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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00768053

PROTOCOL NO.: B1801019 (0881X1-4508)

PROTOCOL TITLE: Final Report: Open-Label Study to Evaluate the EULAR-RAID Score, Rheumatoid Arthritis Impact of Disease Score, in Rheumatoid Arthritis Patients Eligible to Etanercept and Who Will Receive Etanercept

Study Centers: 18 centers in France took part in the study.

Study Initiation and Completion Dates: October 2008 to April 2010

Phase of Development: Phase 4

Study Objectives:

Primary: To evaluate the psychometric (metrological) properties of the European League against Rheumatism – Rheumatoid Arthritis Impact of Disease (EULAR-RAID) score in rheumatoid arthritis (RA) subjects eligible to etanercept (ETN) who received ETN:

- To evaluate the simplicity of the EULAR-RAID score (time to completion),
- To evaluate the reliability of the EULAR-RAID score,
- To evaluate the face validity of the EULAR-RAID score versus disease activity score based on a 28-joint count (DAS28) and patient global assessment (PGA) of health status, and
- To evaluate the sensitivity to change of the EULAR-RAID score versus each component of the RAID score.

Secondary:

- To determine the Minimal Clinically Important Improvement (MCII) of the EULAR-RAID score,

- To determine the Patient Acceptable Symptom State (PASS) of the EULAR-RAID score,
- To evaluate the effects of ETN on clinical outcomes, and
- To evaluate safety and tolerability of ETN.

METHODS

Study Design: This was a 12-week, open-label, 1-arm, multicenter study conducted in subjects with RA who were eligible to receive ETN. All subjects participating in the study received ETN, administered as a once weekly subcutaneous (SC) injection using a 50 mg pre-filled syringe. A temporary dose interruption of up to 2 weeks was permitted if a mild or moderate toxicity event occurred. If a subject had to stop ETN for more than 2 weeks because of a toxicity event, the subject was withdrawn from the study and was not replaced. Study medication could have been prescribed as monotherapy or in combination with other suitable RA treatments. At or after baseline visit, the dose of methotrexate (MTX) or other disease modifying antirheumatic drugs (DMARDs) was optimized prior to study entry. The dose of MTX (or other DMARDs) could have been reduced or interrupted if a toxicity event occurred. Dose increase of MTX (or other DMARDs) was allowed if medically appropriate. Dose adjustments of concomitant steroids were at the discretion of the investigator at or after the baseline visit. Subjects participated in the study for approximately 22 weeks, including a screening period of up to 6 weeks, a 12-week open-label treatment period, and a 4-week follow-up period.

Number of Subjects (Planned and Analyzed): The planned enrollment for this study was 107 subjects. A total of 120 subjects were screened and 108 subjects received ETN. Twelve subjects did not receive study drug and were excluded from the efficacy and safety analyses.

Diagnosis and Main Criteria for Inclusion: Subjects eligible to participate in this study were 18 years old or older, met the 1987 American College of Rheumatology (ACR) revised criteria for RA, experienced active RA with a DAS >3.2, and objective evidence of 4 clinical synovitis or a plasma C-reactive protein (CRP) >10 mg/L, or erythrocyte sedimentation rate (ESR) >28 mm/hour and with a functional status Class I, II, or III as defined by ACR revised criteria. Eligible subjects showed failure of MTX, taken for at least 3 months and at least 15 mg/week or maximum-tolerated dosage. Subjects must have been willing and able to self-inject ETN or had a designee who could do so, and able to store injectable ETN at 2°C to 8°C.

Study Treatment: Subjects were treated with ETN administered once weekly as a 50 mg SC injection during the 12-week treatment phase. ETN was supplied by the sponsor as pre-filled syringes containing 50 mg of ETN. The first dose of ETN was given at the baseline visit (Visit 1) and was administered in the investigator site office.

Efficacy Evaluations:

Primary Efficacy Endpoints:

- Time for completion the EULAR-RAID score (simplicity),
- Reliability of the EULAR-RAID score between screening and baseline visits,
- Face validity of the EULAR-RAID score: correlations with the EULAR-RAID score and the DAS28 and PGA of health status, and
- Sensitivity to change of the EULAR-RAID score versus each component (or domain) of the EULAR-RAID score.

Secondary Efficacy Endpoints:

- MCII of the EULAR-RAID score,
- Proportion of subjects achieving a MCII,
- PASS of the EULAR-RAID,
- Proportion of subjects achieving a PASS,
- Proportion of subjects achieving >1.2 improvement in DAS28 at 12 weeks,
- Proportion of subjects achieving remission (DAS28 <2.6) at 12 weeks,
- Proportion of subjects achieving low disease activity (DAS28 ≤3.2) at 12 weeks,
- Time to sustained low disease activity score (LDAS),
- Proportion of subjects achieving a moderate or good EULAR response at 12 weeks,
- Proportion of subjects achieving a >0.6 DAS28 response at 12 weeks,
- ACR20, ACR50, ACR70, and ACR90 responses at 12 weeks.

