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

PROTOCOL NO.: 0881K1-6000 (B1801017) and 0881K1-3329 (B1801015)

PROTOCOL TITLE: A 3 Month, Randomized, Open Label, Parallel Group, Descriptive Study to Explore and Compare Perceptions and Satisfaction for Two Different Delivery Mechanisms For Etanercept (Etanercept Auto-Injector and the Etanercept Prefilled Syringe) in Patients With Rheumatoid Arthritis

Study Centers: Studies 0881K1-3329 and 0881K1-6000 were two studies in which subjects underwent exactly the same procedures. Study 0881K1-3329 was conducted in Austria, Belgium, Greece, Spain and Switzerland, whereas study 0881K1-6000 was conducted in Denmark, Finland, France, Germany, Netherlands, Norway, Sweden, and the United Kingdom (UK). A total of 103 centers took part in this study and randomized subjects; 3 each in Denmark, Greece, Austria and the Netherlands, 2 in Finland, 19 in France, 27 in Germany, 7 each in Norway, Switzerland and Belgium, 4 in Sweden, 8 in Spain and 10 in the UK.

Study Initiation and Final Completion Dates:

For Study 0881K1-6000: 03 September 2007 to 20 May 2009

For Study 0881K1-3329: 15 November 2007 to 13 April 2009

Phase of Development: Phase 3

Study Objectives:

Primary: To compare subject satisfaction with two different delivery devices for etanercept, the prefilled syringe (PFS) and the autoinjector (AI), after 12 weeks of use in subjects with rheumatoid arthritis (RA). The study hypothesis was that the AI would be non-inferior to the PFS after 12 weeks of use, based on the subjects' responses to the question "How satisfied are you with your injection device?", using a 10 point scale from totally dissatisfied to totally satisfied. If non-inferiority was established, testing on superiority was performed.

Secondary:

- To compare subject satisfaction with the two different delivery devices by asking "Are you satisfied with your injection device?", using a dichotomous Yes or No.

- To identify subject and device attributes associated with subject satisfaction. The following attributes were investigated:

Subject Characteristics	RA Characteristics
Age, Sex, Social-educational status Psychological status (via Hospital Anxiety Depression [HAD] scale) Willingness to self-manage (via Patient Activation Measure [PAM] short form) Prior injection or self-injection experience	Duration Disease Activity (Disease Activity Score based on a 28-joint count [DAS28], Subject and physician global) Functional Status (Health Assessment Questionnaire [HAQ]) Prior treatment

- To compare device attributes and subject perceptions with 2 different delivery devices for etanercept after 4 and 12 weeks of use. Device attributes and subject perceptions were measured by asking subjects the following concepts and evaluating them with an appropriate Likert scale:
    - Ease of use and convenience of injection device operation;
    - Confidence in the device;
    - Presence or absence of fear of the device;
    - Device characteristics;
    - Side effects related to administration;
    - Anxiety measure (Short form State-Trait Anxiety Inventory [SF-STAI]).
- To identify subject attributes associated with subject perceptions using the attributes listed above.

METHODS

Study Design: Studies 0881K1-3329 and 0881K1-6000 were identical studies; the data was pooled for reporting purposes. Each study was a phase 3, multicenter, open-label, randomized, 2-arm parallel-designed study. Subjects were randomized to receive treatment with etanercept 50 mg once-weekly subcutaneously (SC) either as PFS or AI in a 1:1 allocation. Subjects participated in the study for approximately 5 months (20 weeks). This included the screening period of up to 6 weeks, the treatment period of 12 weeks, and the 2 weeks follow-up telephone call to assess for adverse events (AEs). The study flow chart is presented in Table 1.

Table 1. Study Flow Chart

Study Procedures	Week –6/-1	Week 1	Week 4	Week 12 / ET	
	Day –42/ -1	Day 1	Day 28	Day 84	Day 99
			±4 Days	±7 Days	±3 Days
	Screening	Treatment			Phone Call
Visit ID (for Sponsor use Only)	**0**	**1**	**2**	**3**	
Informed consent	X				
Demographics, educational status	X				
Injection and self injection experience	X				
Medical and RA history, prior medication, weight	X				
Physical examination, vital signs[a]	X	X		X	
TB test[b]	X				
Blood test, urinalysis (safety baseline)	X				
Pregnancy test[c]	X	X[c]		X	
Randomization		X			
Instruction[d]		X			
HAQ		X	X	X	
RA efficacy assessments	X[e]	X[f]	X[f]	X[e]	
General health (VAS)	X			X	
PAM short form		X			
Hospital anxiety depression (HAD) scale		X			
Subject satisfaction[g]		X[g]	X	X	
Device attributes and subject perceptions[g]		X[g]	X	X	
Anxiety measure (SF-STAI)[g]		X[g]	X	X	
Administer etanercept[h]		X[h]----------X			
Device query monitoring		X----------X			
Compliance		X----------X			
Concomitant medications	X	X	X	X	
Adverse events[i]	X	X	X	X	X[i]

AEs = adverse events; DAS28 = disease activity score based on a 28-joint count; ET = Early Termination of subject participation; HAQ = health assessment questionnaire; PAM = patient activation measure; RA = rheumatoid arthritis; SF-STAI = short form state-trait anxiety inventory; TB = tuberculosis; VAS = visual analogue scale.

a. Sitting blood pressure and pulse rate.
b. Required according to local license and guidelines.
c. Serum Test at screening. Urine Test at Baseline, if positive Serum test.
d. Includes recording of time required for instruction.
e. DAS28, plus subject and physician global assessment (VAS).
f. Subject and physician global assessment (VAS) only.
g. Via subject questionnaire. At Visit 1, the questionnaires must be filled after the instruction in the device and the first administration.
h. First administration by subject or through trained carer (voluntary care giver).
i. Investigators were requested to contact each subject via telephone for the assessment of AEs approximately 15 days after the last intake of study medication.

Number of Subjects (Planned and Analyzed): A total of 798 subjects (264 in Study 0881K1-3329 and 534 in Study 0881K1-6000) were planned. A total of 640 subjects (161 in Study 0881K1-3329 and 479 in Study 0881K1-6000) were randomly assigned to receive test article as follows: 325 in the AI group and 315 in the PFS group. Two subjects withdrew consent just after randomization without receiving any injection, thus the safety population included 638 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects eligible to participate were male and female aged 18 years and older, diagnosed with RA (according to the American College of Rheumatology criteria), eligible for treatment with etanercept according to the Summary of Product Characteristics and applicable local guidelines and were willing and able to self-inject etanercept or had a carer perform injections. All women of childbearing potential had to have a negative serum β-human chorionic gonadotropin pregnancy test at screening. Sexually active men and women had to use a reliable form of contraception during the study.

Exclusion Criteria: Subjects with sepsis or at a risk of sepsis, subjects with prior experience of biologics and anti-tumor necrosis factor (TNF) treatment for their RA including etanercept, subjects with current or recent infections (including chronic or localized), subjects with sensitivity to latex and subjects vaccinated with live vaccine in the previous 4 weeks, or expected to require such vaccination during the course of the study, were excluded from the study.

Study Treatment: Etanercept was supplied as a sterile solution in either a PFS or an AI containing 50 mg of etanercept. All subjects received 1 SC injection of 50 mg etanercept per week, at approximately the same time of day (±4 hours) and on the same day of the week, for 12 weeks. Injections were administered in the abdomen, thigh, or upper arm with the location rotated with each dose.

Efficacy Endpoints: The primary endpoint was subject satisfaction at Visit 3 (Week 12). This endpoint was measured by asking subjects: "How satisfied are you with your injection device?", using a 0-10 point scale from totally dissatisfied to totally satisfied. If there was no evaluation available after the first administration of test agent, the subject was not considered for the analysis of the primary endpoint.

Secondary Endpoints:

- Subject satisfaction was also determined by asking "Are you satisfied with your injection device?" using a dichotomous Yes or No.
- Subject attributes associated with subject satisfaction. Influence of the following attributes on subject satisfaction were investigated:

Subject Characteristics:

- Age, Sex, and social-educational status were recorded in the Case Report Form (CRF)
- Psychological status was determined with the HAD Scale
- Willingness to self manage was determined with the PAM Short Form
- Prior self-injection experience was recorded in the CRF

RA characteristics:

- Duration of disease was calculated from the date of diagnosis, as recorded in the CRF
- Disease activity was determined by calculating the DAS28. The number of swollen joints and tender joints were assessed using the 28 joint count. The erythrocyte sedimentation rate (ESR) was measured in mm/hour. In addition, the subject's assessment of general health measured on a visual analogue scale (VAS) of 100 mm was obtained. Using these data, the DAS 28 was calculated using the following formula: DAS28=0.56∗√(tender joint count[TJC] 28)+0.28 ∗ sqrt (swollen joint count [SJC] 28)+0.70∗logarithm (ESR)+0.014∗ VAS general health.
- Subject and physician global assessment of disease activity was measured on a VAS of 100 mm
- Functional status was determined using the HAQ
- Prior treatment was expressed as the number of previous disease modifying antirheumatic drugs (DMARDs)
- Prior injection experience was recorded on the CRF

- Device attributes and subject perceptions were measured by asking subjects the following concepts and questions and evaluating them with a Likert scale.
  - Ease of use and convenience of injection device operation
  - Confidence in the device
  - Presence or absence of fear of the device
  - Device characteristics
  - Side effects related to administration
  - The SF-STAI
- Subject attributes associated with subject perception. The same attributes as listed above for their influence on subject satisfaction was also investigated on an influence on subject perception.

Safety Evaluations: The safety of etanercept was determined using the following assessments: monitoring of AEs, vital signs, physical examinations and premature withdrawals.

Statistical Methods:

Analysis Populations: There were 3 populations analyzed for this study:

- The modified Intent-To-Treat (mITT) population included all randomized subjects who received at least one injection of test article and who had at least one available evaluation after the first administration of test agent.

- The Per-Protocol (PP) population included subjects from the mITT who completed the study with no major protocol violation.

- The Safety set included all randomized subjects who received at least one injection of test article.

For quantitative data, number of subjects (n), mean and standard deviation (SD), median, minimum, maximum, and number of missing data were presented. For qualitative data, number of subjects (n), frequency and percentage on available data, and number of missing data will be presented.

Statistical testing, unless otherwise stated, was two-sided and used the 5% significance level.

Safety analysis was done on the safety population based on the device actually used by each subject. Between-group comparisons of AEs were analyzed using the Fisher exact test. The efficacy and health outcomes assessments were done according to the randomization group regardless of the device actually used. Missing or incomplete data were not replaced, except in case of last observation carried forward (LOCF) analysis where missing values on Day 84 were replaced by the last values obtained during the on-therapy study interval.

Primary Endpoint Analysis: Non-inferiority of AI over PFS was assessed on the subject satisfaction after 12 weeks of use in the PP and mITT populations. The lower limit of the 95% confidence interval (CI) of the difference between AI and PFS groups, derived from a repeated-measures analysis of variance (ANOVA) using a mixed linear model, was compared to a non-inferiority margin of -1. In case of non-inferiority of AI, superiority of AI over PFS was investigated.

