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

PROTOCOL NO.: 0881X1-4437 (B1801018)

PROTOCOL TITLE: An Open-Label, Randomized Study to Evaluate the Radiographic Efficacy and Safety of Enbrel™ (Etanercept) Added to Methotrexate in Comparison With Usual Treatment in Subjects With Moderate Rheumatoid Arthritis Disease Activity

Study Centers: Thirty-seven centers took part in the study and randomized subjects; 7 in France, 6 in Germany, 5 in Poland, 4 each in Hungary and Spain, 3 each in Croatia, the Czech Republic and the United Kingdom (UK) and 1 each in Italy and Turkey.

Study Initiation and Final Completion Dates: September 2008 to January 2010
The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To evaluate the impact of etanercept (ETN) 50 mg once weekly plus methotrexate (MTX) in comparison with usual treatment on radiographic disease progression at 52 weeks in subjects with moderate rheumatoid arthritis (RA) who failed treatment with MTX.

Secondary Objectives:

- To compare the effects of ETN 50 mg once weekly plus MTX and usual treatment on clinical outcomes;
- To compare the effects of ETN 50 mg once weekly plus MTX and usual treatment on health-related quality of life and dimensions of impact of disease on subjects over 52 weeks;
- To evaluate the safety of the treatment regimen over 52 weeks.

METHODS

Study Design: This was a 52-week prospective, open-label, randomized, parallel-group, multicenter, European, outpatient study with a third-party blinded radiographer in subjects with moderate RA disease activity as defined by a Disease Activity Score based on a 28-joint count (DAS28) score of >3.20 and ≤5.10.

Subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment arms (A or B).

- Arm A: 50 mg ETN subcutaneous (SC) injection once weekly (pre-filled syringe) plus continuation of current dose of MTX (either oral, SC, or intramuscular).

- Arm B: usual care therapy, utilizing disease-modifying antirheumatic drugs (DMARDs) from a list of the 6 most commonly prescribed in the participating countries (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine A, and gold).

Subjects participated in the study for approximately 62 weeks. This includes a Screening period of up to 6 weeks, an open-label treatment period of 52 weeks and a 4-week follow-up period. The duration of this trial was approximately 30 months. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Study Procedure[a]	Wk -6 to 0	Wk 0	Wk 4	Wk 12	Wk 24	Wk 40	Wk 52	Early Discontinuation	Week 56
Study Interval	**Screening**	**Randomization**	**Treatment**						**Follow-Up[b]**
Visit ID	**Visit -1**	**Visit 0[c]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**		
Informed consent	X								
Demographics	X								
Medical and RA history	X								
Inclusion and exclusion criteria	X	X							
Prior medications	X								
Physical examination including weight[d]	X	X	X	X	X	X	X	X	
Vital signs (sitting blood pressure, pulse)	X	X	X	X	X	X	X	X	
TB test/chest X-ray[e]	X								
HbsAg, HCV antibody tests	X								
Local blood test including ESR[f]	X		X	X	X	X	X	X	
Central blood test –plasma CRP	X						X	X	
RF, anti-CCP	X								
Pregnancy test[g]	X	X							
Urinalysis	X		X	X	X	X	X	X	
X-rays of hands and feet[h] (modified TSS)	X						X	X[i]	
DAS28/ACR joint count	X	X[j]	X	X	X	X	X	X	
Subject General Health (VAS)	X	X	X	X	X	X	X	X	
Subject pain assessment (VAS)	X	X	X	X	X	X	X	X	
Subject global assessment of disease activity (VAS)	X	X	X	X	X	X	X	X	
Physician global assessment of disease activity (VAS)	X	X	X	X	X	X	X	X	
Subject self-addressed disability (VAS)	X	X	X	X	X	X	X	X	
HAQ		X	X	X	X	X	X	X	
EQ-5D		X		X	X		X	X	
SF-36		X		X	X		X	X	
WPAI:RA		X		X	X		X	X	