Other Efficacy Variables: Other efficacy variables assessed included: number of painful joints (28-joint count), number of swollen joints (28-joint count), PGA of disease activity, physician global assessment of disease activity, PGA of health status, ESR, plasma CRP, and correlation between efficacy parameters.

Health Outcomes Assessments: Health outcomes assessments included the EULAR-RAID score, and the Modified Health Assessment Questionnaire (MHAQ).

Safety Evaluations: The safety of ETN was assessed throughout the study and included monitoring of AEs, physical examinations, vital signs measurements, injection site reactions, premature withdrawal, and laboratory test results.

Statistical Methods: Efficacy and safety were analyzed on all subjects who received at least 1 injection of ETN.

Efficacy: The reliability of the EULAR-RAID score was assessed by calculating intraclass correlation coefficient (ICC) with standard error of measurement (SEM) and 95% confidence interval (CI) between screening and baseline scores. The minimal detectable change was also calculated. Face validity was assessed using a correlation coefficient between the EULAR-RAID score and the DAS28 and also between the EULAR-RAID score and the PGA of health status. Correlations were estimated at each time point as well as for the time-normalized average (area under the curve [AUC]/time between first and last observations). Sensitivity to change of the EULAR-RAID score versus each component of the EULAR-RAID score was assessed by comparing the changes from baseline using a paired t-test. Results were expressed in terms of standardized response mean (SRM).

The MCII and PASS were determined according to the following definitions and the proportions of subjects achieving these endpoints were described: The MCII score was defined as the 75th percentile of the change in the EULAR-RAID score between baseline and final visit among subjects whose final evaluation of the response therapy corresponded to improvement compared to state at study entry. The PASS score was defined as the 75th percentile of the EULAR-RAID score at the final visit for subjects who considered their state acceptable at the end of the study. The proportions of subjects achieving the MCII and the PASS were described.

The DAS28, EULAR response criteria, and ACR20, ACR50, ACR70, and ACR90 response rate were described at each time point.

DAS28, number of painful and swollen joints, PGA of disease activity, PGA of health status, the physician global assessment of disease activity, ESR, and CRP were described as raw values and changes from baseline. The changes from baseline were analyzed using a 1-way analysis of variance (ANOVA) for repeated measures with visit as fixed factor and adjusted for baseline.

Each component of the EULAR-RAID score was described as raw values and changes from baseline. The changes from baseline were also analyzed using a 1-way ANOVA for repeated measures with visit as fixed factor and adjusted for baseline.

Statistical testing, unless otherwise stated, was 2-sided and used the 5% significance level in accordance with standard practice.

Safety: Safety results were summarized according to the sponsor's reporting standards.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 1.

Table 1. Subject Disposition

Number of Subjects	Enbrel 50 mg
Screened	120
Treated	108
Discontinued	11
Adverse events	10
Lost to follow up	1

A total of 120 subjects were screened and 108 subjects received treatment. Twelve subjects did not receive the study drug and were excluded from the efficacy and safety analysis. Eleven subjects were prematurely withdrawn from the study. The main reason for discontinuation was occurrence of an AE (10 subjects).

Subjects ranged in age from 20.2 to 85.1 years and the mean age at baseline was 53.6 (±12.9) years. Gender distribution was 27 (25%) men and 81 (75%) women. Forty-one (38.3%) subjects were educated to high school or baccalaureate level and 19 (17.8%) subjects were educated to university level, while 47 (43.9%) subjects had only reading/writing capacity. Four (3.7%) subjects had an educational or professional activity in the health area.

The mean duration of RA was 8.0 (±6.8) years. According to the ACR classification, 67 subjects (62.0%) had a global functional status in RA of Class II (able to perform usual self-care and vocational activities, but limited in avocational activities), 32 subjects (29.6%) were classified Class I, and 9 subjects (8.3%) were considered Class III (able to perform usual self-care activities, but limited in vocational and avocational activities). Twenty subjects (18.5%) underwent surgery for RA prior to the screening visit. At screening, the mean value for CRP was 18.4 (±30.2) mg/L (range 0.5 to 206.0 mg/L). The mean ESR was 25.2 (±18.6) mm/hour (range 2.0 to 97.0 mm/hour). Fifty-four subjects (60.7%) had a positive result for anti-cyclic citrullinated peptide (anti-CCP) and 56 subjects (57.7%) had a positive result for rheumatoid factor (RF).

At screening, the mean physician's global assessment of RA activity was 6.0 (±1.3) on a 0 (inactive) to 10 (extremely active) numerical rating scale (NRS), and the mean subject's global assessment of RA activity was 6.7 (±1.6) on the same NRS. The DAS28 was between 3.2 and 5.1 for 40 subjects (37.7%) and >5.1 for 66 subjects (62.3%).