Secondary Analyses: Generalized estimating equations models were used to analyze the proportion of satisfied subjects as well as the subject perception. A multiple correspondence analysis (MCA) and ascending hierarchical classification were performed to identify subject attributes that are associated with subject perceptions.

The question “To what extent would you consider alternative devices if you were to continue on etanercept?” (Q24) was subsequently found to have been wrongly translated in the French version of the device attributes and subjects perceptions questionnaire used in France, Belgium and Switzerland. Data were then invalidated (put to missing) for the sites using the corresponding version. Due to the resulting high number of missing values, question Q24 was not introduced in MCA as initially planned. For the analysis of subject and RA attributes associated with subject perceptions, items used in MCA were recoded by merging modalities with low sample sizes to get more accurate analyses.

RESULTS

Subject Disposition and Demography: Subject disposition is presented in Table 2.

Table 2. Subject Disposition

		AI N (%)	PFS N (%)	Total N (%)
Screened	698			
Assigned to treatment		325	315	640
Treated		325	313	638
Completed		299 (92.0)	294 (93.3)	593 (92.7)
Discontinued		26 (8.0)	21 (6.7)	47 (7.3)
Adverse event		19 (5.8)	13 (4.1)	32 (5.0)
Subject request		1 (0.3)	6 (1.9)	7 (1.1)
Investigator request		2 (0.6)	0	2 (0.3)
Discontinuation of study by sponsor		1 (0.3)	0	1 (0.2)
Protocol violation		2 (0.6)	1 (0.3)	3 (0.5)
Failed to return		1 (0.3)	0	1 (0.2)
Other		0	1 (0.3)	1 (0.2)
Analysis Sets				
mITT set		324	313	637
PP set		294	284	578
Safety set		325	313	638

AI = auto-injector; mITT = modified intent-to-treat; N = number of subjects; PFS = pre-filled syringe; PP = per-protocol.

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

Table 3. Demographic and Baseline Characteristics, mITT Population

Characteristic	AI N=324	PFS N=313	Total N=637
Age (years)			
n	324	313	637
Mean (SD)	54.8 (12.8)	54.7 (12.9)	54.8 (12.9)
Median	56.0	55.0	55.0
Min, max	22.0, 84.0	19.0, 84.0	19.0, 84.0
Gender			
n	324	313	637
Men	85 (26.2%)	77 (24.6%)	162 (25.4%)
Women	239 (73.8%)	236 (75.4%)	475 (74.6%)
Socio-educational level			
n	323	311	634
Reading/writing capacity	122 (37.8%)	129 (41.5%)	251 (39.6%)
High school/baccalaureate level	147 (45.5%)	136 (43.7%)	283 (44.6%)
University level	54 (16.7%)	46 (14.8%)	100 (15.8%)
Educational or professional activity in the health area			
n	324	313	637
No	299 (92.3%)	297 (94.9%)	596 (93.6%)
Yes	25 (7.7%)	16 (5.1%)	41 (6.4%)

AI = auto-injector; max = maximum, min = minimum, mITT = modified intent-to-treat; n = number of subjects per characteristic, N = number of subjects; PFS = pre-filled syringe; SD = standard deviation.

Efficacy Results:

Primary Endpoint**:** Mean subject satisfaction was relatively stable between baseline (after the training) and Day 84 in both groups: 8.4 (±2.1) and 8.3 (±2.4) points in the AI group, and 7.2 (±2.5) and 7.2 (±2.6) points in the PFS group. The subject satisfaction with the injection device evaluated on a 0 (totally dissatisfied) to 10 point (totally satisfied) scale is described in the mITT and PP populations at Week 12 (Day 84) in Table 4.

Table 4. Subject Satisfaction[a] at Week 12 (Day 84), mITT and PP Populations

	AI N=324	PFS N=313
mITT Population		
n	306	300
Mean (SD)	8.3 (2.4)	7.2 (2.6)
Median	9.0	8.0
Min, max	0.0, 10.0	0.0, 10.0
PP Population		
n	292	281
Mean (SD)	8.4 (2.2)	7.2 (2.6)
Median	9.0	8.0
Min, max	0.0, 10.0	0.0, 10.0

AI = auto-injector; BMI = body mass index; max = maximum; min = minimum; mITT = modified intent-to-treat; n = number of subjects in population set; N = number of subjects; PFS = pre-filled syringe; PP = per-protocol; SD = standard deviation.
a. 0 - totally dissatisfied, 10 - totally satisfied.

In the mITT population, the estimate of the mean difference between the 2 groups (AI - PFS) was quite stable all over the study, with better satisfaction for the group of subjects using the AI than the group of subjects using the PFS. This difference (2-sided 95% CI) was 1.11 (0.71; 1.50) on Day 84. Results were similar in the PP population (Table 5).

Table 5. Subject Satisfaction[a] - Estimated Mean Differences, mITT and PP Populations

	Difference (AI-PFS)		
	Mean (SE)	95%CI	p-Value
mITT Population			
Day 84	1.11 (0.20)	(0.71 ; 1.50)	<0.001
PP Population			
Day 84	1.25 (0.20)	(0.85; 1.64)	<0.001

AI = auto-injector; CI = confidence interval; mITT = modified Intent-to-Treat; PFS = pre-filled syringe; PP = per protocol; SE = standard error.
a. 0 - totally dissatisfied, 10 - totally satisfied

The lower bound of the 2-sided 95% CI on the mean difference in subject satisfaction on Day 84 was greater than the pre-defined clinically relevant non-inferiority margin of -1. Therefore, the difference between the 2 groups was statistically significantly higher than -1.

Secondary Endpoints:

Proportion of Satisfied Subjects: The proportion of subjects satisfied with their injection device remained relatively stable between baseline and Day 84. In the AI group, 98.4% of the subjects were satisfied at baseline after the training and this proportion was 93.3% on Day 84. In the PFS group, 89.2% of the subjects were satisfied at baseline after the training and this proportion was 87.7% on Day 84. The probability of being satisfied with the device was significantly greater in the AI group than in the PFS group with an estimate of the odds ratio (2-sided 95% CI) between groups of 1.96 (1.12; 3.43) on Day 84 (Table 6). A summary of the proportion of satisfied subjects is presented in Table 7.

Table 6. Proportion of Satisfied Subjects - Estimated Odds Ratios - mITT Set

	Odds Ratio (AI/PFS)		
	Estimate	**95% CI**	**p-Value**
Baseline - after the training	9.34	(3.24; 26.91)	<0.001
Baseline - after the 1st injection	3.36	(1.70; 6.66)	<0.001
Day 28	1.73	(0.98; 3.05)	0.058
Day 84	1.96	(1.12; 3.43)	0.019
Last observation	1.97	(1.15; 3.37)	0.013

AI = auto-injector; CI = confidence interval; mITT = modified Intent-to-Treat; PFS = pre-filled syringe.

Table 7. Proportion of Satisfied Subjects - Observed Data - mITT Set

Visit	**AI N=324**	**PFS N=313**
Baseline - after the training		
n	308	296
Yes	303 (98.4%)	264 (89.2%)
No	5 (1.6%)	32 (10.8%)
Baseline - after the 1st injection		
n	303	278
Yes	292 (96.4%)	247 (88.8%)
No	11 (3.6%)	31 (11.2%)
Day 28		
n	301	297
Yes	279 (92.7%)	263 (88.6%)
No	22 (7.3%)	34 (11.4%)
Day 84		
n	297	284
Yes	277 (93.3%)	249 (87.7%)
No	20 (6.7%)	35 (12.3%)
Last observation		
n	323	312
Yes	300 (92.9%)	271 (86.9%)
No	23 (7.1%)	41 (13.1%)

AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Influence of Subject Attributes on Satisfaction: Mean satisfaction according to subject attributes is described in Table 8.

Table 8. Influence of Subject Attributes on the Mean (SD) Satisfaction at Endpoint - mITT Set

Visit	AI N=324	PFS N=313
Age		
≤ Q1	8.18 (2.52)	6.58 (2.73)
]Q1-Q2]	8.81 (1.84)	7.01 (2.70)
]Q2-Q3]	8.31 (2.44)	7.56 (2.67)
> Q3	7.74 (2.54)	7.63 (2.28)
Gender		
Male	8.45 (2.31)	8.13 (2.07)
Female	8.21 (2.40)	6.89 (2.72)
Socio-educational level		
Reading/writing capacity	8.11 (2.24)	7.53 (2.44)
High school/baccalaureate level	8.32 (2.50)	6.90 (2.87)
University level	8.44 (2.36)	7.09 (2.38)
Educational or professional activity in the health area		
No	8.26 (2.34)	7.18 (2.66)
Yes	8.40 (2.89)	7.44 (2.13)
HAD anxiety subscale score at Baseline		
≤ Q1	8.56 (2.29)	7.67 (2.44)
]Q1-Q2]	8.13 (2.47)	7.32 (2.56)
]Q2-Q3]	7.87 (2.68)	6.93 (2.53)
> Q3	8.46 (2.06)	6.67 (2.97)
HAD depression subscale score at Baseline		
≤ Q1	8.75 (2.02)	7.70 (2.37)
]Q1-Q2]	7.97 (2.58)	7.35 (2.66)
]Q2-Q3]	8.28 (2.39)	7.17 (2.49)
> Q3	8.03 (2.48)	6.23 (2.94)
PAM at baseline		
≤ Q1	7.91 (2.58)	7.06 (2.72)
]Q1-Q2]	8.48 (2.14)	7.42 (2.36)
]Q2-Q3]	8.02 (2.56)	6.97 (2.83)
> Q3	8.49 (2.32)	7.38 (2.63)
Prior injection experience		
Yes	8.29 (2.35)	7.05 (2.53)
No	8.24 (2.42)	7.37 (2.75)
Prior self-injection experience		
Yes	8.10 (2.51)	6.57 (2.51)
No	8.34 (2.32)	7.49 (2.64)
Duration of RA at screening		
≤ Q1	7.99 (2.56)	7.32 (2.59)
]Q1-Q2]	8.39 (2.34)	6.68 (2.83)
]Q2-Q3]	8.52 (2.37)	7.24 (2.67)
> Q3	8.29 (2.14)	7.40 (2.47)
DAS28 at screening		
≤ Q1	8.24 (2.50)	7.01 (2.50)
]Q1-Q2]	8.11 (2.59)	7.36 (2.64)
]Q2-Q3]	8.45 (2.19)	7.58 (2.55)
> Q3	8.31 (2.23)	6.90 (2.85)
Subject's global assessment of RA activity at screening		
≤ Q1	8.45 (2.14)	7.55 (2.43)
]Q1-Q2]	8.41 (2.15)	7.31 (2.61)
]Q2-Q3]	8.07 (2.60)	7.11 (2.53)
> Q3	8.17 (2.59)	6.88 (2.83)
Physician's global assessment of RA activity at screening		
≤ Q1	8.23 (2.40)	7.40 (2.24)
]Q1-Q2]	8.36 (2.00)	6.92 (2.73)
]Q2-Q3]	8.03 (2.75)	7.14 (2.96)

Table 8. Influence of Subject Attributes on the Mean (SD) Satisfaction at Endpoint - mITT Set

Visit	AI N=324	PFS N=313
> Q3	8.47 (2.34)	7.32 (2.59)
HAQ-DI at Baseline		
≤ Q1	8.61 (2.07)	7.67 (2.24)
]Q1-Q2]	8.27 (2.37)	7.40 (2.39)
]Q2-Q3]	8.33 (2.37)	7.03 (2.84)
> Q3	7.96 (2.58)	6.57 (2.95)
Maximum combination of DMARDs		
1 DMARD	8.29 (2.41)	7.23 (2.66)
2 DMARDs	8.18 (2.42)	7.19 (2.53)
3 DMARDs	8.94 (1.84)	6.85 (3.04)
At least 4 DMARDs	9.50 (1.00)	

For continuous subject attributes, summary statistics were provided by quarter. Quarters are defined as follows:
1st quarter: ≤ Quartile 1
2nd quarter:]Quartile 1 – Quartile 2]
3rd quarter:]Quartile 2 – Quartile 3]
4th quarter: > Quartile 3
AI = auto-injector; DMARD = disease modifying antirheumatic drug; HAD = hospital anxiety depression; HAQ-DI = health assessment questionnaire – disability index; mITT = modified intent-to-treat; N = number of subjects; PAM = patient activation measure; PFS = pre-filled syringe; Q = Quartile; RA = rheumatoid arthritis; SD = standard deviation.

