CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

103795/5123

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DURG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics (HFM-215)

Statistical Review

FDA NUMBER:	103795/5123
TASK TYPE:	sBLA
SPONSOR:	Amgen, Inc.
PRODUCT:	Enbrel (Etanercept)
INDICATION:	Akylosing Spondylitis
DATE:	30 April 2003
FROM:	Chao Wang, PhD (HFM-219)
TO:	William Tauber, MD (HFM-570)
THROUGH:	G. Gupta, PhD (HFM-219)
CC:	Original/DCC (HFM-99)
	ChronFile (HFM-210)
	S Ellenberg, PhD (HFM-215)
	P A Lachenbruch, PhD (HFM-215)
	K Jones (HFM-588)

/S/

/S/ 6-27-03

Table of Contents

List of Tables

Introduction

This sBLA submission contains 3 clinical study reports to support the label expension to include indication for ankylosing spondylitis. Among them, study 016.0037 is a phase 3 trial (N=277) conducted under IND. This study will be the focus of this review. Study 47687 is also a phase 3 (N=84) that was not conducted under IND. Study 016.0626 is a phase 2 trial (N=40). These two studies will not be reviewed because of the small size.

Upon prior agreement with the FDA, no integrated summaries of efficacy and safety were submitted by the sponsor.

Statistical Review

Study 016.0037

Study Design

This study was entitled "Multicenter, Double-blind, Placebo-controlled, Randomized Phase 3 Study of Etanercept (ENBREL®) in the Treatment of Patients with Ankylosing Spondylitis (AS)."

Patients who met the eligibility criteria were randomized to receive placebo or etanercept, 25 mg subcutaneously (SC) twice weekly, for 24 weeks in a blinded fashion. Prior to randomization, patients were stratified based upon concomitant disease-modifying antirheumatic drugs (DMARDs) at baseline; allowable DMARDs included hydroxychloroquine, sulfasalazine, and methotrexate. Patients were randomized with equal allocation within each stratum to either etanercept or placebo. Efficacy and safety evaluations were performed at Weeks 2, 4, 8, 12, and 24.

Twenty eight (28) US centers participated in the study.

Objective

Primary objective

- To evaluate the proportions of patients with AS treated with etanercept at a dose of 25 mg twice weekly, relative to placebo, who achieved the Assessments in Ankylosing Spondylitis Response Criteria (ASAS 20) at Week 12.

Conditional primary objective to be assessed if the primary objective was met

- ASAS 20 at Week 24.

Secondary objectives

- Comparisons of the proportions of patients who achieved higher levels of response (ASAS 50 and ASAS 70) at Weeks 12 and 24;
- Proportions of patients who achieved the ASAS definition of partial remission and the time to partial remission;
- Safety of etanercept in patients with AS.

Tertiary objectives

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),
- Spinal mobility (modified Schober's test, chest expansion score, and occiput-to-wall measurements),
- Peripheral joint counts,
- Acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]),
- Assessor global assessments over time in the study,
- Patient-reported improvement at Week 2 of the study.

Definitions

ASAS 20

An improvement of at least 20% and absolute improvement of at least 10 units on a 0-100 scale in at least 3 of the following domains:

- Patient global assessment represented by VAS global assessment (0-100 mm scale)
- Pain assessment represented by the average of VAS total and nocturnal pain scores (each on a 0-100 mm scale)
- Function represented by BASFI (average of 10 VAS, each a 0-100 mm scale)
- Inflammation represented by the average of the last two VAS (0-100 mm scale) in the BASDAI concerning morning stiffness intensity and duration

- Absence of deterioration (of at least 20% and absolute change of at least 10 units on a 0-100 scale) in the potential remaining domain

Partial remission

Value of < 20 (on a scale of 0-100) in each of the following 4 domains:

- VAS Patient Global Assessment
- VAS Pain Score
- BASFI
- BASDAI – two morning stiffness-related scores

Power and Sample Size

The protocol assumes response rates of 40% in the placebo group and 65% in the etanercept group at Week 12. The study was to enroll 200 patients (1:1 to etanercept or placebo) with 93% power for a two-sided 0.05-level test. This sample size was chosen based on a phase 2 trial which demonstrated that 30% of placebo (n=20) and 85% (n=20) of etanercept patients achieved an ASAS 20% response at 16 weeks.