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Study Procedure[a]	Wk -6 to 0	Wk 0	Wk 4	Wk 12	Wk 24	Wk 40	Wk 52	Early Discontinuation	Week 56
Study Interval	**Screening**	**Randomization**	**Treatment**						**Follow-Up[b]**
Visit ID	**Visit -1**	**Visit 0[c]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**		
RA-WIS		X		X	X		X	X	
Employment status		X		X	X		X	X	
PASS			X	X	X	X	X	X	
MCII				X			X	X	
Ultrasonography (optional)[k]	X	X	X	X	X	X	X	X	
Concomitant medications		X	X	X	X	X	X	X	
Adverse events[l]		X	X	X	X	X	X	X	X
Randomization / first dose of ETN		X							
Drug accountability			X	X	X	X	X	X	
Dispense/prescribe subject medication		X	X	X	X	X			
Dispense diary card		X	X	X	X	X			

ACR = American college of rheumatology; Anti-CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein; DAS28 = Disease Activity Score based on a 28-joint count; EQ-5D = Euro Qol-5D; ETN = etanercept; ESR = erythrocyte sedimentation rate; HAQ = health assessment questionnaire; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MCII = minimal clinically important improvement; PASS = patient acceptable symptom state; RA = rheumatoid arthritis; RA-WIS = Rheumatoid Arthritis Work Instability Scale; RF = rheumatoid factor; SF-36 = SF-36 health survey; TB = tuberculosis; TSS = total sharp score; VAS = visual analogue score; Wk = week; WPAI:RA = work productivity and activity improvement questionnaire: rheumatoid arthritis.

a. The visit window for Visits 1 to 5 was ±4 days.
b. A follow-up telephone call or visit taken place 28 days after the end of study visit (Visit 5) or early discontinuation visit to assess new and ongoing adverse events.
c. At randomization in both arms of the study, the dose of the methotrexate (MTX) could not be increased, as it was optimized prior to entering the study.
d. Complete physical examination for Screening visit, including height and weight; abbreviated at subsequent visits (the abbreviated physical examination include cardiovascular and respiratory systems; other body systems was examined at the discretion of the Investigator).
e. Required according to local license and guidelines.
f. To include routine chemistry and hematology, ESR.
g. For women of child bearing potential only (serum test at Screening, urine test at Baseline). Pregnancy testing could be repeated during the study at the discretion of the Investigator.
h. Screening X-ray assessments for eligibility to be read locally, and confirmed by a central blinded assessor. A central blind assessor was conducted X-ray assessments.
i. Unless discontinuation was within 3 months of Screening due to the safety risks of unnecessary exposure and small analytical impact.
j. The ESR value at the Screening visit was be used for the DAS28 calculation at the randomization visit.
k. For selected centers.
l. From the signing of the informed consent form until end of study.

Number of Subjects (Planned and Analyzed): A total of 700 subjects were planned and 141 subjects were randomized (45 in Poland, 29 in Hungary, 20 in Croatia, 11 each in the Czech Republic, France and the UK, 8 in Germany, 4 in Spain, 1 each in Italy and Turkey): 71 in Arm A and 70 in Arm B of the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years of age who met the 1987 American College of Rheumatology (ACR) revised criteria for RA, documented evidence, confirmed by a blinded third party assessor, of at least 1 erosion observed by X-ray at randomization based on X-ray taken at the Screening visit and who had received MTX as stable dose for 28 days prior to the Screening visit, with active disease as defined by a DAS28 score of >3.20 and ≤5.10 at both the Screening and randomization visits were included in the study. All women of childbearing potential required a negative pregnancy test screening and at randomization. Sexually active men and women had to use a medically acceptable form of contraception during the study.

Exclusion Criteria: Subjects with previous treatment with ETN, infliximab, adalimumab, other tumor necrosis factor-alpha (TNF-α) inhibitors, anakinra or other biological agents and who received any DMARD, other than MTX, within 28 days before screening were excluded.

Study Treatment: Arm A: ETN was provided by the sponsor as 50 mg pre-filled syringe. The first dose of ETN was given at the randomization visit (Visit 0) in the Investigator site office. ETN was to be administered at approximately the same time of day (±4 hours) and on the same day of the week. ETN injections could be administered in the abdomen, thigh, or upper arm, with rotation of the injection site at each dose. In the event of a missed dose, ETN was to be taken immediately unless the dose was 1 day prior to the next scheduled dose. A temporary dose interruption of ETN of up to 4 weeks was permitted if a mild or moderate toxicity event occurred.