Device Attributes and Subject Perceptions : Device attributes and subject perceptions were evaluated with 0 to 4 Likert scales, scales numbers interpretation varying between questions.

On Day 84, there was a statistically significant difference in favor of the group of subjects using the AI compared to the group of subjects using the PFS in the ease of use (Table 9, Table 10, Table 11) and convenience (Table 12) of the device (except for time to perform the injection, similar for both devices), the confidence (Table 13) and the degree of nervousness and anxiety felt (Table 14) when using the device. The characteristics of the device (look, feeling, comfort of use) (Table 15) were appreciated as better by the subjects using the AI than by the subjects using the PFS. After the first injection and at Day 28, odds-ratio indicated that subjects using the PFS experienced less pain after injection (Table 16) than subjects using the AI, but there was no statistically significant difference between the 2 groups of subjects in the experience of pain on Day 84. Therefore, subjects who used the AI would be less likely to consider changing device and would be more likely to recommend the device than subjects using the PFS (Table 17, Table 18 and Table 19).

The short form of STAI included 6 items (Table 20) related to anxiety (calm, tense, upset, relaxed, content, and worried) rated on a 4-point scale from 1 to 4. The SF-STAI mean global score decreased from 10.3 (±3.6) at baseline after the training to 10.0 (±3.7) on Day 84 in the AI group and from 11.4 (±3.7) to 10.5 (±3.4) respectively in the PFS group. Therefore, in both groups subjects felt slightly better on Day 84 than at baseline after the training. The difference was not statistically significant between the 2 groups (AI-PFS) on Day 84, with the estimate of the mean difference (2-sided 95% CI) equal to -0.41 (-0.97; 0.15).

Table 9. Device Attributes and Subject Perceptions Questionnaire-Questions 1 to 5 - Observed Data - mITT Set

Visit	Question 1		Question 2		Question 3		Question 4		Question 5	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)
Baseline - after the training										
n	305	302	307	297	299	294	306	296	303	300
Very easy	193 (63.3%)	121 (40.1%)	213 (69.4%)	167 (56.2%)	236 (78.9%)	205 (69.7%)	215 (70.3%)	183 (61.8%)	172 (56.8%)	118 (39.3%)
1	67 (22.0%)	102 (33.8%)	64 (20.8%)	99 (33.3%)	52 (17.4%)	71 (24.1%)	65 (21.2%)	79 (26.7%)	87 (28.7%)	110 (36.7%)
2	29 (9.5%)	53 (17.5%)	22 (7.2%)	25 (8.4%)	8 (2.7%)	12 (4.1%)	14 (4.6%)	23 (7.8%)	25 (8.3%)	46 (15.3%)
3	11 (3.6%)	19 (6.3%)	4 (1.3%)	5 (1.7%)	1 (0.3%)	5 (1.7%)	10 (3.3%)	8 (2.7%)	18 (5.9%)	20 (6.7%)
Very difficult	5 (1.6%)	7 (2.3%)	4 (1.3%)	1 (0.3%)	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (1.0%)	1 (0.3%)	6 (2.0%)
Baseline - after the 1st injection										
n	318	302	316	302	304	289	309	290	308	291
Very easy	8 (2.5%)	10 (3.3%)	3 (0.9%)	25 (8.3%)	240 (78.9%)	203 (70.2%)	209 (67.6%)	182 (62.8%)	166 (53.9%)	131 (45.0%)
1	16 (5.0%)	17 (5.6%)	11 (3.5%)	40 (13.2%)	40 (13.2%)	63 (21.8%)	61 (19.7%)	70 (24.1%)	83 (26.9%)	87 (29.9%)
2	23 (7.2%)	45 (14.9%)	66 (20.9%)	113 (37.4%)	11 (3.6%)	21 (7.3%)	21 (6.8%)	32 (11.0%)	33 (10.7%)	43 (14.8%)
3	74 (23.3%)	92 (30.5%)	119 (37.7%)	83 (27.5%)	7 (2.3%)	1 (0.3%)	9 (2.9%)	4 (1.4%)	20 (6.5%)	24 (8.2%)
Very difficult	197 (61.9%)	138 (45.7%)	117 (37.0%)	41 (13.6%)	6 (2.0%)	1 (0.3%)	9 (2.9%)	2 (0.7%)	6 (1.9%)	6 (2.1%)
Day 28										
n	300	289	299	290	289	281	299	290	297	289
Very easy	185 (61.7%)	141 (48.8%)	215 (71.9%)	189 (65.2%)	243 (84.1%)	222 (79.0%)	218 (72.9%)	174 (60.0%)	162 (54.5%)	126 (43.6%)
1	66 (22.0%)	92 (31.8%)	53 (17.7%)	75 (25.9%)	35 (12.1%)	42 (14.9%)	57 (19.1%)	77 (26.6%)	83 (27.9%)	82 (28.4%)
2	26 (8.7%)	35 (12.1%)	21 (7.0%)	18 (6.2%)	6 (2.1%)	10 (3.6%)	15 (5.0%)	23 (7.9%)	32 (10.8%)	45 (15.6%)
3	12 (4.0%)	16 (5.5%)	10 (3.3%)	4 (1.4%)	4 (1.4%)	5 (1.8%)	7 (2.3%)	12 (4.1%)	18 (6.1%)	23 (8.0%)
Very difficult	11 (3.7%)	5 (1.7%)	0 (0.0%)	4 (1.4%)	1 (0.3%)	2 (0.7%)	2 (0.7%)	4 (1.4%)	2 (0.7%)	13 (4.5%)
Day 84										
n	298	295	295	294	288	291	297	295	292	294
Very easy	207 (69.5%)	160 (54.2%)	222 (75.3%)	185 (62.9%)	246 (85.4%)	218 (74.9%)	241 (81.1%)	187 (63.4%)	186 (63.7%)	139 (47.3%)
1	51 (17.1%)	77 (26.1%)	47 (15.9%)	90 (30.6%)	30 (10.4%)	56 (19.2%)	39 (13.1%)	77 (26.1%)	68 (23.3%)	79 (26.9%)
2	21 (7.0%)	37 (12.5%)	16 (5.4%)	15 (5.1%)	7 (2.4%)	14 (4.8%)	8 (2.7%)	23 (7.8%)	23 (7.9%)	47 (16.0%)
3	14 (4.7%)	16 (5.4%)	5 (1.7%)	3 (1.0%)	3 (1.0%)	3 (1.0%)	8 (2.7%)	7 (2.4%)	8 (2.7%)	21 (7.1%)
Very difficult	5 (1.7%)	5 (1.7%)	5 (1.7%)	1 (0.3%)	2 (0.7%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	7 (2.4%)	8 (2.7%)
Last observation										
n	322	312	322	312	320	312	323	313	323	312
Very easy	218 (67.7%)	166 (53.2%)	233 (72.4%)	193 (61.9%)	271 (84.7%)	236 (75.6%)	258 (79.9%)	198 (63.3%)	202 (62.5%)	147 (47.1%)
1	55 (17.1%)	81 (26.0%)	54 (16.8%)	96 (30.8%)	32 (10.0%)	58 (18.6%)	43 (13.3%)	79 (25.2%)	76 (23.5%)	84 (26.9%)
2	26 (8.1%)	40 (12.8%)	20 (6.2%)	18 (5.8%)	12 (3.8%)	15 (4.8%)	10 (3.1%)	25 (8.0%)	26 (8.0%)	50 (16.0%)
3	15 (4.7%)	18 (5.8%)	10 (3.1%)	4 (1.3%)	3 (0.9%)	3 (1.0%)	9 (2.8%)	8 (2.6%)	11 (3.4%)	22 (7.1%)
Very difficult	8 (2.5%)	7 (2.2%)	5 (1.6%)	1 (0.3%)	2 (0.6%)	0 (0.0%)	3 (0.9%)	3 (1.0%)	8 (2.5%)	9 (2.9%)

Table 9. Device Attributes and Subject Perceptions Questionnaire-Questions 1 to 5 - Observed Data - mITT Set

Visit	Question 1		Question 2		Question 3		Question 4		Question 5	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)

Question 1: Overall, how easy was it to perform an injection with this device?
Question 2: How easy was it to learn to use the device?
Question 3: How easy is it to dispose of the device?
Question 4: How easy is it to know when the injection is completed?
Question 5: How easy is it to hold the device whilst injecting?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 10. Device Attributes and Subject Perceptions Questionnaire-Question 6 - Observed Data - mITT Set

Visit	AI (N=324)	PFS (N=313)
Baseline - after the training		
n	306	299
None	184 (60.1%)	143 (47.8%)
1	80 (26.1%)	64 (21.4%)
2	28 (9.2%)	58 (19.4%)
3	13 (4.2%)	21 (7.0%)
Extreme	1 (0.3%)	13 (4.3%)
Baseline - after the 1st injection		
n	311	291
None	193 (62.1%)	152 (52.2%)
1	69 (22.2%)	56 (19.2%)
2	21 (6.8%)	55 (18.9%)
3	20 (6.4%)	19 (6.5%)
Extreme	8 (2.6%)	9 (3.1%)
Day 28		
n	298	287
None	181 (60.7%)	156 (54.4%)
1	65 (21.8%)	65 (22.6%)
2	28 (9.4%)	33 (11.5%)
3	16 (5.4%)	23 (8.0%)
Extreme	8 (2.7%)	10 (3.5%)
Day 84		
n	297	291
None	205 (69.0%)	158 (54.3%)
1	55 (18.5%)	58 (19.9%)
2	23 (7.7%)	44 (15.1%)
3	10 (3.4%)	22 (7.6%)
Extreme	4 (1.3%)	9 (3.1%)
Last observation		
n	323	313
None	223 (69.0%)	168 (53.7%)
1	58 (18.0%)	62 (19.8%)
2	26 (8.0%)	49 (15.7%)
3	12 (3.7%)	25 (8.0%)
Extreme	4 (1.2%)	9 (2.9%)

Question 6: Did you feel any hand discomfort whilst using the device?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 11. Device Attributes and Subject Perceptions Questionnaire-Question 7 - Observed Data - mITT Set

