept (SSZ)	24	34.17	39.5	39.5	31.4	-44	84	(20.91, 47.43)

(ETN) or (SSZ) was the study drug the subject took in study previous study.
CI = confidence interval; ETN = etanercept; IQR = interquartile range; SSZ = sulphasalazine.

Table 8. BASFI – Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	57	32.08	34.6	24	19.61	-11.2	67.7	(26.88, 37.29)
	Etanercept (SSZ)	25	12.03	14.1	14.5	13.75	-24.5	37.9	(6.35, 17.70)
Week 12	Etanercept (ETN)	54	32.47	34.4	24.9	19.54	-14.2	72.3	(27.14, 37.80)
	Etanercept (SSZ)	22	23.46	20.2	29.2	20.69	-6.4	65.6	(14.29, 32.63)
Week 24	Etanercept (ETN)	53	33.54	33.6	24	20.46	-8.6	74.6	(27.90, 39.18)
	Etanercept (SSZ)	22	25.93	26.9	27.3	20.1	-19	62.5	(17.01, 34.84)
Week 38	Etanercept (ETN)	52	32.95	34.3	23.6	20.81	-19	74.8	(27.16, 38.75)
	Etanercept (SSZ)	24	23.41	24.2	17.3	21.14	-32.8	61.8	(14.48, 32.34)

(ETN) or (SSZ) was the study drug the subject took in study previous study.
BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; ETN = etanercept; IQR = interquartile range; SSZ = sulphasalazine.

Table 9. BASDAI Morning Stiffness – Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	57	47.02	49	41	29.09	-22	99	(39.30, 54.74)
	Etanercept (SSZ)	24	9.79	7.5	33.5	34.64	-61	99	(-4.84, 24.42)
Week 12	Etanercept (ETN)	54	48.76	49.5	41	27.53	-6	100	(41.24, 56.27)
	Etanercept (SSZ)	22	30.55	32.5	61	37.9	-51	99	(13.74, 47.35)
Week 24	Etanercept (ETN)	54	49.54	50	45	29.51	-33	100	(41.48, 57.59)
	Etanercept (SSZ)	22	31.68	41	43	39.19	-67	100	(14.31, 49.06)
Week 38	Etanercept (ETN)	52	46.00	47.5	43	31.45	-50	100	(37.24, 54.76)
	Etanercept (SSZ)	24	31.13	42.5	47	43.76	-65	100	(12.65, 49.60)

Stiffness = mean of level of morning stiffness and length of morning stiffness.
(ETN) or (SSZ) was the study drug the subject took in study previous study.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; ETN = etanercept; IQR = interquartile range; SSZ = sulphasalazine.

Table 10. BASMI – Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	57	1.21	1	2	1.18	-1	4	(0.90, 1.52)
	Etanercept (SSZ)	25	0.00	0	2	1.04	-2	2	(-0.43, 0.43)
Week 12	Etanercept (ETN)	57	1.05	1	2	1.34	-3	4	(0.70, 1.41)
	Etanercept (SSZ)	25	0.52	1	1	1.05	-2	3	(0.09, 0.95)
Week 24	Etanercept (ETN)	54	1.06	1	2	1.35	-2	4	(0.69, 1.42)
	Etanercept (SSZ)	25	1.00	1	2	1.47	-2	4	(0.39, 1.61)
Week 38	Etanercept (ETN)	57	1.21	1	2	1.40	-3	4	(0.84, 1.58)
	Etanercept (SSZ)	24	0.83	1	1	1.31	-2	4	(0.28, 1.39)

(ETN) or (SSZ) was the study drug the subject took in study previous study.
BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; ETN = etanercept; IQR = interquartile range; SSZ = sulphasalazine.