Efficacy Results:

Time for Completing the EULAR-RAID Questionnaire (Simplicity): The time for completing the questionnaire was calculated on the complete questionnaire, including, in addition to the 7 items of the EULAR-RAID questionnaire, questions on pain, MHAQ, sleep, and coping. Therefore, time for completing only the EULAR-RAID questionnaire was not available.

Reliability of the EULAR-RAID Score: The reliability of the EULAR-RAID score based on screening and baseline visits was substantial, with an ICC equal to 0.85 (95% CI: 0.79, 0.90) and a SEM equal to 0.65 (95%CI: 0.57, 0.75). The minimal detectable change was 1.80 (Table 2).

Table 2: Reliability of the EULAR-RAID Score Based on Screening and Baseline Scores

	All Injected Subjects (N=108)		
	Value	95% CI	p-Value
Intraclass correlation coefficient: ICC	0.85	(0.79, 0.90)	0.000
Standard error of measurement: SEM	0.65	(0.57, 0.75)	
Minimal detectable change: MDC[a]	1.80		

EULAR = European league against rheumatism; RAID = rheumatoid arthritis impact of disease; CI = confidence interval.
[a] MDC = SEM x probit (0.975) x sqrt (2).

Face Validity of the EULAR-RAID Score: The correlation coefficients (CC) of the EULAR-RAID score with DAS28 and PGA of health status were significantly different from 0 at each time point. The validity of the EULAR- RAID score was greater during the treatment phase (CC of 0.64 at Week 4 and 0.55 at Week 12 with DAS28; 0.93 at Week 4 and 0.89 at Week 12 with PGA of health status) than at screening or baseline (0.33 with DAS28 and 0.77 with PGA of health status at baseline). Results are summarized in Table 3.

Table 3.Correlation coefficients of EULAR-RAID score with DAS28 and Patient Global Assessment of Health Status

All injected subjects (N=108)	Correlation Coefficient with EULAR-RAID Score (95% CI)		p-Value
Screening			
DAS28	0.25	(0.06, 0.42)	0.011
Patient global assessment of health status	0.65	(0.52, 0.75)	<0.001
Baseline			
DAS28	0.33	(0.15, 0.49)	<0.001
Patient global assessment of health status	0.77	(0.68, 0.84)	<0.001
Week 4			
DAS28	0.64	(0.50, 0.74)	<0.001
Patient global assessment of health status	0.93	(0.90, 0.95)	<0.001
Week 12			
DAS28	0.55	(0.40, 0.68)	<0.001
Patient global assessment of health status	0.89	(0.84, 0.93)	<0.001
Time-normalized average[a]			
DAS28	0.59	(0.45, 0.70)	<0.001
Patient global assessment of health status	0.92	(0.89, 0.95)	<0.001

EULAR = European league against rheumatism; RAID = rheumatoid arthritis impact of disease; DAS28 = disease activity score based on a 28-joint count; CI = confidence interval.
[a] EULAR-RAID score profile from baseline to last observation postbaseline.

Sensitivity to Change of the EULAR-RAID Score versus Each Component of the RAID Score: All the values of SRM were negative. There was a decrease of the score of each item at Week 4 and Week 12, showing an improvement from baseline. The EULAR-RAID score

was particularly sensitive to fatigue numerical rating scale (NRS) values at Week 4 and Week 12 but was also sensitive to physical well-being at Week 4 and to sleep at Week 12. The EULAR-RAID was not sensitive to the other components whatever the time point. Results of the sensitivity to change of the EULAR-RAID score are summarized in Table 4.

Table 4 Sensitivity to Change of the EULAR-RAID Score – Standardized Response Mean

All Injected Subjects		SRM (95% CI) (N=108)	Comparison with Change in EULAR-RAID Score p-value (T)
Change from baseline to Week 4			
EULAR-RAID score	-1.01	(-1.25, -0.82)	
Pain NRS value	-1.06	(-1.29, -0.87)	<0.001
Functional disability NRS value	-1.02	(-1.26, -0.82)	<0.001
Fatigue NRS value	-0.86	(-1.07, -0.67)	0.837
Sleep NRS value	-0.64	(-0.85, -0.46)	0.035
Physical well-being NRS value	-0.90	(-1.15, -0.69)	0.351
Emotional well-being NRS value	-0.68	(-0.94, -0.47)	0.025
Coping NRS value	-0.60	(-0.83, -0.39)	<0.001
Change from baseline to Week 12			
EULAR-RAID score	-1.37	(-1.71, -1.12)	
Pain NRS value	-1.37	(-1.73, -1.09)	<0.001
Functional disability NRS value	-1.24	(-1.57, -0.99)	0.052
Fatigue NRS value	-1.15	(-1.41, -0.95)	0.895
Sleep NRS value	-0.92	(-1.15, -0.73)	0.153
Physical well-being NRS value	-1.27	(-1.55, -1.04)	0.029
Emotional well-being NRS value	-1.06	(-1.33, -0.86)	0.043
Coping NRS value	-0.96	(-1.28, -0.70)	<0.001