Visit	AI (N=324)	PFS (N=313)
Baseline - after the training		
n	305	297
< 5	172 (56.4%)	155 (52.2%)
5-10	95 (31.1%)	98 (33.0%)
11-20	19 (6.2%)	24 (8.1%)
21-30	18 (5.9%)	14 (4.7%)
> 30	1 (0.3%)	6 (2.0%)
Baseline - after the 1st injection		
n	312	287
< 5	188 (60.3%)	166 (57.8%)
5-10	84 (26.9%)	80 (27.9%)
11-20	21 (6.7%)	24 (8.4%)
21-30	18 (5.8%)	14 (4.9%)
> 30	1 (0.3%)	3 (1.0%)
Day 28		
n	299	289
< 5	181 (60.5%)	163 (56.4%)
5-10	77 (25.8%)	86 (29.8%)
11-20	22 (7.4%)	26 (9.0%)
21-30	17 (5.7%)	8 (2.8%)
> 30	2 (0.7%)	6 (2.1%)
Day 84		
n	295	295
< 5	191 (64.7%)	170 (57.6%)
5-10	65 (22.0%)	91 (30.8%)
11-20	20 (6.8%)	20 (6.8%)
21-30	15 (5.1%)	11 (3.7%)
> 30	4 (1.4%)	3 (1.0%)
Last observation		
n	323	313
< 5	207 (64.1%)	180 (57.5%)
5-10	74 (22.9%)	96 (30.7%)
11-20	22 (6.8%)	21 (6.7%)
21-30	16 (5.0%)	12 (3.8%)
> 30	4 (1.2%)	4 (1.3%)

Question 7: How long does it take to perform the injection, including any preparation and disposal?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 12. Device Attributes and Subject Perceptions Questionnaire-Questions 8 to 10 - Observed Data - mITT Set

Visit	Question 8		Question 9		Question 10	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)
Baseline - after the training						
n	311	307	311	307	312	307
Not at all	179 (57.6%)	162 (52.8%)	207 (66.6%)	185 (60.3%)	157 (50.3%)	133 (43.3%)
1	56 (18.0%)	67 (21.8%)	58 (18.6%)	61 (19.9%)	72 (23.1%)	74 (24.1%)
2	37 (11.9%)	43 (14.0%)	23 (7.4%)	38 (12.4%)	51 (16.3%)	64 (20.8%)
3	23 (7.4%)	23 (7.5%)	14 (4.5%)	14 (4.6%)	22 (7.1%)	26 (8.5%)
Very much	16 (5.1%)	12 (3.9%)	9 (2.9%)	9 (2.9%)	10 (3.2%)	10 (3.3%)
Baseline - after the 1st injection						
n	318	310	318	310	320	310
Not at all	200 (62.9%)	173 (55.8%)	220 (69.2%)	186 (60.0%)	167 (52.2%)	129 (41.6%)
1	62 (19.5%)	62 (20.0%)	61 (19.2%)	62 (20.0%)	79 (24.7%)	85 (27.4%)
2	20 (6.3%)	34 (11.0%)	18 (5.7%)	35 (11.3%)	46 (14.4%)	57 (18.4%)
3	23 (7.2%)	28 (9.0%)	11 (3.5%)	14 (4.5%)	23 (7.2%)	26 (8.4%)
Very much	13 (4.1%)	13 (4.2%)	8 (2.5%)	13 (4.2%)	5 (1.6%)	13 (4.2%)
Day 28						
n	314	307	315	307	313	307
Not at all	241 (76.8%)	209 (68.1%)	260 (82.5%)	232 (75.6%)	186 (59.4%)	164 (53.4%)
1	38 (12.1%)	56 (18.2%)	33 (10.5%)	49 (16.0%)	58 (18.5%)	63 (20.5%)
2	16 (5.1%)	20 (6.5%)	13 (4.1%)	13 (4.2%)	36 (11.5%)	44 (14.3%)
3	9 (2.9%)	13 (4.2%)	4 (1.3%)	8 (2.6%)	21 (6.7%)	23 (7.5%)
Very much	10 (3.2%)	9 (2.9%)	5 (1.6%)	5 (1.6%)	12 (3.8%)	13 (4.2%)
Day 84						
n	301	300	302	299	301	300
Not at all	214 (71.1%)	193 (64.3%)	238 (78.8%)	219 (73.2%)	182 (60.5%)	144 (48.0%)
1	43 (14.3%)	53 (17.7%)	37 (12.3%)	47 (15.7%)	62 (20.6%)	69 (23.0%)
2	21 (7.0%)	34 (11.3%)	17 (5.6%)	17 (5.7%)	28 (9.3%)	53 (17.7%)
3	14 (4.7%)	14 (4.7%)	7 (2.3%)	13 (4.3%)	21 (7.0%)	23 (7.7%)
Very much	9 (3.0%)	6 (2.0%)	3 (1.0%)	3 (1.0%)	8 (2.7%)	11 (3.7%)
Last observation						
n	324	313	324	313	324	313
Not at all	230 (71.0%)	202 (64.5%)	254 (78.4%)	229 (73.2%)	192 (59.3%)	151 (48.2%)
1	47 (14.5%)	55 (17.6%)	40 (12.3%)	50 (16.0%)	67 (20.7%)	72 (23.0%)
2	23 (7.1%)	35 (11.2%)	19 (5.9%)	18 (5.8%)	32 (9.9%)	55 (17.6%)

Table 12. Device Attributes and Subject Perceptions Questionnaire-Questions 8 to 10 - Observed Data - mITT Set

Visit	Question 8		Question 9		Question 10	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)
3	14 (4.3%)	15 (4.8%)	7 (2.2%)	13 (4.2%)	22 (6.8%)	23 (7.3%)
Very much	10 (3.1%)	6 (1.9%)	4 (1.2%)	3 (1.0%)	11 (3.4%)	12 (3.8%)

Question 8: How much do you think injecting etanercept will interfere with your ability to enjoy social or leisure activities?
Question 9: Do you think injecting etanercept will interfere with your usual daily activities?
Question 10: How much do you think injecting etanercept will interfere with travelling on holiday/ business/ visiting?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 13. Device Attributes and Subject Perceptions Questionnaire-Questions 11 to 15 - Observed Data - mITT Set

Visit	Question 11		Question 12		Question 13		Question 14		Question 15	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)
Baseline - after the training										
n	319	310	319	309	319	309	320	307	318	309
Not at all	6 (1.9%)	14 (4.5%)	5 (1.6%)	6 (1.9%)	6 (1.9%)	10 (3.2%)	5 (1.6%)	4 (1.3%)	4 (1.3%)	4 (1.3%)
1	21 (6.6%)	24 (7.7%)	18 (5.6%)	5 (1.6%)	21 (6.6%)	9 (2.9%)	15 (4.7%)	11 (3.6%)	14 (4.4%)	5 (1.6%)
2	43 (13.5%)	59 (19.0%)	25 (7.8%)	42 (13.6%)	28 (8.8%)	50 (16.2%)	30 (9.4%)	50 (16.3%)	20 (6.3%)	41 (13.3%)
3	98 (30.7%)	96 (31.0%)	86 (27.0%)	92 (29.8%)	71 (22.3%)	87 (28.2%)	86 (26.9%)	98 (31.9%)	91 (28.6%)	107 (34.6%)
Very much	151 (47.3%)	117 (37.7%)	185 (58.0%)	164 (53.1%)	193 (60.5%)	153 (49.5%)	184 (57.5%)	144 (46.9%)	189 (59.4%)	152 (49.2%)
Baseline - after the 1st injection										
n	319	307	319	307	320	308	320	308	320	308
Not at all	9 (2.8%)	10 (3.3%)	6 (1.9%)	8 (2.6%)	7 (2.2%)	10 (3.2%)	6 (1.9%)	4 (1.3%)	6 (1.9%)	4 (1.3%)
1	12 (3.8%)	23 (7.5%)	8 (2.5%)	6 (2.0%)	14 (4.4%)	10 (3.2%)	8 (2.5%)	16 (5.2%)	9 (2.8%)	7 (2.3%)
2	35 (11.0%)	45 (14.7%)	22 (6.9%)	35 (11.4%)	24 (7.5%)	35 (11.4%)	26 (8.1%)	33 (10.7%)	20 (6.3%)	32 (10.4%)
3	93 (29.2%)	103 (33.6%)	87 (27.3%)	88 (28.7%)	81 (25.3%)	95 (30.8%)	85 (26.6%)	102 (33.1%)	84 (26.3%)	99 (32.1%)
Very much	170 (53.3%)	126 (41.0%)	196 (61.4%)	170 (55.4%)	194 (60.6%)	158 (51.3%)	195 (60.9%)	153 (49.7%)	201 (62.8%)	166 (53.9%)
Day 28										
n	315	304	315	304	315	303	316	303	315	305
Not at all	7 (2.2%)	10 (3.3%)	7 (2.2%)	5 (1.6%)	9 (2.9%)	13 (4.3%)	6 (1.9%)	9 (3.0%)	5 (1.6%)	5 (1.6%)
1	16 (5.1%)	17 (5.6%)	12 (3.8%)	17 (5.6%)	13 (4.1%)	14 (4.6%)	12 (3.8%)	12 (4.0%)	12 (3.8%)	10 (3.3%)
2	25 (7.9%)	46 (15.1%)	14 (4.4%)	23 (7.6%)	21 (6.7%)	23 (7.6%)	23 (7.3%)	25 (8.3%)	13 (4.1%)	30 (9.8%)
3	72 (22.9%)	92 (30.3%)	65 (20.6%)	79 (26.0%)	65 (20.6%)	91 (30.0%)	64 (20.3%)	86 (28.4%)	73 (23.2%)	85 (27.9%)
Very much	195 (61.9%)	139 (45.7%)	217 (68.9%)	180 (59.2%)	207 (65.7%)	162 (53.5%)	211 (66.8%)	171 (56.4%)	212 (67.3%)	175 (57.4%)
Day 84										
n	305	299	305	300	303	299	305	299	304	299
Not at all	7 (2.3%)	6 (2.0%)	4 (1.3%)	4 (1.3%)	9 (3.0%)	5 (1.7%)	7 (2.3%)	5 (1.7%)	8 (2.6%)	3 (1.0%)
1	5 (1.6%)	16 (5.4%)	7 (2.3%)	15 (5.0%)	9 (3.0%)	18 (6.0%)	8 (2.6%)	12 (4.0%)	6 (2.0%)	11 (3.7%)
2	19 (6.2%)	25 (8.4%)	17 (5.6%)	22 (7.3%)	18 (5.9%)	25 (8.4%)	17 (5.6%)	23 (7.7%)	15 (4.9%)	26 (8.7%)
3	67 (22.0%)	91 (30.4%)	54 (17.7%)	64 (21.3%)	52 (17.2%)	70 (23.4%)	52 (17.0%)	75 (25.1%)	61 (20.1%)	77 (25.8%)
Very much	207 (67.9%)	161 (53.8%)	223 (73.1%)	195 (65.0%)	215 (71.0%)	181 (60.5%)	221 (72.5%)	184 (61.5%)	214 (70.4%)	182 (60.9%)
Last observation										
n	324	311	324	312	324	312	324	312	324	312
Not at all	8 (2.5%)	6 (1.9%)	5 (1.5%)	5 (1.6%)	10 (3.1%)	6 (1.9%)	8 (2.5%)	6 (1.9%)	9 (2.8%)	4 (1.3%)
1	5 (1.5%)	17 (5.5%)	9 (2.8%)	15 (4.8%)	10 (3.1%)	19 (6.1%)	8 (2.5%)	13 (4.2%)	7 (2.2%)	12 (3.8%)
2	25 (7.7%)	28 (9.0%)	20 (6.2%)	24 (7.7%)	23 (7.1%)	26 (8.3%)	23 (7.1%)	23 (7.4%)	19 (5.9%)	27 (8.7%)
3	70 (21.6%)	91 (29.3%)	59 (18.2%)	66 (21.2%)	59 (18.2%)	72 (23.1%)	58 (17.9%)	77 (24.7%)	67 (20.7%)	80 (25.6%)
Very much	216 (66.7%)	169 (54.3%)	231 (71.3%)	202 (64.7%)	222 (68.5%)	189 (60.6%)	227 (70.1%)	193 (61.9%)	222 (68.5%)	189 (60.6%)