MTX was administered once weekly in a single oral, intramuscular, or SC dose of 12.5 mg to 25 mg as judged appropriate by the Investigator. The dose of MTX could be reduced or temporarily interrupted for up to 4 weeks if a mild or moderate toxicity event occurred. Following dose reduction or interruption, MTX was resumed at a dose of at least 12.5 mg.

Arm B: Choice and administration of medications in the usual care arm were as decided by the Investigator. Combination DMARD therapy was permitted, but risk assessment and safety monitoring was the responsibility of the Investigator. MTX could be continued, switched, or other DMARDs could be added. Switching between DMARDs was allowed.

For both arms, Investigators were to optimize MTX therapy before randomization. Subjects were not permitted to up titrate the dose of MTX at the randomization visit.

Efficacy Endpoints:

Primary Endpoint: Change from randomization in modified total sharp score (TSS) at 52 weeks.

Secondary Endpoints:

- Change from randomization in erosions at 52 weeks;
- Change from randomization in joint space narrowing at 52 weeks;
- Proportion of subjects showing no radiographic progression over 52 weeks (TSS change <0.5);
- Proportion of subjects achieving >1.2 improvement in DAS28 at 12, 24, and 52 weeks;
- Proportion of subjects achieving remission (DAS28 <2.6) at 12, 24, and 52 weeks;
- Proportion of subjects achieving low disease activity (DAS28 <3.2) at 12, 24, and 52 weeks;
- Proportion of subjects achieving a moderate or good European League Against Rheumatism (EULAR) response at 12, 24 and 52 weeks;
- Proportion of subjects achieving a >0.6 DAS28 response at 12, 24, and 52 weeks;
- ACR20, ACR50, ACR70, and ACR90 response at 12, 24, and 52 weeks;
- Use of corticosteroids to manage flare-ups (temporary increases in corticosteroid dose or use of intra-articular steroids) across the 52-week treatment period;
- Proportion of subjects achieving a minimal clinically important improvement (MCII);
- Proportion of subjects achieving a patient acceptable symptom state (PASS).

Radiographic Determinations: Radiographs of each hand-wrist and foot were to be taken at Screening and at Week 52, with images scored for erosions and joint space narrowing and the modified TSS calculated. A blinded third party assess reviewed the Screening and treatment X-rays for TSS.

Safety Evaluations: Safety and tolerability of ETN in this subject population were evaluated using the following assessments: physical examination/vital signs measurement, hematology and chemistry profiles, urinalysis, premature withdrawal, monitoring of adverse events (AEs), including injection site reactions, and serious AEs (SAEs).

Safety data were collected up to approximately 28 days after the last dose of subject medication had been collected.

Statistical Methods:

Analysis Populations: There were 3 populations defined:

- Modified Intent-to-Treat Population: The primary efficacy analysis was based on a modified intent-to-treat (mITT) population including all randomized subjects with an erosion at randomization, confirmed by the blinded expert assessor, who received at least 1 dose of study medication and provided pre and post-randomization data. For the primary endpoint, an X-ray had to be available at the Screening visit and at Week 52 (or early discontinuation visit).

- Per Protocol Population: The per-protocol (PP) population included subjects from mITT who completed the study with no major protocol violation that could potentially alter the interpretation of the efficacy analysis.

- Safety Population: Safety analysis was based on the safety population including all randomized subjects who received at least 1 dose of study medication.

The primary endpoint was analyzed using an analysis of covariance (ANCOVA) on the ranks of the modified TSS including study center and treatment as fixed factors and Baseline modified TSS rank as covariate.

The same approach had to be used for the analysis of erosion and joint space narrowing scores.