Abbreviations: EULAR = European league against rheumatism; RAID = rheumatoid arthritis impact of disease; SRM = standardized response mean; CI = confidence interval; NRS = numerical rating scale.
(T) paired t-test: hypothesis tested.
Hypothesis 0: Change from baseline EULAR-RAID score – Change from baseline component X (for each subject) = 0.
Hypothesis 1: Change from baseline EULAR-RAID score – Change from baseline component X (for each subject) $\neq 0$.

Minimal Clinically Important Improvement (MCII) of the EULAR-RAID Score: The score of the EULAR-RAID corresponding to MCII in the last 48 hours was calculated on subjects with moderate or slightly important improvement at observation using the 75th percentile of change between baseline and observation. MCII thresholds were -0.19 at Week 4 and -1.29 at Week 12, indicating that 75% of subjects with a moderate or slightly important improvement at Week 4 and Week 12 had a EULAR-RAID score change from baseline of <-0.19 and <-1.29, respectively. The proportion of subjects achieving a MCII is summarized in Table 5.

Table 5 Proportion of Subjects Achieving the MCII Scores – All Injected Subjects

Number (%) of subjects with EULAR-RAID score change from baseline to time-point <MCII threshold (N=108)	MCII Threshold at Week 4 -0.19[a]	MCII Threshold at Week 12 -1.29[b]
Week 4 (n=102)	80 (78.4%)	63 (61.8%)
Week 12 (n=99)	87 (87.9%)	78 (78.8%)
Last observation (n=108)	94 (87.0%)	83 (76.9%)

EULAR = European league against rheumatism; RAID = rheumatoid arthritis impact of disease; MCII = Minimal Clinically Important Improvement.
[a] MCII score was calculated on subjects with moderate or slightly important improvement at Week 4.
[b] MCII score was calculated on subjects with moderate or slightly important improvement at Week 12.

At Week 4, 77 subjects (76.2%) reported an improvement (very important for 47 subjects, moderately important for 15 subjects and slightly important for 15 subjects), 18 subjects (17.8%) reported no change and 6 subjects (5.9%) reported a worsening. At Week 12, 77 subjects (78.6%) reported an improvement (very important for 59 subjects, moderately important for 16 subjects, slightly important for 1 subject, and not at all important for 1 subject), 13 subjects (13.3%) had no change and 8 subjects (8.2%) reported a worsening.

Patient Acceptable Symptom State (PASS) of the EULAR-RAID Score: The PASS threshold of the EULAR-RAID score was equal to 5.58 at baseline, meaning that 75% of the subjects assessing their symptom state as satisfactory at baseline had a EULAR-RAID score at baseline <5.58. The PASS threshold decreased to 4.15 at Week 4, and 3.27 at Week 12. At Week 4, 71.6%, 57.8%, and 49.0% of the subjects, respectively, achieved a EULAR-RAID score <5.58 (PASS at baseline), <4.15 (PASS at Week 4), and <3.27 (PASS at Week 12). At Week 12, the proportions increased to 81.8%, 74.7%, and 64.6% of the subjects for a EULAR-RAID score <5.58, <4.15, and <3.27, respectively. The proportions of subjects achieving a PASS are summarized in Table 6.

Table 6 Proportion of Subjects Achieving the PASS – All Injected Subjects

Number (%) of Subjects with EULAR-RAID Score <PASS (N=108)	PASS at Baseline 5.58	PASS at Week 4 4.15	PASS at Week 12 3.27
Week 4 (n=102)	73 (71.6%)	59 (57.8%)	50 (49.0%)
Week 12 (n=99)	81 (81.8%)	74 (74.7%)	64 (64.6%)
Last observation (n=108)	87 (80.6%)	78 (72.2%)	67 (62.0%)

EULAR = European league against rheumatism; RAID = rheumatoid arthritis impact of disease; PASS = Patient Acceptable Symptom State.

DAS28: The DAS28 was calculated from the number of swollen joints and painful joints using the 28-joint count, the ESR measured in mm/hour, and the PGA of disease activity measured on a numerical rating scale of 11 points (0 to 10). The higher the score is, the more active the disease.