Table 13. Device Attributes and Subject Perceptions Questionnaire-Questions 11 to 15 - Observed Data - mITT Set

Visit	Question 11		Question 12		Question 13		Question 14		Question 15	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)

Question 11: Overall, how confident are you in your management of your weekly injections?
Question 12: How confident are you that you inject the right amount of medicine every time?
Question 13: How confident are you that you can inject yourself properly with the device?
Question 14: Are you confident that you have good control over the injection process?
Question 15: How confident are you that you injected yourself successfully?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 14. Device Attributes and Subject Perceptions Questionnaire - Questions 16 to 19 - Observed Data - mITT Set

Visit	Question 16		Question 17		Question 18		Question 19	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)
Baseline - after the training								
n	320	311	320	310	319	309	320	310
Not at all	149 (46.6%)	105 (33.8%)	156 (48.8%)	101 (32.6%)	207 (64.9%)	119 (38.5%)	188 (58.8%)	130 (41.9%)
1	84 (26.3%)	87 (28.0%)	80 (25.0%)	77 (24.8%)	60 (18.8%)	68 (22.0%)	73 (22.8%)	84 (27.1%)
2	39 (12.2%)	52 (16.7%)	47 (14.7%)	64 (20.6%)	30 (9.4%)	61 (19.7%)	37 (11.6%)	63 (20.3%)
3	39 (12.2%)	45 (14.5%)	30 (9.4%)	34 (11.0%)	16 (5.0%)	38 (12.3%)	16 (5.0%)	17 (5.5%)
Very much	9 (2.8%)	22 (7.1%)	7 (2.2%)	34 (11.0%)	6 (1.9%)	23 (7.4%)	6 (1.9%)	16 (5.2%)
Baseline - after the 1st injection								
n	319	308	320	308	319	308	320	308
Not at all	167 (52.4%)	129 (41.9%)	177 (55.3%)	119 (38.6%)	207 (64.9%)	136 (44.2%)	204 (63.8%)	143 (46.4%)
1	87 (27.3%)	93 (30.2%)	80 (25.0%)	96 (31.2%)	72 (22.6%)	76 (24.7%)	71 (22.2%)	92 (29.9%)
2	39 (12.2%)	37 (12.0%)	38 (11.9%)	43 (14.0%)	24 (7.5%)	46 (14.9%)	29 (9.1%)	45 (14.6%)
3	22 (6.9%)	31 (10.1%)	21 (6.6%)	29 (9.4%)	13 (4.1%)	29 (9.4%)	13 (4.1%)	19 (6.2%)
Very much	4 (1.3%)	18 (5.8%)	4 (1.3%)	21 (6.8%)	3 (0.9%)	21 (6.8%)	3 (0.9%)	9 (2.9%)
Day 28								
n	316	305	315	305	315	305	315	306
Not at all	179 (56.6%)	141 (46.2%)	194 (61.6%)	135 (44.3%)	215 (68.3%)	149 (48.9%)	218 (69.2%)	166 (54.2%)
1	81 (25.6%)	85 (27.9%)	68 (21.6%)	85 (27.9%)	58 (18.4%)	64 (21.0%)	53 (16.8%)	72 (23.5%)
2	32 (10.1%)	34 (11.1%)	34 (10.8%)	38 (12.5%)	26 (8.3%)	40 (13.1%)	33 (10.5%)	38 (12.4%)
3	18 (5.7%)	29 (9.5%)	11 (3.5%)	29 (9.5%)	11 (3.5%)	18 (5.9%)	7 (2.2%)	12 (3.9%)
Very much	6 (1.9%)	16 (5.2%)	8 (2.5%)	18 (5.9%)	5 (1.6%)	34 (11.1%)	4 (1.3%)	18 (5.9%)
Day 84								
n	306	300	305	299	305	300	306	299
Not at all	204 (66.7%)	147 (49.0%)	196 (64.3%)	137 (45.8%)	216 (70.8%)	138 (46.0%)	216 (70.6%)	171 (57.2%)
1	59 (19.3%)	76 (25.3%)	65 (21.3%)	83 (27.8%)	53 (17.4%)	66 (22.0%)	55 (18.0%)	68 (22.7%)
2	27 (8.8%)	45 (15.0%)	21 (6.9%)	37 (12.4%)	20 (6.6%)	43 (14.3%)	22 (7.2%)	26 (8.7%)
3	11 (3.6%)	21 (7.0%)	18 (5.9%)	25 (8.4%)	12 (3.9%)	29 (9.7%)	7 (2.3%)	19 (6.4%)
Very much	5 (1.6%)	11 (3.7%)	5 (1.6%)	17 (5.7%)	4 (1.3%)	24 (8.0%)	6 (2.0%)	15 (5.0%)
Last observation								
n	324	312	324	312	324	312	324	312
Not at all	209 (64.5%)	152 (48.7%)	205 (63.3%)	141 (45.2%)	226 (69.8%)	143 (45.8%)	225 (69.4%)	177 (56.7%)
1	68 (21.0%)	79 (25.3%)	70 (21.6%)	89 (28.5%)	57 (17.6%)	70 (22.4%)	60 (18.5%)	71 (22.8%)
2	29 (9.0%)	47 (15.1%)	23 (7.1%)	37 (11.9%)	24 (7.4%)	43 (13.8%)	25 (7.7%)	27 (8.7%)
3	12 (3.7%)	21 (6.7%)	20 (6.2%)	26 (8.3%)	12 (3.7%)	29 (9.3%)	7 (2.2%)	20 (6.4%)
Very much	6 (1.9%)	13 (4.2%)	6 (1.9%)	19 (6.1%)	5 (1.5%)	27 (8.7%)	7 (2.2%)	17 (5.4%)

Table 14. Device Attributes and Subject Perceptions Questionnaire - Questions 16 to 19 - Observed Data - mITT Set

Visit	Question 16		Question 17		Question 18		Question 19	
	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)	AI (N=324)	PFS (N=313)

Question 16: Overall, how nervous do you feel about your injections?
Question 17: Overall, how nervous do you feel about inserting the needle into your skin?
Question 18: Do you dislike injecting yourself with this device?
Question 19: Overall, are you emotionally distressed or anxious about your injections?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 15. Characteristics of the Device – Questions 20 to 22 - Observed Data - mITT Set

Visit	Question 20		Question 21		Question 22	
	AI N=324	PFS N=313	AI N=324	PFS N=313	AI N=324	PFS N=313
Baseline - after the training						
n	319	310	320	308	320	309
Not at all	8 (2.5%)	36 (11.6%)	8 (2.5%)	29 (9.4%)	12 (3.8%)	44 (14.2%)
1	11 (3.4%)	22 (7.1%)	10 (3.1%)	32 (10.4%)	15 (4.7%)	35 (11.3%)
2	80 (25.1%)	130 (41.9%)	81 (25.3%)	124 (40.3%)	75 (23.4%)	111 (35.9%)
3	116 (36.4%)	77 (24.8%)	117 (36.6%)	83 (26.9%)	107 (33.4%)	85 (27.5%)
Very much	104 (32.6%)	45 (14.5%)	104 (32.5%)	40 (13.0%)	111 (34.7%)	34 (11.0%)
Baseline - after the 1st injection						
n	320	307	320	305	320	305
Not at all	5 (1.6%)	32 (10.4%)	5 (1.6%)	26 (8.5%)	6 (1.9%)	40 (13.1%)
1	9 (2.8%)	25 (8.1%)	4 (1.3%)	21 (6.9%)	13 (4.1%)	26 (8.5%)
2	79 (24.7%)	135 (44.0%)	80 (25.0%)	136 (44.6%)	70 (21.9%)	111 (36.4%)
3	112 (35.0%)	72 (23.5%)	113 (35.3%)	82 (26.9%)	110 (34.4%)	94 (30.8%)
Very much	115 (35.9%)	43 (14.0%)	118 (36.9%)	40 (13.1%)	121 (37.8%)	34 (11.1%)
Day 28						
N	315	304	313	304	313	302
Not at all	4 (1.3%)	30 (9.9%)	3 (1.0%)	25 (8.2%)	13 (4.2%)	47 (15.6%)
1	14 (4.4%)	33 (10.9%)	11 (3.5%)	41 (13.5%)	20 (6.4%)	35 (11.6%)
2	64 (20.3%)	103 (33.9%)	64 (20.4%)	114 (37.5%)	56 (17.9%)	93 (30.8%)
3	109 (34.6%)	96 (31.6%)	121 (38.7%)	84 (27.6%)	98 (31.3%)	86 (28.5%)
Very much	124 (39.4%)	42 (13.8%)	114 (36.4%)	40 (13.2%)	126 (40.3%)	41 (13.6%)
Day 84						
N	304	298	304	296	302	297
Not at all	5 (1.6%)	31 (10.4%)	9 (3.0%)	28 (9.5%)	12 (4.0%)	36 (12.1%)
1	11 (3.6%)	30 (10.1%)	9 (3.0%)	32 (10.8%)	11 (3.6%)	26 (8.8%)
2	59 (19.4%)	107 (35.9%)	61 (20.1%)	104 (35.1%)	55 (18.2%)	94 (31.6%)
3	99 (32.6%)	74 (24.8%)	102 (33.6%)	80 (27.0%)	83 (27.5%)	86 (29.0%)
Very much	130 (42.8%)	56 (18.8%)	123 (40.5%)	52 (17.6%)	141 (46.7%)	55 (18.5%)
Last observation						
n	324	311	324	311	324	310
Not at all (%)	5 (1.5%)	31 (10.0%)	9 (2.8%)	28 (9.0%)	14 (4.3%)	38 (12.3%)
1	12 (3.7%)	32 (10.3%)	11 (3.4%)	34 (10.9%)	15 (4.6%)	27 (8.7%)
2	68 (21.0%)	114 (36.7%)	68 (21.0%)	111 (35.7%)	60 (18.5%)	100 (32.3%)
3	105 (32.4%)	77 (24.8%)	109 (33.6%)	84 (27.0%)	89 (27.5%)	89 (28.7%)
Very much	134 (41.4%)	57 (18.3%)	127 (39.2%)	54 (17.4%)	146 (45.1%)	56 (18.1%)

Table 15. Characteristics of the Device – Questions 20 to 22 - Observed Data - mITT Set

Visit	Question 20		Question 21		Question 22	
	AI N=324	PFS N=313	AI N=324	PFS N=313	AI N=324	PFS N=313

Question 20: How much do you like the look of the device?
Question 21: How much do you like the feel of the device?
Question 22: How much does the device look like something you would feel comfortable to use?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 16. Side Effects from Using the Device – Q23 - Observed Data - mITT Set

Visit	AI N=324	PFS N=313
Baseline – after the 1st injection		
n	318	307
None	137 (43.1%)	163 (53.1%)
1	105 (33.0%)	90 (29.3%)
2	47 (14.8%)	37 (12.1%)
3	20 (6.3%)	15 (4.9%)
Severe	9 (2.8%)	2 (0.7%)
Day 28		
n	316	305
None	105 (33.2%)	121 (39.7%)
1	108 (34.2%)	109 (35.7%)
2	56 (17.7%)	46 (15.1%)
3	37 (11.7%)	23 (7.5%)
Severe	10 (3.2%)	6 (2.0%)
Day 84		
n	304	298
None	110 (36.2%)	118 (39.6%)
1	85 (28.0%)	89 (29.9%)
2	62 (20.4%)	53 (17.8%)
3	36 (11.8%)	27 (9.1%)
Severe	11 (3.6%)	11 (3.7%)

Q23: Do you experience pain during or immediately after the injection?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe.