DAS28 and EULAR response criteria as well as ACR response rates and MCII and PASS achievement was analyzed using a generalized estimating equations (GEE) model, using a logit link, a binomial distribution and an auto-regressive correlation structure, with study center, treatment group, visit and the interaction between treatment group and visit as fixed factors. Other continuous efficacy endpoints had to be analyzed using a mixed model for repeated measures with study center, treatment group, visit and treatment-by-visit interaction as fixed factors, with baseline and baseline-by-visit interaction as covariates.

The percentage of subjects with an AE or a SAE was compared between treatment groups using a Fisher's exact test, as well as the percentage of laboratory data abnormalities. The changes from baseline in laboratory data and vital signs were analyzed using an analysis of covariance adjusted for baseline.

Due to early termination of the study by the sponsor, only disposition of randomized subjects, description of demographic data on safety population and safety analyses were performed; efficacy analyses were not performed.

RESULTS

Subject Disposition and Demography: A total of 141 subjects were randomized in this study: 70 subjects in the group receiving usual care and 71 subjects in the group receiving ETN + MTX. Seven subjects randomized in Arm B did not receive at least 1 dose of the study treatment and were excluded from the safety population. The safety population included therefore 134 subjects: 63 subjects receiving usual care and 71 subjects receiving ETN + MTX. Among the 141 randomized subjects, 1 subject performed all planned visits and 140 (99.3%) subjects were discontinued before completion of the study. Overall,

115 (82.1%) subjects prematurely withdrew because of discontinuation of study by the sponsor. Subject disposition is summarized in Table 2.

Table 2. Subject Disposition – All Randomized Subjects

Number of Subjects	Usual Care n (%)	ETN + MTX n (%)	Total n (%)
Assigned to treatment	70	71	141
Completed	1	0	1 (0.7)
Discontinued	69 (98.6)	71 (100.0)	140 (99.3)
Adverse events	0	3 (4.2)	3 (2.1)
Lack of efficacy	3 (4.3)	0)	3 (2.1)
Subject request	8 (11.6)	1 (1.4)	9 (6.4)
Death	1 (1.4)	0	1 (0.7)
Discontinuation of study by sponsor	52 (75.4)	63 (88.7)	115 (82.1)
Protocol violation	3 (4.3)	2 (2.8)	5 (3.6)
Lost to follow-up	1 (1.4)	2 (2.8)	3 (2.1)
Other (unspecified)	1 (1.4)	0	1 (0.7)
Analyzed for safety[a]	63	71	134

ETN = etanercept; MTX = methotrexate; n = number of subjects with specified criteria.
a. All randomized subjects with at least 1 dose of study treatment.

The majority of the 134 subjects in the safety population were women (79.1%). Mean age was 55.5 years, ranging from 25 to 81 years. Baseline demographic characteristics were mostly similar between the 2 treatment groups. Mean duration of RA was 8.9 years, ranging from 1 to 33 years, and for most subjects (74.6%) RA was Class II according to ACR classification. A summary of subject demography and baseline characteristics is presented for the safety population in Table 3.

Table 3. Demographic and Other Baseline Characteristics - Safety Population

	Usual Care N=63	ETN + MTX N=71	Total N=134
Age (years)			
Mean (SD)	57.3 (12.1)	53.8 (13.1)	55.5 (12.7)
Median	59.4	54.6	56.3
Minimum, maximum	27.2, 78.2	25.2, 81.4	25.2, 81.4
Gender			
Male	13 (20.6%)	15 (21.1%)	28 (20.9%)
Female	50 (79.4%)	56 (78.9%)	106 (79.1%)
Rheumatoid Arthritis History			
Duration of the disease (years)			
Mean (SD)	8.3 (7.0)	9.3 (7.6)	8.9 (7.3)
Median	6.0	7.0	7.0
Minimum, maximum	1.0, 31.0	2.0, 33.0	1.0, 33.0
ACR classification			
Class I	3 (4.8%)	6 (8.5%)	9 (6.7%)
Class II	46 (73.0%)	54 (76.1%)	100 (74.6%)
Class III	14 (22.2%)	11 (15.5%)	25 (18.7%)

ACR = American college of rheumatology; ETN = etanercept; MTX = methotrexate; N = number of subjects in treatment arm; SD = standard deviation.

Efficacy Results: Efficacy data were not analyzed due to early termination of the study.