DAS28 Evolution and EULAR Response Criteria: All injected subjects had a DAS28 score higher than 3.2 (moderate or high disease activity) at screening or at baseline. The mean DAS28 score at baseline was 5.5 (±0.8). At last observation, 25.5% of subjects

achieved remission (DAS28 <2.6) and 43.4% achieved a low disease activity (DAS28 ≤3.2). Compared to baseline, 76.2% of subjects had an improvement of DAS28 (decrease in DAS28 >1.2) at last observation, 89.5% of subjects had a DAS28 response (decrease in DAS28 >0.6) and 85.7% of subjects had a moderate or good EULAR response criteria. A higher proportion of subjects achieved a moderate or a good EULAR response at Week 12 (87.4%) compared to Week 4 (85.7%). Results of the DAS endpoints are summarized in Table 7

Table 7 DAS28 Evolution and EULAR Response Criteria – All Injected Subjects

All Injected Subjects (N=108)	Week 4 n=99	Week 12 n=96	Last Observation n=106
	Number of subjects (%)		
Remission (DAS28 <2.6)	10 (10.1%)	27 (28.1%)	27 (25.5%)
Low disease activity (DAS28 ≤3.2)	28 (28.3%)	45 (46.9%)	46 (43.4%)
Improvement in DAS28 (decrease in DAS28 >1.2)	66 (67.3%)	74 (77.9%)	80 (76.2%)
DAS28 response (decrease in DAS28 >0.6)	87 (88.8%)	87 (91.6%)	94 (89.5%)
Moderate or good EULAR response criteria	84 (85.7%)	83 (87.4%)	90 (85.7%)
DAS28			
Mean (SD)	3.9 (1.1)	3.4 (1.2)	3.5 (1.2)
Change from baseline - Adjusted mean [95%CI][a]	-1.71 [-1.92, -1.50]	-2.08 [-2.29, -1.87]	-2.02 [-2.23, -1.81]

DAS28 = disease activity score based on a 28-joint count; EULAR = European league against rheumatism; SD = standard deviation; CI = confidence interval; ANOVA = analysis of variance.
[a] At Week 4 and Week 12: 1-way ANOVA for repeated measures with visit as fixed factor and adjusted for baseline; at last observation: 1-sample t-test

The general improvement during the treatment phase was also confirmed when analyzing DAS28 as a quantitative variable. The adjusted mean change from baseline in DAS28 showed a significant decrease of 1.71 units at Week 4 ($p < 0.001$) and 2.08 units at Week 12 ($p < 0.001$).

The median (range) change from baseline to Week 12 in DAS28 was -2.4 (-4.3, 0.5) in subjects considering their symptom state at Week 12 as acceptable and -1.4 (-4.0, 0.6) in subjects considering their symptom state as unacceptable. The comparison of these data showed a significant difference ($p < 0.05$, Wilcoxon test) according to the symptom state at Week 12. Moreover, for both symptom states, acceptable or unacceptable, the change from baseline to Week 12 in DAS28 was significantly different from 0.

Time to Achievement of Sustained Low Disease Activity Score (LDAS): Measurement of time to sustained low disease activity score (DAS28 ≤3.2) beyond Week 12 was not possible within the study duration.

Comparison of DAS28, DAS28-HS and DAS28-RAID: The DAS28 is a composite index usually including the PGA of disease activity. It was also calculated using the PGA of health status (DAS28-HS) and the RAID score (DAS28-RAID). The results of scores DAS28-HS and DAS28-RAID were classified into 3 classes (≤3.2, >3.2 to 5.1, and >5.1), or into 2 classes (<2.6, ≥2.6) at baseline and Week 12 as the changes from baseline, were very close to the results obtained with DAS28.

For DAS28, DAS28-HS, and DAS28-RAID the ICC was close to 1 (ICC >0.81), the reliability between screening and baseline was substantial and the minimal detectable change was lower than 1. On the other side, for PGA of disease activity (ICC = 0.63; 95% CI: 0.50, 0.73) and PGA of health status (ICC = 0.75; 95% CI: 0.66, 0.82), the reliability was moderate and the minimal detectable change was close to 3.0.

The sensitivity to change from baseline to Week 12 was evaluated by SRM. For DAS28, DAS28-HS, and DAS28-RAID, the SRM was close to -2, whereas it was close to -1 for PGA of disease activity, PGA of health status, and EULAR-RAID score, but for all scores the SRM was significantly different from 0 (upper bound of the 95% CI lower than 0). The MCII threshold at Week 12 (calculated on subjects with moderately or slightly important improvement) ranged from -1.53 (DAS28) to -1.00 (PGA of disease activity and PGA of health status). In the same way, the threshold for PASS at Week 12 ranged from 3.00 (PGA of disease activity and PGA of health status) to 3.92 (DAS28) (Table 8).