Table 17. Device Attributes and Subject Perceptions Questionnaire - Q24 - Observed Data - mITT

Visit	AI N=324	PFS N=313
Baseline - after the training		
n	244	236
Very little	118 (48.4%)	45 (19.1%)
1	38 (15.6%)	37 (15.7%)
2	34 (13.9%)	67 (28.4%)
3	23 (9.4%)	40 (16.9%)
Very much	31 (12.7%)	47 (19.9%)
Baseline - after the 1st injection		
n	253	239
Very little	127 (50.2%)	53 (22.2%)
1	44 (17.4%)	42 (17.6%)
2	41 (16.2%)	64 (26.8%)
3	16 (6.3%)	36 (15.1%)
Very much	25 (9.9%)	44 (18.4%)
Day 28		
n	248	236
Very little	128 (51.6%)	63 (26.7%)
1	35 (14.1%)	37 (15.7%)
2	34 (13.7%)	59 (25.0%)
3	21 (8.5%)	40 (16.9%)
Very much	30 (12.1%)	37 (15.7%)
Day 84		
n	240	232
Very little	117 (48.8%)	66 (28.4%)
1	21 (8.8%)	49 (21.1%)
2	50 (20.8%)	53 (22.8%)
3	20 (8.3%)	26 (11.2%)
Very much	32 (13.3%)	38 (16.4%)
Last observation		
n	255	242
Very little	123 (48.2%)	68 (28.1%)
1	24 (9.4%)	50 (20.7%)
2	53 (20.8%)	56 (23.1%)
3	21 (8.2%)	28 (11.6%)
Very much	34 (13.3%)	40 (16.5%)

Q24: To what extent would you consider alternative devices if you were to continue on etanercept?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects in each visit; N = total number of subjects in each device group; PFS = pre-filled syringe.

Table 18. Device Attributes and Subject Perceptions Questionnaire - Q25 - Observed Data - mITT

Visit	AI N=324	PFS N=313
Baseline - after the training		
n	308	304
Not at all	6 (1.9%)	21 (6.9%)
1	9 (2.9%)	27 (8.9%)
2	26 (8.4%)	91 (29.9%)
3	46 (14.9%)	62 (20.4%)
Yes definitely	221 (71.8%)	103 (33.9%)
Baseline - after the 1st injection		
n	319	307
Not at all	6 (1.9%)	14 (4.6%)
1	7 (2.2%)	25 (8.1%)
2	32 (10.0%)	83 (27.0%)
3	46 (14.4%)	82 (26.7%)
Yes definitely	228 (71.5%)	103 (33.6%)
Day 28		
n	316	306
Not at all	9 (2.8%)	14 (4.6%)
1	10 (3.2%)	31 (10.1%)
2	24 (7.6%)	62 (20.3%)
3	43 (13.6%)	72 (23.5%)
Yes definitely	230 (72.8%)	127 (41.5%)
Day 84		
n	301	296
Not at all	10 (3.3%)	13 (4.4%)
1	7 (2.3%)	16 (5.4%)
2	23 (7.6%)	73 (24.7%)
3	37 (12.3%)	57 (19.3%)
Yes definitely	224 (74.4%)	137 (46.3%)
Last observation		
n	324	313
Not at all	13 (4.0%)	14 (4.5%)
1	9 (2.8%)	17 (5.4%)
2	27 (8.3%)	76 (24.3%)
3	42 (13.0%)	63 (20.1%)
Yes definitely	233 (71.9%)	143 (45.7%)

Q25: Would you recommend this device to someone else who needed to self inject?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects in each visit; N = number of subjects in each device group; PFS = pre-filled syringe.

Table 19. Device Attributes and Subject Perceptions Questionnaire - Q26 - Observed Data - mITT

Visit	AI N=324	PFS N=313
Day 84		
n	301	297
Not at all	9 (3.0%)	11 (3.7%)
1	9 (3.0%)	23 (7.7%)
2	28 (9.3%)	53 (17.8%)
3	33 (11.0%)	56 (18.9%)
Very likely	222 (73.8%)	154 (51.9%)

Q26: If your doctor advised you to, how likely would you to be continue injecting regularly with this device?
AI = auto-injector; mITT = modified intent-to-treat; n = number of subjects in each visit; N = total number of subjects in each device group; PFS = pre-filled syringe.

Table 20. SF-STAI: Global Score (6-24)[a] - Observed Data - mITT Set

Visit	AI N=324	PFS N=313
Baseline - after the training		
n	314	310
Mean (SD)	10.3 (3.6)	11.4 (3.7)
Median	10	11
Min, Max	6.0, 23.0	6.0, 23.0
Baseline - after the 1st injection		
n	319	308
Mean (SD)	9.7 (3.5)	10.8 (3.5)
Median	9	10
Min, Max	6.0, 23.0	6.0, 23.0
Day 28		
n	315	304
Mean (SD)	10.1 (3.5)	10.7 (3.5)
Median	9	10.4
Min, Max	6.0 , 21.0	6.0, 22.0
Day 84		
n	303	298
Mean (SD)	10.0 (3.7)	10.5 (3.4)
Median	9	10
Min, Max	6.0, 21.0	6.0, 21.0
Last observation		
n	324	312
Mean (SD)	10.2 (3.7)	10.6 (3.4)
Median	9.8	10
Min, Max	6.0, 21.0	6.0, 21.0

AI = auto-injector; mITT = modified intent-to-treat; Max = maximum; Min = minimum; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe; SD = standard deviation; SF-STAI = Short form State-Trait Anxiety Inventory.
a. The higher the score was, the more anxious the subject was.

Subject and RA Attributes Associated with Subject Perceptions: Results in both AI and PFS groups were similar. 'Very satisfied' subjects were the more involved in the management of their health condition, while 'less satisfied' subjects were the most anxious and depressed.

The subject and RA attributes associated with subject perceptions at last observation by clusters are presented in Table 21.

Table 21. Subject and Rheumatoid Arthritis Attributes Associated With Subject Perceptions at Last Observation by Clusters, mITT Population

	AI (N=302)			PFS (N=296)		
Subject/RA Attributes	**Very Satisfied n=204**	**Satisfied n=51**	**Less Satisfied n=47**	**Very Satisfied n=133**	**Satisfied n=71**	**Less Satisfied n=92**
Gender						
n	204	51	47	133	71[a]	92[b]
Men	63 (30.9%)	12 (23.5%)	7 (14.9%)	40 (30.1%)	21 (29.6%)	13 (14.1%)
Women	141 (69.1%)	39 (76.5%)	40 (85.1%)	93 (69.9%)	50 (70.4%)	79 (85.9%)
HAD anxiety subscale score at baseline (0-21)						
n	203	51	47	132	71	92
Mean (SD)	6.8 (4.2)	7.9 (3.8)	8.3 (3.7)	6.4 (4.5)	7.4 (4.0)	8.7 (3.8)
Median	6.0	8.0	8.0	6.0	7.0[a]	8.0[b]
Min, max	0.0, 18.0	1.0, 15.0	1.0, 18.0	0.0, 19.0	0.0, 19.0	1.0, 19.0
HAD depression subscale score at baseline (0-21)						
n	203	51	47	133	71	92
Mean (SD)	5.8 (3.8)	6.6 (3.9)	7.3 (4.1)	5.0 (3.9)	5.2 (3.5)	6.7 (3.6)
Median	5.0	5.8	7.0	4.0	4.7	6.0
Min, max	0.0, 18.0	1.0, 18.0	1.0, 17.5	0.0, 18.7	0.0, 14.0	0.0, 16.0
PAM (%)						
n	198	51	47	131	71	91
Mean (SD)	61.6 (13.3)[c]	56.6 (11.5)	57.4 (13.8)	60.1 (14.0)	56.5 (11.7)	55.3 (11.9)[b]
Median	56.4	56.4	56.4	56.4	52.9	56.4
Min, max	37.3, 100.0	33.5, 86.3	33.5, 91.6	8.2, 100.0	36.0, 86.3	27.1, 100.0
Prior injection experience						
n	204	51[a]	47[b]	133	71	92
Yes	108 (52.9%)	24 (47.1%)	33 (70.2%)	73 (54.9%)	39 (54.9%)	55 (59.8%)
No	96 (47.1%)	27 (52.9%)	14 (29.8%)	60 (45.1%)	32 (45.1%)	37 (40.2%)
Prior self-injection experience						
n	204[c]	51[a]	47	133	71	92
Yes	65 (31.9%)	8 (15.7%)	18 (38.3%)	42 (31.6%)	26 (36.6%)	29 (31.5%)
No	139 (68.1%)	43 (84.3%)	29 (61.7%)	91 (68.4%)	45 (63.4%)	63 (68.5%)
DAS28 at screening						
n	197	50	45	128	70	89
Mean (SD)	5.3 (1.1)	5.4 (1.3)	5.5 (1.1)	5.5 (1.1)	5.0 (1.3)	5.5 (1.2)
Median	5.2	5.3	5.5	5.5[c]	4.9[a]	5.4
Min, max	2.1, 8.8	2.1, 8.2	2.6, 7.5	3.0, 8.2	2.1, 7.4	1.7, 8.5
Subject's global assessment of RA activity at screening						
n	202	50	46	132	71	91
Mean (SD)	63.5 (20.2)	64.7 (19.2)	65.7 (19.5)	62.5 (21.4)	57.5 (24.0)[a]	68.2 (17.6)[b]
Median	68.0	67.3	69.5	65.0	62.0	70.5
Min, max	8.0, 98.0	5.0, 100.0	4.0, 97.0	10.0, 100.0	3.0, 100.0	25.5, 97.0
HAQ-DI at baseline						
n	204	51	45	133	71	92
Mean (SD)	1.4 (0.7)	1.5 (0.6)	1.5 (0.6)	1.3 (0.7)	1.3 (0.6)	1.6 (0.6)
Median	1.4	1.5	1.6	1.4	1.3[a]	1.6[b]
Min, max	0.0, 2.9	0.4, 2.9	0.0, 2.6	0.0, 2.8	0.0, 2.9	0.0, 2.6

AI = auto-injector; DAS28 = Disease Activity Score based on a 28-joint count; HAD = Hospital Anxiety Depression; HAQ-DI = Health Assessment Questionnaire – Disability Index; max = maximum; min = minimum; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PAM = Patient Activation Measure; PFS = pre-filled syringe; RA = rheumatoid arthritis; SD = standard deviation.

a. Cluster satisfied statistically significantly different from cluster less satisfied.
b. Cluster less satisfied statistically significantly different from cluster very satisfied.
c. Cluster very satisfied statistically significantly different from cluster satisfied.