Safety Results:

Treatment Emergent Adverse Events (TEAEs): The incidence of all causality TEAEs by system organ class and preferred term reported for ≥2% of subjects in either group is summarized in Table 4. AEs (drug-related and not related) were reported from Baseline visit (V0) by a total of 67 (50.0%) of 134 subjects: 28 subjects (44.4%) in the group under usual care and 39 subjects (54.9%) in the arm receiving ETN + MTX. All AEs except 1 (RA worsening in the arm receiving ETN + MTX) were TEAEs. The most commonly reported TEAEs (≥2% of subjects) were hypertension (6 subjects, 4.5%), injection site rash, upper respiratory tract infection, urinary tract infection (4 subjects each, 3.0%), injection site reaction, asthenia, nausea, nasopharyngitis, transaminase increased and back pain (3 subjects each, 2.2%). Statistically significant differences were found between the two arms: 19.0% of the subjects under usual care reported gastrointestinal disorders compared to 5.6% of the subjects receiving ETN + MTX (p=0.030), 4.8% of the subjects under usual care reported general disorders and administration site conditions compared to 16.9% of the subjects receiving ETN + MTX (p=0.030).

Table 4. Treatment-Emergent Adverse Events (All Causality) Reported for ≥2% of Subjects in Either Treatment Group

Number (%) of Adverse Events by: System Organ Class and MedDRA Preferred Term	Usual Care N=63 n (%)	ETN + MTX N=71 n (%)	Total N=134 n (%)
Subjects with any TEAE	28 (44.4)	39 (54.9)	67 (50.0)
Eye disorders	2 (3.2)	2 (2.8)	4 (3.0)
Conjunctivitis	0	2 (2.8)	2 (1.5)
Gastrointestinal disorders	12 (19.0)	4 (5.6)	16 (11.9)[a]
Nausea	3 (4.8)	0	3 (2.2)
Abdominal pain upper	2 (3.2)	0	2 (1.5)
Aphthous stomatitis	2 (3.2)	0	2 (1.5)
Gastritis	2 (3.2)	0	2 (1.5)
General disorders and administration site conditions	3 (4.8)	12 (16.9)	15 (11.2)[a]
Injection site rash	0 (0.0)	4 (5.6)	4 (3.0)
Injection site reaction	0	3 (4.2)	3 (2.2)
Asthenia	1 (1.6)	2 (2.8)	3 (2.2)
Fatigue	0	2 (2.8)	2 (1.5)
Infections and infestations	9 (14.3)	16 (22.5)	25 (18.7)
Upper respiratory tract infection	1 (1.6)	3 (4.2)	4 (3.0)
Urinary tract infection	2 (3.2)	2 (2.8)	4 (3.0)
Nasopharyngitis	0	3 (4.2)	3 (2.2)
Pneumonia	0	2 (2.8)	2 (1.5)
Rhinitis	0	2 (2.8)	2 (1.5)
Investigations	4 (6.3)	5 (7.0)	9 (6.7)
Transaminases increased	1 (1.6)	2 (2.8)	3 (2.2)
Musculoskeletal and connective tissue disorders	4 (6.3)	5 (7.0)	9 (6.7)
Back pain	1 (1.6)	2 (2.8)	3 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (4.2)	3 (2.2)
Basal cell carcinoma	0	2 (2.8)	2 (1.5)
Nervous system disorders	1 (1.6)	6 (8.5)	7 (5.2)
Hypoaesthesia	0	2 (2.8)	2 (1.5)
Psychiatric disorders	1 (1.6)	3 (4.2)	4 (3.0)
Depressed mood	0	2 (2.8)	2 (1.5)
Skin and subcutaneous tissue disorders	3 (4.8)	5 (7.0)	8 (6.0)
Ecchymosis	2 (3.2)	0	2 (1.5)
Vascular disorders	6 (9.5)	4 (5.6)	10 (7.5)
Hypertension	4 (6.3)	2 (2.8)	6 (4.5)

ETN = etanercept; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; N = number of subjects per treatment group; n = number of subjects; TEAE = treatment-emergent adverse event.

a. P-value = 0.030, Fisher's exact test.