Table 8 Reliability Between Screening and Baseline, Sensitivity to Change from Baseline to Week 12 and MCII and PASS at Week 12 – All Injected Subjects (N=108)

Score	DAS28	DAS28-HS	DAS28-RAID	PGA of Disease Activity	PGA of Health Status	EULAR-RAID Score
Reliability based on screening and baseline visits						
ICC [95%CI]	0.92 [0.88, 0.94]	0.92 [0.88, 0.94]	0.94 [0.91, 0.96]	0.63 [0.50, 0.73]	0.75 [0.66, 0.82]	0.85 [0.79, 0.90]
MDC	0.66	0.66	0.58	2.98	3.08	1.80
Sensitivity to change from baseline to Week 12						
SRM [95%CI]	-1.94 [-2.36, -1.63]	-1.84 [-2.28, -1.54]	-1.94 [-2.37, -1.63]	-1.36 [-1.73,- -1.08]	-0.94 [-1.26, -0.69]	-1.37 [-1.71, -1.12]
MCII at Week 12[a]	-1.53	-1.51	-1.37	-1.00	-1.00	-1.29
PASS at Week 12[b]	3.92	3.83	3.81	3.00	3.00	3.27

DAS28 = disease activity score based on a 28-joint count; HS = health status; RAID = rheumatoid arthritis impact of disease; PGA = patient's global assessment; EULAR = European league against rheumatism; ICC = intraclass correlation coefficient; CI = confidence interval; MDC=minimal detectable change; SRM = standardized response mean; MCII = minimal clinically important improvement; PASS = patient acceptable symptom state.

[a] The score corresponding to MCII was calculated on subjects with moderately or slightly important improvement.

[b] PASS threshold of the score on subjects assessing their symptom state as acceptable.

American College of Rheumatology (ACR) Response Rates: The proportion of subjects achieving ACR20, ACR50, ACR70, and ACR90 was respectively 56.1%, 27.0%, 6.9%, and 2.0% at Week 4, and increased to 71.3%, 47.3%, 16.3%, and 3.0% at Week 12 as summarized in Table 9.

Table 9 ACR Response Rate – All Injected Subjects (N=108)

		Week 4		Week 12		Last observation	
ACR20	Number of subjects (%) [n]	55 (56.1%)	[98]	67 (71.3%)	[94]	75 (72.8%)	[103]
ACR50	Number of subjects (%) [n]	27 (27.0%)	[100]	44 (47.3%)	[93]	47 (44.3%)	[106]
ACR70	Number of subjects (%) [n]	7 (6.9%)	[102]	16 (16.3%)	[98]	16 (14.8%)	[108]
ACR 90	Number of subjects (%) [n]	2 (2.0%)	[102]	3 (3.0%)	[99]	3 (2.8%)	[108]

ACR = American College of Rheumatology.

Other Efficacy Variables: Other efficacy parameters were the number of painful and swollen joints, PGA of disease activity, physician global assessment of disease activity, PGA of health status, ESR, and plasma CRP. There was a significant improvement of all those parameters from baseline to Week 4 and Week 12 (except at Week 12 for CRP). Results of these variables are provided in Table 10.

Table 10 Evolution of Other Efficacy Variables – All Injected Subjects

	Baseline or Screening	Week 4	Week 12	Last Observation
Number of painful joints				
n	108	102	99	108
Mean (SD)	10.7 (5.8)	5.2 (5.0)	4.2 (4.8)	4.3 (4.7)
Change from baseline Adjusted mean [95% CI][a]		-5.70 [-6.50, -4.90]	-6.52 [-7.33, -5.71]	-6.42 [-7.43, -5.40]
Number of swollen joints				
n	108	102	99	108
Mean (SD)	8.6 (4.1)	4.0 (3.5)	2.2 (2.5)	2.4 (2.6)
Change from baseline Adjusted mean [95% CI][a]		-4.79 [-5.35, -4.23]	-6.47 [-6.91, -6.04]	-6.24 [-6.93, -5.54]
PGA of disease activity				
n	108	101	99	108
Mean (SD)	6.5 (1.9)	3.9 (2.5)	3.3 (2.3)	3.4 (2.4)
Change from baseline Adjusted mean [95% CI][a]		-2.61 [-3.06, -2.17]	-3.16 [-3.58, -2.74]	-3.12 [-3.58, -2.66]
Physician global assessment of disease activity				
n	108	101	99	108
Mean (SD)	6.0 (1.4)	3.4 (2.1)	2.6 (2.0)	2.8 (2.1)
Change from baseline Adjusted mean [95% CI][a]		-2.64 [-3.03, -2.26]	-3.36 [-3.74, -2.98]	-3.26 [-3.66, -2.86]
PGA of health status				
n	108	102	98	108
Mean (SD)	5.9 (2.2)	4.0 (2.5)	3.3 (2.5)	3.5 (2.6)
Change from baseline Adjusted mean [95%CI][a]		-1.83 [-2.24, -1.42]	--2.51 [-2.98, -2.03]	-2.38 [-2.93, -1.83]
ESR (mm/hour)				
n	107	100	96	106
Mean (SD)	25.2 (18.6)	16.7 (15.4)	15.2 (11.7)	17.0 (15.6)
Change from screening Adjusted mean [95% CI][a]		-9.01 [-11.3, -6.72]	-8.90 [-11.0, -6.79]	-8.49 [-11.4, -5.55]
Plasma C-reactive protein (mg/L)				
n	108	102	97	107
Mean (SD)	18.4 (30.2)	7.9 (13.9)	10.5 (34.5)	15.4 (54.8)
Change from screening Adjusted mean [95% CI][a]		-10.20 [-12.7, -7.71]	-6.79 [-13.8, 0.17]	-3.17 [-14.9, 8.54]