Other Efficacy Criteria: Subject's and physician's global assessments of efficacy measured on a 0 (no efficacy) to 100 (very effective) scale, subject's global assessment of general health measured on a 0 (extremely bad) to 100 (very well) scale, HAQ-DI measured on a 0 (good) to 3 (bad) scale and DAS28 in the mITT population are presented in Table 22.

Table 22. Other Efficacy Criteria: Subject's and Physician's Global Assessments, HAQ-DI and DAS28, mITT Population

	AI N=324	PFS N=313
SGA of efficacy		
Day 84		
n	305	296
Mean (SD)	72.1 (26.0)	69.5 (27.7)
Median	80.0	80.0
Min, max	0.0, 100.0	0.0, 100.0
Change between baseline and Day 84		
n	259	255
Mean (SD)	22.6 (35.9)	20.3 (36.8)
Median	27.0	24.0
Min, max	-87.5, 97.0	-84.5, 98.0
SGA of general health		
Day 84		
n	301	295
Mean (SD)	65.7 (24.1)	67.2 (24.2)
Median	69.0	72.0
Min, max	0.0, 100.0	2.0, 100.0
Change between screening and Day 84		
n	295	293
Mean (SD)	17.2 (28.2)	19.3 (29.0)
Median	16.5	18.0
Min, max	-72.0, 86.0	-47.0, 96.5
HAQ-DI (0-3)		
Day 84		
n	307	302
Mean (SD)	0.9 (0.7)	0.9 (0.7)
Median	0.9	0.9
Min, max	0.0, 2.9	0.0, 2.9
Change between baseline and Day 84		
n	306	302
Mean (SD)	-0.5 (0.6)	-0.5 (0.6)
Median	-0.4	-0.4
Min, max	-2.6, 1.1	-2.6, 1.1
PGA of efficacy		
Day 84		
n	306	302
Mean (SD)	72.3 (24.4)	72.2 (23.4)
Median	80.0	79.0
Min, max	0.0, 100.0	0.0, 100.0
Change between baseline and Day 84		
n	286	276
Mean (SD)	26.6 (32.5)	28.6 (30.1)
Median	31.0	31.5
Min, max	-82.5, 92.0	-85.0, 90.0
DAS28		
Day 84		
n	258	264
Mean (SD)	3.5 (1.4)	3.5 (1.4)
Median	3.3	3.3

Table 22. Other Efficacy Criteria: Subject's and Physician's Global Assessments, HAQ-DI and DAS28, mITT Population

	AI N=324	PFS N=313
Min, max	0.7, 7.9	0.6, 7.8
Change between screening and Day 84		
n	250	257
Mean (SD)	-1.9 (1.3)	-1.8 (1.4)
Median	-1.9	-1.8
Min, max	-5.4, 1.9	-6.0, 2.3

AI = auto-injector; DAS28 = disease activity score based on a 28-joint count; HAQ-DI = health assessment questionnaire-disability index; mITT = modified intent-to-treat; n = number of subjects at each visit; N = number of subjects; PFS = pre-filled syringe; PGA = physician's global assessment; SD = standard deviation; SGA = subject's global assessment.

Safety Results: A total of 1366 AEs were reported by 412 subjects during the study of which 828 AEs (60.6%) were considered related to etanercept. For most AEs, no action was taken. Medications were prescribed for 23.7% of the AEs and temporary discontinuation of test article was required for 51 (3.7%) AEs. Nineteen (1.4%) AEs led to permanent discontinuation of test article, 21 AEs led to study withdrawal and 27 AEs led to hospitalization. The number of subjects reporting AEs from the day of the first injection of Etanercept is summarized in Table 23.

Table 23. Summary of Adverse Events from the Day of the First Injection of Etanercept, Safety Population

	AI N=325	PFS N=313	Total N=638
Number (%) of subjects with at least 1 AE	209 (64.3%)	203 (64.9%)	412 (64.6%)
Number of AEs	601	765	1366
Number (%) of subjects with at least 1 AE related to study product	143 (44.0%)	141 (45.0%)	284 (44.5%)
Number of AEs related to study product	361	467	828
Number (%) of subjects with at least 1 SAE	18 (5.5%)	9 (2.9%)	27 (4.2%)
Number of SAEs	23	16	39
Number (%) of subjects with at least 1 SAE related to study product	5 (1.5%)	5 (1.6%)	10 (1.6%)
Number of SAEs related to study product	6	7	13
Number (%) of subjects with at least 1 AE leading to study withdrawal	13 (4.0%)	5 (1.6%)	18 (2.8%)
Number of AEs leading to study withdrawal	15	6	21
Number (%) of subjects with at least 1 AE leading to test article permanent discontinuation	7 (2.2%)	9 (2.9%)	16 (2.5%)
Number of AEs leading to test article permanent discontinuation	9	10	19

AE/SAE results are not separated out.
AE = adverse event; AI= auto-injector; N = number of subjects; PFS = pre-filled syringe; SAE = serious adverse event.

A summary of all-causality AEs reported by ≥2% of subjects is presented in Table 24.

Table 24. Adverse Events (≥2% subjects) - From the Day of the First Injection of Etanercept - Safety Set

System Organ Class Preferred Term	AI N=325	PFS N=313	Total N=638
	n (%)	n (%)	n (%)
All	209 (64.3%)	203 (64.9%)	412 (64.6%)
General disorders and administration site conditions	110 (33.8%)	116 (37.1%)	226 (35.4%)
Injection site erythema	25 (7.7%)	29 (9.3%)	54 (8.5%)
Injection site haematoma	15 (4.6%)	6 (1.9%)	21 (3.3%)
Injection site pain	20 (6.2%)	13 (4.2%)	33 (5.2%)
Injection site reaction	46 (14.2%)	55 (17.6%)	101 (15.8%)
Injection site haemorrhage	10 (3.1%)	6 (1.9%)	16 (2.5%)
Injection site irritation	3 (0.9%)	10 (3.2%)	13 (2.0%)
Infections and infestations	79 (24.3%)	86 (27.5%)	165 (25.9%)
Nasopharyngitis	22 (6.8%)	26 (8.3%)	48 (7.5%)
Bronchitis	7 (2.2%)	12 (3.8%)	19 (3.0%)
Influenza	9 (2.8%)	8 (2.6%)	17 (2.7%)
Upper respiratory tract infection	9 (2.8%)	2 (0.6%)	11 (1.7%)
Urinary tract infection	5 (1.5%)	9 (2.9%)	14 (2.2%)
Gastrointestinal disorders	22 (6.8%)	23 (7.3%)	45 (7.1%)
Nausea	7 (2.2%)	9 (2.9%)	16 (2.5%)
Musculoskeletal and connective tissue disorders	27 (8.3%)	35 (11.2%)	62 (9.7%)
Rheumatoid arthritis	6 (1.8%)	10 (3.2%)	16 (2.5%)
Nervous system disorders	20 (6.2%)	16 (5.1%)	36 (5.6%)
Headache	9 (2.8%)	6 (1.9%)	15 (2.4%)
Skin and subcutaneous tissue disorders	18 (5.5%)	29 (9.3%)	47 (7.4%)
Pruritus	6 (1.8%)	9 (2.9%)	15 (2.4%)

AE/SAE results are not separated out.
AE = adverse event; AI= auto-injector; N = number of subjects; n = number of subjects with adverse events; PFS = pre-filled syringe; SAE = serious adverse event.

More than half of the AEs reported during the study were considered related to study product. There was no statistically significant difference between the 2 groups for the report of AEs related to study product.

Overall, when all injection site reactions (ISR) were pooled (injection site dermatitis, erythema, haematoma, haemorrhage, induration, inflammation, irritation, pain, pruritus, rash, reaction, swelling and urticaria), 97 subjects in the AI group (29.8%), and 107 subjects in the PFS group (34.2%) reported at least 1 ISR for a total of 265 and 333 events, respectively. The most frequent AEs related to study product were administration site conditions: injection site reaction, injection site erythema and injection site pain. There was no statistically significant difference between the 2 groups in the number of subjects reporting ISR. Most ISR (570/598) were considered related to study product. No ISR was considered a serious adverse event (SAE). A summary of treatment related adverse events reported by ≥2% subjects is presented in Table 25.

Table 25. Treatment Related Adverse Events With ≥2% Threshold

System Organ Class Preferred Term	AI N=325	PFS N=313	Total N=638
	n (%)	n (%)	n (%)
All	143 (44.0%)	141 (45.0%)	284 (44.5%)
General disorders and administration site conditions	100 (30.8%)	106 (33.9%)	206 (32.3%)
Injection site erythema	25 (7.7%)	28 (8.9%)	53 (8.3%)
Injection site haematoma	11 (3.4%)	5 (1.6%)	16 (2.5%)
Injection site haemorrhage	8 (2.5%)	4 (1.3%)	12 (1.9%)
Injection site irritation	3 (0.9%)	9 (2.9%)	12 (1.9%)
Injection site pain	19 (5.8%)	13 (4.2%)	32 (5.0%)
Injection site rash	2 (0.6%)	7 (2.2%)	9 (1.4%)
Injection site reaction	46 (14.2%)	53 (16.9%)	99 (15.5%)
Infections and infestations	34 (10.5%)	28 (8.9%)	62 (9.7%)
Nasopharyngitis	8 (2.5%)	4 (1.3%)	12 (1.9%)
Skin and subcutaneous tissue disorders	15 (4.6%)	19 (6.1%)	34 (5.3%)
Pruritus	5 (1.5%)	7 (2.2%)	12 (1.9%)

AE/SAE results are not separated out.
AE = adverse event; AI= auto-injector; N = number of subjects; n = number of subjects with adverse events; PFS = pre-filled syringe; SAE = serious adverse event.

Twenty-seven (27, 4.2%) subjects reported SAEs during this study from the day of the first injection of etanercept, 9 subjects in the PFS group and 18 subjects in the AI group. Thirteen (13/39, 33%) of these SAEs were considered related to the study product.

All causality serious adverse events (SAEs) are presented in Table 26 and treatment related SAEs in Table 27.