Table 11. BASDAI Fatigue – Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	57	35.25	31.0	46.0	26.61	-16	96	(28.19, 42.31)
	Etanercept (SSZ)	25	10.40	11.0	31.0	22.22	-41	53	(1.23, 19.57)
Week 12	Etanercept (ETN)	54	36.72	35.0	41.0	27.31	-14	96	(29.27, 44.18)
	Etanercept (SSZ)	22	32.86	26.5	57.0	30.90	-22	85	(19.17, 46.56)
Week 24	Etanercept (ETN)	54	38.83	37.5	40.0	26.33	-24	92	(31.65, 46.02)
	Etanercept (SSZ)	22	28.09	33.0	54.0	32.09	-34	78	(13.86, 42.32)
Week 38	Etanercept (ETN)	52	40.46	40.0	37.5	25.53	-9	95	(33.35, 47.57)
	Etanercept (SSZ)	24	29.88	30.0	58.0	34.33	-41	77	(15.38, 44.37)

(ETN) or (SSZ) was the study drug the subject took in study previous study.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; ETN = etanercept; IQR = interquartile range; N = number of subjects; SSZ = sulphasalazine.

Table 12. ASQoL - Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	34	6.21	5.5	8	5.09	-1	18	(4.43, 7.98)
	Etanercept (SSZ)	15	2.27	0.0	4	3.88	-2	12	(0.12, 4.42)
Week 12	Etanercept (ETN)	27	6.78	5.0	11	6.16	-2	18	(4.34, 9.21)
	Etanercept (SSZ)	13	5.00	4.0	8	5.23	-2	17	(1.84, 8.16)
Week 24	Etanercept (ETN)	32	7.75	7.0	10	5.35	0	18	(5.82, 9.68)
	Etanercept (SSZ)	13	5.38	3.0	9	5.88	-1	17	(1.83, 8.94)
Week 38	Etanercept (ETN)	28	7.64	8.0	10	5.88	-3	18	(5.36, 9.92)
	Etanercept (SSZ)	15	4.40	3.0	9	6.19	-4	17	(0.97, 7.83)

(ETN) or (SSZ) was the study drug the subject took in study previous study.
ASQoL = Ankylosing Spondylitis Quality of Life; CI = confidence interval; ETN = etanercept; IQR = interquartile range; SSZ = sulphasalazine.

Table 13. Haywood : Total Score - Change From Baseline per Visit and per Treatment

Visit	Treatment	Number of Subjects	Mean	Median	IQR	Standard Deviation	Minimum	Maximum	95% CI
Week 0	Etanercept (ETN)	30	20.70	22.5	23.0	14.88	-2.0	47	(15.14, 26.26)
	Etanercept (SSZ)	16	7.19	6.5	12.0	8.23	-3.0	24	(2.80, 11.57)
Week 12	Etanercept (ETN)	28	21.97	20.5	26.2	16.61	-13.0	52	(15.53, 28.41)
	Etanercept (SSZ)	11	19.00	13.0	31.0	17.09	-3.0	49	(7.52, 30.48)
Week 24	Etanercept (ETN)	31	23.81	21.0	30.0	15.46	-1.6	52	(18.14, 29.48)
	Etanercept (SSZ)	12	19.33	14.0	32.0	17.63	-2.0	50	(8.13, 30.53)
Week 38	Etanercept (ETN)	27	25.98	28.0	21.8	16.51	-8.6	55	(19.45, 32.51)
	Etanercept (SSZ)	14	16.14	15.0	24.0	19.25	-16	50	(5.03, 27.26)

CI = confidence interval; ETN = etanercept; IQR = interquartile range; N = number of subjects; SSZ = sulphasalazine.

Safety Results: Treatment-emergent AEs (TEAEs) were reported by 66 (78.6%) of subjects as summarized in Table 14. Upper respiratory tract infection and arthritis were reported in the highest percentage of subjects.