PGA = patient global assessment; ESR = erythrocyte sedimentation rate; SD = standard deviation; CI = confidence interval; ANOVA = analysis of variance.
[a] At Week 4 and Week 12: 1-way ANOVA for repeated measures with visit as fixed factor and adjusted for baseline; at last observation: 1-sample t-test.

Correlation between Efficacy Parameters: At baseline and Week 12, the correlations between PGA of disease activity, PGA of health status, EULAR-RAID score, and MHAQ were all significantly positive. At baseline, the correlation coefficients varied from 0.38 to 0.77. At Week 12, the correlations were stronger than at baseline, with correlation coefficients ranging from 0.62 to 0.93.

Health Outcomes Assessments

EULAR-RAID: Compared to baseline, a decrease in mean EULAR-RAID global score was observed at each time point. The adjusted mean of the change from baseline in global score showed a significant decrease of 2.10 units at Week 4 ($p < 0.001$) and of 2.85 units at Week 12 ($p < 0.001$). Results of the EULAR-RAID score are provided in Table 11.

Table 11 Evolution of EULAR-RAID Global Score – All Injected Subjects

	Baseline	Week 4	Week 12	Last Observation
n	108	102	99	108
Mean (SD)	5.9 (1.7)	3.8 (2.5)	3.0 (2.3)	3.2 (2.4)
Change from baseline Adjusted mean [95% CI][a]		-2.10 [-2.49, -1.71]	-2.85 [-3.25, -2.45]	-2.78 [-3.19, -2.36]

EULAR = European league against rheumatism; RAID = rheumatoid arthritis impact of disease; SD = standard deviation; CI = confidence interval; ANOVA = analysis of variance.
[a] At Week 4 and Week 12: 1-way ANOVA for repeated measures with visit as fixed factor and adjusted for baseline; at last observation: 1-sample t-test

The median (range) EULAR-RAID global score change from baseline to Week 12 was −3.3 (−7.7, 1.9) in subjects considering their symptom state at Week 12 as acceptable and -1.3 (4.9, 2.0) in subjects considering their symptom state as unacceptable. The comparison of these data showed a significant difference ($p < 0.05$ from Wilcoxon test) according to the symptom state at Week 12. Moreover, for both symptom states at Week 12, acceptable or unacceptable, the change from baseline to Week 12 was significantly different from 0.

Mini-RAID: From Day 1 to Day 14, the mean mini-RAID score tended to decrease and was 5.4 (±1.9) at Day 1, and 3.9 (±2.4) at Day 14, respectively. The impact of RA seemed to decrease with time. Among 106 injected subjects (98.1%) who had at least 1 mini-RAID score available over 14 days, the mean time to reach the MDC (1.80) was 4.3 (±3.8) days. Mean time to reach the MCII (-1.29) was 3.7 (±3.8) days, and the mean time to reach the PASS (3.27) was 4.8 (±4.4) days.

Safety Results: Table 12 summarizes the numbers of subjects reporting treatment-emergent adverse events (TEAEs) during the study, by category. TEAEs were reported by 76 (70.4%) subjects. Most TEAEs (84.7%) were of no or mild toxicity, 11.0% were of moderate toxicity, and 4.3% were considered by the investigator to be of severe toxicity. Among the 255 TEAEs reported during the study, 220 (86.3%) resolved and 35 (13.7%) were persisting. For most AEs (61.6%), no action was taken. Medications were prescribed for 31.0% of the TEAEs and temporary discontinuation of study medication was required for 10 AEs (3.9%). Six (6, 2.4%) AEs led to permanent discontinuation of study medication, 2 TEAEs (0.8%) led to hospitalization, and 5 TEAEs (2.0%) led to study withdrawal.

Table 12. Summary of Treatment Emergent Adverse Events

All Injected Subjects	N=108
Number (%) of subjects with at least 1 TEAE	76 (70.4%)
Number of AEs	255
Number (%) of subjects with at least 1 AE related to study medication	56 (51.9%)
Number of AEs related to study medication	198
Number (%) of subjects with at least 1 SAE	5 (4.6%)
Number of SAEs	5
Number (%) of subjects with at least 1 SAE related to study medication	3 (2.8%)
Number of SAEs related to study medication	3
Number (%) of subjects with at least 1 AE leading to study withdrawal	5 (4.6%)
Number of AEs leading to study withdrawal	5
Number (%) of subjects with at least 1 AE leading to permanent discontinuation of study medication	6 (5.6%)
Number of AEs leading to permanent discontinuation of study medication	6

TEAE = treatment-emergent adverse events; AE = adverse events; SAE = serious adverse events.