Table 26. Serious Adverse Events - From the Day of the First Injection of Etanercept - Safety Set

System Organ Class Preferred Term	AI N=325	PFS N=313	Total N=638
	n (%)	n (%)	n (%)
All	18 (5.5%)	9 (2.9%)	27 (4.2%)
Blood and lymphatic system disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Anaemia	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cardiac disorders	1 (0.3%)	0 (0.0%)	1 (0.2%)
Palpitations	1 (0.3%)	0 (0.0%)	1 (0.2%)
Sinus bradycardia	1 (0.3%)	0 (0.0%)	1 (0.2%)
Eye disorders	1 (0.3%)	0 (0.0%)	1 (0.2%)
Retinal vein thrombosis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Gastrointestinal disorders	2 (0.6%)	2 (0.6%)	4 (0.6%)
Abdominal pain upper	0 (0.0%)	1 (0.3%)	1 (0.2%)
Diarrhoea	1 (0.3%)	0 (0.0%)	1 (0.2%)
Gastric ulcer	0 (0.0%)	1 (0.3%)	1 (0.2%)
Intestinal haemorrhage	1 (0.3%)	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions	1 (0.3%)	1 (0.3%)	2 (0.3%)
Pain	1 (0.3%)	0 (0.0%)	1 (0.2%)
Pyrexia	0 (0.0%)	1 (0.3%)	1 (0.2%)
Infections and infestations	4 (1.2%)	4 (1.3%)	8 (1.3%)
Bronchitis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Cystitis	0 (0.0%)	2 (0.6%)	2 (0.3%)
Erysipelas	1 (0.3%)	0 (0.0%)	1 (0.2%)
Groin abscess	1 (0.3%)	0 (0.0%)	1 (0.2%)
Herpes zoster	0 (0.0%)	1 (0.3%)	1 (0.2%)
Infection	0 (0.0%)	1 (0.3%)	1 (0.2%)
Respiratory tract infection	1 (0.3%)	0 (0.0%)	1 (0.2%)
Sinusitis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.3%)	0 (0.0%)	1 (0.2%)
Complication of device insertion	1 (0.3%)	0 (0.0%)	1 (0.2%)
Investigations	0 (0.0%)	1 (0.3%)	1 (0.2%)
Heart rate irregular	0 (0.0%)	1 (0.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	3 (0.9%)	1 (0.3%)	4 (0.6%)
Bursitis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Muscular weakness	1 (0.3%)	0 (0.0%)	1 (0.2%)
Osteoarthritis	0 (0.0%)	1 (0.3%)	1 (0.2%)
Rheumatoid arthritis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Lymphoma	0 (0.0%)	1 (0.3%)	1 (0.2%)
Prostate cancer	1 (0.3%)	0 (0.0%)	1 (0.2%)
Nervous system disorders	4 (1.2%)	1 (0.3%)	5 (0.8%)
Cerebral infarction	1 (0.3%)	0 (0.0%)	1 (0.2%)
Cervical root pain	1 (0.3%)	0 (0.0%)	1 (0.2%)
Dizziness	1 (0.3%)	1 (0.3%)	2 (0.3%)
Syncope vasovagal	1 (0.3%)	0 (0.0%)	1 (0.2%)
Renal and urinary disorders	0 (0.0%)	1 (0.3%)	1 (0.2%)
Renal failure	0 (0.0%)	1 (0.3%)	1 (0.2%)
Reproductive system and breast disorders	1 (0.3%)	0 (0.0%)	1 (0.2%)
Nipple disorder	1 (0.3%)	0 (0.0%)	1 (0.2%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (0.3%)	1 (0.2%)
Rash pruritic	0 (0.0%)	1 (0.3%)	1 (0.2%)

Table 26. Serious Adverse Events - From the Day of the First Injection of Etanercept - Safety Set

System Organ Class Preferred Term	AI N=325	PFS N=313	Total N=638
	n (%)	n (%)	n (%)
Surgical and medical procedures	1 (0.3%)	1 (0.3%)	2 (0.3%)
Breast cyst excision	0 (0.0%)	1 (0.3%)	1 (0.2%)
Knee arthroplasty	1 (0.3%)	0 (0.0%)	1 (0.2%)

AI = auto-injector; N = number of subjects; n = number of subjects with adverse events; PFS = pre-filled syringe.

Table 27. Treatment Related Serious Adverse Events

System Organ Class Preferred Term	AI N=325	PFS N=313	Total N=638
	n (%)	n (%)	n (%)
All	5 (1.5)	5 (1.6)	10 (1.6)
Eye disorders	1 (0.3)	0 (0.0)	1 (0.2)
Retinal vein thrombosis	1 (0.3%)	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions	0 (0.0%)	1 (0.3%)	1 (0.2%)
Pyrexia	0 (0.0%)	1 (0.3%)	1 (0.2%)
Infections and infestations	2 (0.6%)	4 (1.3%)	6 (0.9%)
Cystitis	0 (0.0%)	2 (0.6%)	2 (0.3%)
Erysipelas	1 (0.3%)	0 (0.0%)	1 (0.2%)
Herpes zoster	0 (0.0%)	1 (0.3%)	1 (0.2%)
Infection	0 (0.0%)	1 (0.3%)	1 (0.2%)
Respiratory tract infection	1 (0.3%)	0 (0.0%)	1 (0.2%)
Sinusitis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.3%)	0 (0.0%)	1 (0.2%)
Bursitis	1 (0.3%)	0 (0.0%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Lymphoma	0 (0.0%)	1 (0.3%)	1 (0.2%)
Reproductive system and breast disorders	1 (0.3%)	0 (0.0%)	1 (0.2%)
Nipple disorder	1 (0.3%)	0 (0.0%)	1 (0.2%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (0.3%)	1 (0.2%)
Rash pruritic	0 (0.0%)	1 (0.3%)	1 (0.2%)

AI = auto-injector; N = number of subjects; n = number of subjects with adverse events; PFS = pre-filled syringe.

Safety Related Discontinuations: A total of 18 subjects (2.8%) experienced AEs that led to study withdrawal: 13 (4.0%) in the AI group and 5 subjects (1.6%) in the PFS group. Sixteen (16) subjects (2.5%) experienced AEs leading to test article permanent discontinuation: 7 (2.2%) in the AI group and 9 (2.9%) in the PFS group. There was no statistically significant difference between the 2 groups concerning the AEs leading to study withdrawal (p=0.093) or the AEs leading to test article permanent discontinuation (p=0.619). The AEs leading to study withdrawal or test article permanent discontinuation are summarized in Table 28 and Table 29 respectively.

Table 28. Adverse Events Leading to Study Withdrawal From the Day of the First Injection of Etanercept, Safety Population

System Organ Class Preferred Term	AI N=325 n (%) Subjects	PFS N=313 n (%) Subjects	Total N=638 n (%) Subjects
All	13 (4.0%)	5 (1.6%)	18 (2.8%)
Blood and lymphatic system disorders	1 (0.3%)	0	1 (0.2%)
Lymphadenopathy	1 (0.3%)	0	1 (0.2%)
Cardiac disorders	1 (0.3%)	0	1 (0.2%)
Palpitations	1 (0.3%)	0	1 (0.2%)
Sinus bradycardia	1 (0.3%)	0	1 (0.2%)
Gastrointestinal disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Intestinal haemorrhage	1 (0.3%)	0	1 (0.2%)
Irritable bowel syndrome	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	3 (0.9%)	1 (0.3%)	4 (0.6%)
Injection site erythema	2 (0.6%)	0	2 (0.3%)
Injection site reaction	1 (0.3%)	1 (0.3%)	2 (0.3%)
Infections and infestations	2 (0.6%)	1 (0.3%)	3 (0.5%)
Herpes zoster	0	1 (0.3%)	1 (0.2%)
Pneumonia	1 (0.3%)	0	1 (0.2%)
Sinusitis	1 (0.3%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	2 (0.6%)	0	2 (0.3%)
Arthralgia	1 (0.3%)	0	1 (0.2%)
Myalgia	1 (0.3%)	0	1 (0.2%)
Nervous system disorders	1 (0.3%)	0	1 (0.2%)
Dizziness	1 (0.3%)	0	1 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.3%)	2 (0.6%)	3 (0.5%)
Alopecia	0	1 (0.3%)	1 (0.2%)
Erythema	1 (0.3%)	0	1 (0.2%)
Pruritus	0	1 (0.3%)	1 (0.2%)
Surgical and medical procedures	1 (0.3%)	0	1 (0.2%)
Cervix operation	1 (0.3%)	0	1 (0.2%)
Vascular disorders	1 (0.3%)	0	1 (0.2%)
Phlebitis	1 (0.3%)	0	1 (0.2%)

AEs = adverse events; AI = auto-injector; N = number of subjects; n = number of subjects with adverse events; PFS = pre-filled syringe.

Table 29. Adverse Events Leading to Test Article Permanent Discontinuation From the Day of the First Injection of Etanercept, Safety Population

System Organ Class Preferred Term	AI N=325 n (%)	PFS N=313 n (%)	Total N=638 n (%)
All	7 (2.2%)	9 (2.9%)	16 (2.5%)
General disorders and administration site conditions	2 (0.6%)	6 (1.9%)	8 (1.3%)
Injection site erythema	0	1 (0.3%)	1 (0.2%)
Injection site reaction	1 (0.3%)	4 (1.3%)	5 (0.8%)
Injection site swelling	1 (0.3%)	0	1 (0.2%)
Swelling	0	1 (0.3%)	1 (0.2%)
Immune system disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Drug hypersensitivity	1 (0.3%)	0	1 (0.2%)
Hypersensitivity	0	1 (0.3%)	1 (0.2%)
Infections and infestations	2 (0.6%)	2 (0.6%)	4 (0.6%)
Infection	0	1 (0.3%)	1 (0.2%)
Pneumonia	1 (0.3%)	0	1 (0.2%)
Respiratory tract infection	1 (0.3%)	0	1 (0.2%)
Sinusitis	1 (0.3%)	1 (0.3%)	2 (0.3%)
Injury, poisoning and procedural complications	1 (0.3%)	0	1 (0.2%)
Joint dislocation	1 (0.3%)	0	1 (0.2%)
Nervous system disorders	1 (0.3%)	0	1 (0.2%)
Syncope vasovagal	1 (0.3%)	0	1 (0.2%)
Vascular disorders	1 (0.3%)	0	1 (0.2%)
Phlebitis	1 (0.3%)	0	1 (0.2%)

AEs = adverse events; AI = auto-injector; N = number of subjects; n = number of subjects with adverse events; PFS = pre-filled syringe.

Deaths: There were no deaths during the study.

Vitals: Vital signs results were similar in both groups, and mean values were stable during the course of the study.

CONCLUSION: In conclusion, this study showed high subject satisfaction when injecting etanercept either as a pre-filled syringe or in the auto-injector, with satisfaction being even higher in the group of subjects using the auto-injector. Characteristics were identified to be associated with subject perceptions, with subjects more involved in the management of their health condition showing higher percentages of subjects who were 'very satisfied', while subjects who were more anxious and depressed, as measured by HAD subscales scores, were more often into the 'less satisfied' category.

Whatever the device, the beneficial effect on health status and RA activity of etanercept could be observed after 12 weeks of treatment with the 50 mg once weekly regimen. The overall safety profile was comparable for both devices and in keeping with the profile as understood to date, with no new signals.