The treatment-related TEAEs for ≥2% of subjects in either treatment group are presented in Table 5.

Table 5. Treatment-Emergent Adverse Events Related to Investigational Product in ≥2% of Subjects in Either Treatment Group - Safety Population

Number (%) of Adverse Events by: System Organ Class and MedDRA Preferred Term	Usual Care N=63 n (%)	ETN + MTX N=71 n (%)
Subjects with any related TEAE	6 (9.5%)	23 (32.4%)
General disorders and administration site conditions	0	9 (12.7%)
Injection site rash	0	4 (5.6%)
Injection site reaction	0	3 (4.2%)
Investigations	0	3 (4.2%)
Transaminases increased	0	2 (2.8%)

ETN = etanercept; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; N = number of subjects per treatment group; n = number of subject; TEAE = treatment-emergent adverse event.

Treatment Emergent SAEs: The treatment-emergent (all causality) SAEs are presented in Table 6. A total of 9 subjects (6.7%) reported serious TEAEs: 5 subjects (7.0%) in the arm receiving ETN + MTX and 4 subjects (6.3%) in the arm receiving usual care.

Table 6. Treatment Emergent Serious Adverse Events - Safety Population

Number (%) of Adverse Events by: System Organ Class and MedDRA Preferred Term	Usual Care N=63 n (%)	ETN + MTX N=71 n (%)	Total N=134 n (%)
Subjects with any serious adverse event	4 (6.3)	5 (7.0)	9 (6.7)
Cardiac disorders	1 (1.6)	1 (1.4)	2 (1.5)
Atrial fibrillation	0	1 (1.4)	1 (0.7)
Cardiac failure	1 (1.6)	0	1 (0.7)
Gastrointestinal disorders	1 (1.6)	1 (1.4)	2 (1.5)
Gastritis	1 (1.6)	0	1 (0.7)
Hiatus hernia	0	1 (1.4)	1 (0.7)
Infections and infestations	1 (1.6)	2 (2.8)	3 (2.2)
Bronchopneumonia	1 (1.6)	0	1 (0.7)
Pneumonia	0	2 (2.8)	2 (1.5)
Pyothorax	0	1 (1.4)	1 (0.7)
Musculoskeletal and connective tissue disorders	1 (1.6)	0	1 (0.7)
Bursitis	1 (1.6)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (2.8)	2 (1.5)
Basal cell carcinoma	0	2 (2.8)	2 (1.5)
Nervous system disorders	0	1 (1.4)	1 (0.7)
Transient ischaemic attack	0	1 (1.4)	1 (0.7)

ETN = etanercept; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; N = number of subjects per treatment group; n = number of subject.

The treatment-related SAEs are presented in Table 7. In the arm receiving ETN + MTX, 1 subject presented with pneumonia and pyothorax of severe intensity, reported at the same date. These 2 SAEs were considered related to study product and led to study withdrawal. Another subject presented with basal cell carcinoma of mild intensity, also considered related to study drug. In the arm receiving usual care, 1 subject presented with bronchopneumonia of severe intensity that was considered related to study product.

Table 7. Serious Treatment-Emergent Adverse Events Related to Investigational Product - Safety Population

System Organ Class and Preferred Term	Usual Care N=63 n (%)	ETN + MTX N=71 n (%)
All adverse events	1 (1.6)	2 (2.8)
Infections and infestations	1 (1.6)	1 (1.4)
Bronchopneumonia	1 (1.6)	0
Pneumonia	0	1 (1.4)
Pyothorax	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.4)
Basal cell carcinoma	0	1 (1.4)

ETN = etanercept; MTX = methotrexate; N = number of subjects per treatment group; n = number of subject.

Death: One TEAE (cardiac failure), occurring in the arm receiving usual care, was considered life threatening and ended by death (Table 8).

Table 8. Death

Treatment	Duration of Treatment	Time From Treatment Discontinuation to Death	Cause of Death	Related to Study Drug
Usual care	23 days[a]	51 days	Cardiac failure	No

a. Day relative to the start of study treatment.