Planned Statistical Methods

The protocol specifies that the modified intent-to-treat (mITT) population be the patient population for the primary analysis. This population includes all patients who receive at least 1 dose of blinded study drug. All tests are to be two sided with alpha=0.05.

Changes (and percent changes) from baseline are to be compared between the two treatment groups using stratified rank test.

Patient Disposition

This study randomized 284 patients. Among them, 7 patients did not receive study drug and were discontinued: 4 patients had been randomized in error (did not meet all inclusion criteria) and 3 withdrew their consent prior to first dose of study drug. Therefore, the analysis population is comprised of 277 patients.

The following sponsor's table shows that the discontinuation rate was low: 4% for both groups at week 12 and 14% and 9% for placebo and etanercept at week 24. The primary

reasons for discontinuation were adverse events for etanercept group (n=7) and lack of efficacy for placebo (n=13).

Table 5.1 Study Completion Status at 12 and 24 Weeks

Patient Status	Placebo (N = 139) n (%)	Etanercept (N = 138) n (%)
Completed 12 weeks in study	134 (96)	132 (96)
Discontinued study due to:		
Adverse event	0	4 (3)
Lack of efficacy (LOE)	2 (1)	1 (1)
Lost to follow-up	0	1 (1)
Patient refusal	2 (1)	0
Physician decision	1 (1)	0
Completed 24 weeks in study	120 (86)	126 (91)
Discontinued study due to:		
Adverse event	1 (1)	7 (5)
Lack of efficacy (LOE)	13 (9)	3 (2)
Lost to follow-up	1 (1)	2 (1)
Patient refusal	2 (1)	0
Physician decision	2 (1)	0

Study Conduct

The majority of patients in the etanercept group who violated conduct of the study might have prejudiced against a successful outcome for the etanercept group (1 patient missed > 4 consecutive doses of study drug, 6 decreased or discontinued concomitant DMARDS, and 17/22 who did not maintain stable NSAIDs decreased or discontinued concomitant NSAIDs).

This reviewer has performed some sensitivity analyses examining the robustness of the efficacy results against protocol violations. The results are presented in the respective section.

Demographics and Baseline Disease Characteristics

Both groups were well matched in most characteristics of demography and disease history.

Results of Efficacy Endpoints

Primary Endpoints

Primary analysis

The sponsor's analyses of the primary and the conditional co-primary endpoint are presented below. These results were verified by this reviewer with independent programming (see Appendix Table 1). The efficacy was demonstrated at every specified time point.

Table 6.1 Primary Endpoint: Number (%) Achieving ASAS 20 Response at Week 12

Parameter	Placebo N = 139	Etanercept N = 138	P-value*
ASAS 20 at 12 weeks	38 (27)	83 (60)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test.

Table 6.2 Conditional Primary Endpoint: Number (%) Achieving ASAS 20 at Week 24

Parameter	Placebo N = 139	Etanercept N = 138	P-value*
ASAS 20 at 24 weeks	32 (23)	80 (58)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test.

The proportions of patients who achieved ASAS20 were comparable with or without concomitant DMARD usage. Note that the treatment effect appeared as early as the 2nd week of study drug administration.

Subgroup analysis

Subgroup analyses conducted by this reviewer included analyses by sex (Table 2), race (Caucasian vs non-Caucasian; Table 3), age (Table 4), body weight (Table 5), duration of ankylosing spondylitis (Table 6), patient global assessment (Table 7), investigator global assessment (Table 8), patient back pain score (Table 9), patient BASFI (Table 10), patient BASADI (Table 11) all at baseline and in quartiles, and DMARD use on study (Table 12). The between group comparison was conducted by Cochran-Mantel-Haenszel test with modified ridit scores (van Elteren test). The hemogeity of treatment effect across subgroups was tested by Breslow-Day test. Odds ratio (etanercept over placebo) for achieving ASAS20 reponse was calculated with 95% confidence interval. The efficacy of etanercept treatment was demonstrated consistently across all subgroups at every time point.

Sensitivity analysis

Sensitivity analyses conducted by this reviewer included (1) exclusion of patients who violated protocol for "patient conduct" at any time on study and (2) treating them as

nonresponders. Protocol violation for patient conduct is defined as "missed >4 consecutive study drug doses," "DMARD does not stable," "NSAID or conticosteroid doses not stable," or "received corticoteroid injection at prohibited time point." The results of the analyses are consistent with the primary analyses, suggesting that the finding of etanercept efficacy is robust against protocol violations. (Appendix Table 13 and Table 14)

Secondary Endpoints

Primary analysis

ASAS50, ASAS70, and partial remission (y/n) were analyzed in the same way as for the primary endpoints. Following tables are presented by the sponsor.