The most frequently reported all causality TEAEs (occurring in ≥2% of subjects) are shown in Table 13.

Table 13 All Causality Treatment Emergent Adverse Events (≥2% Subjects)

Adverse Event (Preferred Term)	All Injected Subjects N=108
	n (%) subjects
Injection site reaction	18 (16.7%)
Erythema	10 (9.3%)
Injection site erythema	8 (7.4%)
Bronchitis	8 (7.4%)
Asthenia	4 (3.7%)
Fatigue	4 (3.7%)
Nausea	3 (2.8%)
Influenza	3 (2.8%)
Nasopharyngitis	3 (2.8%)
Tonsillitis	3 (2.8%)

MedDRA: Medical Dictionary for Regulatory Activities (version 12.0)

Fifty-six (51.9%) subjects experienced a total of 198 TEAEs (77.6%) considered related to ETN. The most frequent TEAEs related to study medication were injection site reaction (18 subjects, 16.7%), injection site erythema (8 subjects, 7.4%), and erythema (9 subjects, 8.3%). Cases of infections and infestations were considered treatment-related for 19 subjects (17.6%), in particular bronchitis (7 subjects, 6.5%).

Six subjects experienced AEs leading to permanent discontinuation of study medication including bacterial arthritis, bronchitis, tooth infection, injection site rash, injection site

reaction, and thrombocytopenia. Five subjects (4.6%) experienced AEs that led to study withdrawal (Table 14). These AEs were mostly injection site reactions (including rash or erythema) and bacterial arthritis.

Table 14 Treatment Emergent Adverse Events Leading to Study Withdrawal

System Organ Class Preferred term	All Injected Subjects N=108
All	5 (4.6%)
General disorders and administration site conditions	2 (1.9%)
Injection site erythema	1 (0.9%)
Injection site rash	1 (0.9%)
Infections and infestations	1 (0.9%)
Arthritis bacterial	1 (0.9%)
Gastrointestinal disorders	1 (0.9%)
Abdominal pain	1 (0.9%)
Musculoskeletal and connective tissue disorders	1 (0.9%)
Rheumatoid arthritis	1 (0.9%)

No subjects died during the study. Five (5, 4.6%) subjects reported 1 SAE each during this study from the day of the first injection of ETN (Table 15). Three of these SAEs were considered treatment related: 2 cases of bacterial arthritis and 1 case of sepsis. All SAEs led to study withdrawal or permanent discontinuation of study medication except the case of sepsis. All SAEs resolved.

Table 15 Serious Adverse Events

Event (preferred term/verbatim)	Start Date	Stop Date	Severity	Outcome	Related to Study Medication
Arthritis bacterial / Elbow septic arthritis	05/12/2008	03/01/2009	Moderate	Recovered	Yes
Rheumatoid arthritis/ Rheumatoid arthritis worsening	12/05/2009	15/05/2009	Mild	Recovered	No
Sepsis/ Septicemia	14/06/2009	26/06/2009	Severe	Recovered	Yes
Abdominal pain/ Abdominal pain	10/07/2009	28/07/2009	Severe	Recovered	No
Arthritis bacterial / Septic arthritis	23/07/2009	18/01/2010	Severe	Recovered	Yes
Oropharyngeal pain/ Pharynx pain	10/10/2009	16/10/2009	Moderate	Recovered	Before first injection

Mean values of sitting blood pressure, body weight, and body mass index remained stable during the study. Mean pulse rate slightly decreased from 75.9 (±11.8) beats per minute (bpm) at baseline to 73.3 (±10.9) bpm at endpoint. No clinical laboratory data were analyzed for the scope of this study.

CONCLUSIONS:

In conclusion, this study showed a good reliability and sensitivity to change of the EULAR-RAID score in RA patients receiving etanercept. The agreement of the EULAR-RAID score was stronger with PGA of health status and PGA of disease activity than with DAS28.

The MCII threshold of the change in EULAR-RAID score was -0.19 at Week 4 and -1.29 at Week 12. The proportion of subjects with change in EULAR-RAID score under the MCII threshold was 78.4% at Week 4 and 78.8% at Week 12.

The PASS threshold of the EULAR-RAID score was equal to 5.58 at baseline and decreased to 4.15 at Week 4 and 3.27 at Week 12.

Improvement in the number of painful and swollen joints, patient global assessment of disease activity, physician global assessment of disease activity, patient global assessment of health status, erythrocyte sedimentation rate, and plasma C-reactive protein after 4 and 12 weeks of treatment with the 50 mg once weekly regimen showed a beneficial effect of etanercept on health status and RA activity.

The overall safety profile was consistent with the profile as understood to date, with no new signals.