Safety Related Discontinuations: Two subjects, both in the arm receiving ETN + MTX, were withdrawn from the study because of AEs: One subject because of pneumonia and pyothorax and another subject because of hepatitis B. These 3 events were considered related to the study drug. Two subjects, both in the arm receiving ETN + MTX, permanently discontinued the study drug because of AEs: One subject because of severe injection site reaction and another subject because of rash pruritic. These 2 events were considered related to the study drug.

Subjects reporting TEAEs leading to study withdrawal and study drug permanent discontinuations are presented in Table 9.

Table 9. Withdrawal and Permanent Discontinuations due to Treatment-Emergent Adverse Events

System Organ Class and Preferred Term	Usual Care N=63 n	ETN + MTX N=71 n (%)
Adverse Events Leading to Study Withdrawal		
All	0	2 (2.8)
Infections and infestations	0	1 (1.4)
Pneumonia	0	1 (1.4)
Pyothorax	0	1 (1.4)
Investigations	0	1 (1.4)
Hepatitis B DNA decreased	0	1 (1.4)
Adverse Events Leading to Study Drug Permanent Discontinuation		
All	0	2 (2.8)
General disorders and administration site conditions	0	1 (1.4)
Injection site reaction	0	1 (1.4)
Skin and subcutaneous tissue disorders	0	1 (1.4)
Rash pruritic	0	1 (1.4)

ETN = etanercept; MTX = methotrexate; N = number of subjects; n = number of subjects with an event.

Other Safety Related Observations: Very few clinically significant abnormalities occurred during the course of the study regarding laboratory data evaluation. In the ETN + MTX group, clinically significant abnormalities occurred for 1 subject at Screening (alanine aminotransferase), for 2 subjects at Week 4 (alanine and aspartate aminotransferases, sodium), and for 1 subject at the end of study (alanine aminotransferase). In the usual care group, clinically significant abnormalities occurred for 1 subject at Screening (creatinine), for 1 subject at Week 24 (white blood cells, neutrophils, lymphocytes, red blood cells, hemoglobin and platelets), and for 1 subject at the end of study (aspartate aminotransferase). No clinically significant abnormality was reported regarding urinalysis.

A decrease in systolic and diastolic blood pressure (BP) in both treatment groups was observed from Week 4. At the end of the study the mean decrease was approximately 2 mmHg in the 2 groups.

Changes in pulse rate were also observed during the study. At Week 4 and Week 12, a statistically significant difference was found between the 2 groups: mean pulse rate increased by around 2 beats per minute (bpm) in the usual care group and decreased by around 1 bpm in the ETN + MTX group. Similar results were observed at end of the study.

No significant change in weight was reported.

CONCLUSIONS: Following early termination of the study by the sponsor, only disposition of randomized subjects, description of demographic data on safety population, safety analyses and ancillary study analysis (up to Week 24) were performed.

The majority of the 134 subjects in the safety population were women (79.1%) and had a mean age of 55.5 years. The mean duration of RA was 8.9 years and 74.6% of subjects had RA that was Class II according to ACR classification.

Among the safety population, 67 subjects (50%) had TEAEs (drug-related and not related): 28 subjects (44.4%) in the group under usual care and 39 subjects (54.9%) in the arm receiving ETN + MTX. The most commonly reported TEAEs were hypertension, injection site rash, upper respiratory tract infection, and urinary tract infection. A total of 9 subjects (6.7%) reported serious TEAEs: 5 subjects in the arm receiving ETN + MTX and 4 subjects in the arm receiving usual care. Four (4) SAEs were considered related to study product: basal cell carcinoma, pneumonia and pyothorax (both reported for the same subject) in the arm receiving ETN + MTX, and bronchopneumonia reported for 1 subject in the arm receiving usual care. One death was reported, following heart failure in a subject receiving usual care.

Very few clinically significant abnormalities occurred during the course of the study regarding laboratory data evaluation. Changes in vital signs were noted in both treatment groups and included a decrease in systolic and diastolic blood pressure (BP) as well as changes in pulse rate. However, no significant changes in weight were reported.

In conclusion, there were no unexpected safety findings reported in this study.