Table 14. Treatment-Emergent Adverse Events Reported by ≥5 % of Subjects

Body System Adverse Event	Etanercept 50 mg Weekly n (%)
Any adverse events	66 (78.6)
Body as a whole	33 (39.3)
Accidental injury	6 (7.1)
Flu syndrome	5 (6.0)
Headache	6 (7.1)
Infection	10 (11.9)
Injection site reaction	5 (6.0)
Pain	5 (6.0)
Musculoskeletal system	18 (21.4)
Arthralgia	5 (6.0)
Arthritis	7 (8.3)
Respiratory system	32 (38.1)
Pharyngitis	6 (7.1)
Upper respiratory system	23 (27.4)
Special senses	10 (11.9)
Iritis	5 (6.0)

Adverse events and serious adverse events were not separated out in the table.
n = number of subjects.

The number of subjects with treatment-related TEAEs is presented in the Table 15.

Table 15. Number (%) of Subjects Reporting Treatment-Emergent Treatment-Related Adverse Events by Drug Relationship

Body System[a] Adverse Event	Etanercept N=84 n (%)
Any related adverse event	16 (19.0)
Body as a whole	4 (4.8)
Infection	2 (2.4)
Injection site reaction	3 (3.6)
Digestive system	2 (2.4)
Dyspepsia	1 (1.2)
Liver function tests abnormal	1 (1.2)
Mouth ulceration	1 (1.2)
Hemic and lymphatic system	4 (4.8)
Lymphoma	1 (1.2)
Neutropenia	3 (3.6)
Respiratory system	12 (14.3)
Cough increased	1 (1.2)
Laryngitis	1 (1.2)
Pharyngitis	1 (1.2)
Upper respiratory infection	9 (10.7)
Special senses	1 (1.2)
Iritis	1 (1.2)

Adverse events and serious adverse events were not separated out in the table.
N = total number of subjects; n = number of subjects with specified event.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same body system.

Serious Adverse Event: Four (4 [4.8%]) subjects reported SAEs during the study. One (1) subject experienced abdominal pain, 1 subject lymphoma (Hodgkin's disease) which lead to discontinuation from the study, 1 subject ileitis (Crohn's disease) which lead to discontinuation from the study, and 1 subject experienced a spinal fracture.

Discontinuations due to AEs: Three (3) (3.6%) were withdrawn from the study because of AEs; 1 from Crohn's disease (SAE), 1 from abnormal liver function tests and 1 from Hodgkin's disease (SAE).

There were no deaths during the study.

CONCLUSIONS: This was a 36-week open-label, multicenter, extension study of subjects with AS, assigned to etanercept 50 mg QW. The purpose of this study was to evaluate the health economics, safety, and efficacy. Eighty four (84) subjects, enrolled in the previous study, were enrolled in this study.

- Results of the primary endpoint analysis suggest there was a reduction in HCRU with etanercept, both when comparing to the year before treatment and when comparing to the group that received sulphasalazine for the first 16 weeks in the previous study, followed by etanercept for 36 weeks in this study. Significant differences were found for therapeutic warm-bath sessions and visits to physiotherapists. Also, etanercept treatment seems to have an effect on work status towards increased productivity. Disease severity

in terms of BASFI and BASDAI seem to be correlated with HCRU and to have a significant effect on days on sick leave.

- The etanercept (ETN) group was associated with quicker improvement in all health outcomes variables included in the study compared to etanercept (SSZ) group.

It was in general seen that subjects who received sulphasalazine in the previous study and etanercept in this study had greater improvement on all efficacy parameters when receiving etanercept. Furthermore, subjects who had received etanercept in the previous study and in this study had improvement on all efficacy parameters which were maintained through the whole study period.

The safety results were as follows:

- Sixty eight (68) subjects (81.0%) reported AEs and 66 (78.6%) of those events were considered treatment emergent;
- The TEAEs reported by the highest percentage of subjects were upper respiratory infection, infection, and arthritis;
- Three (3) subjects were withdrawn from the study because of safety-related AEs;
- Four (4) SAEs and no deaths occurred during the course of this study;
- There was one (1) case of malignancy. No cases of demyelinating disorders, ulcerative colitis, or tuberculosis but 1 case of worsening of Crohn's disease during the study.

Etanercept was safe and generally well tolerated at subcutaneously doses of 50 mg QW for 36 weeks.