Table 6.3.3 Secondary Endpoint:
Number (%) of Patients Who Achieved Partial Remission of AS

Time point	Placebo N = 139 n (%)	Etanercept N = 138 n (%)	P-value*
Week 2	4 (3)	15 (11)	0.0083
Week 4	6 (4)	25 (18)	0.0003
Week 8	6 (4)	25 (18)	0.0003
Week 12	11 (8)	29 (21)	0.0020
Week 24	5 (4)	24 (17)	0.0002
Any time during the study	15 (11)	42 (30)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test.

APPEARS THIS WAY
ON ORIGINAL

Table 6.3.1 Secondary Endpoints: Number (%) Achieving ASAS 20, ASAS 50, and ASAS 70 Over Time

Parameter	Placebo N = 139	Etanercept N = 138	P-value*
ASAS 20 (n [%]) at:			
2 weeks	30 (22)	63 (46)	< 0.0001
4 weeks	34 (24)	69 (50)	< 0.0001
8 weeks	37 (27)	82 (59)	< 0.0001
12 weeks	38 (27)	83 (60)	< 0.0001
24 weeks	32 (23)	80 (58)	< 0.0001
ASAS 50 (n [%]) at:			
2 weeks	10 (7)	33 (24)	0.0001
4 weeks	12 (9)	48 (35)	< 0.0001
8 weeks	17 (12)	59 (43)	< 0.0001
12 weeks	18 (13)	62 (45)	< 0.0001
24 weeks	14 (10)	58 (42)	< 0.0001
ASAS 70 (n [%]) at:			
2 weeks	3 (2)	16 (12)	0.0020
4 weeks	5 (4)	32 (23)	< 0.0001
8 weeks	7 (5)	32 (23)	< 0.0001
12 weeks	10 (7)	40 (29)	< 0.0001
24 weeks	7 (5)	39 (28)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test.

Results of independent analyses conducted by this reviewer (Table 15 - Table 17) are consistent with those of the sponsor's, indicating that etanercept was efficacious by these measures at all time points.

Percent change from baseline in patient global assessment, investigator global assessment, patient back pain score, BASFI, and BASDAI were analyzed by the sponsor using generalized Cochran-Mantel-Haenszel test adjusted for baseline DMARDS strata. Results are shown below. This reviewer conducted independent analyses using Wilcoxon rank-sum test for between group differences. To minimize the impact of possible distribution violation, this reviewer computed Hodges-Lehman nonparametric estimates with 95% confidence interval for the differences in medians. Results are presented in Appendix Table 18 - Table 22. The results of the independent analyses are consistent with the sponsor's analyses, indicating that etanercept was also efficacious by these secondary endpoints.

Table 6.4.1 Patient Global Assessments: Mean (median) Values and Percent Improvement from Baseline

Patient's global assessment	Mean (median) Values: Placebo N = 139	Mean (median) Values: Etanercept N = 138	Mean (median) Percent Improvement from Baseline: Placebo N = 139	Mean (median) Percent Improvement from Baseline: Etanercept N = 138	P-value*
Baseline	62.9 (64.0)	62.9 (66.0)	---	---	
2 weeks	56.2 (59.0)	41.8 (39.5)	7.4 (7.8)	30.8 (26.8)	< 0.0001
4 weeks	56.8 (57.0)	37.7 (34.5)	5.4 (5.2)	36.4 (43.4)	< 0.0001
8 weeks	56.6 (58.0)	36.8 (32.0)	6.5 (4.9)	37.6 (47.8)	< 0.0001
12 weeks	55.9 (57.0)	35.2 (31.5)	9.8 (8.8)	40.2 (50.8)	< 0.0001
24 weeks	56.3 (57.0)	36.0 (29.0)	7.8 (6.5)	38.6 (46.3)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

Table 6.4.2 Nocturnal Back Pain and Total Back Pain: Mean (median) Values and Percent Improvement from Baseline

Parameter	Mean (median) Values: Placebo N = 139	Mean (median) Values: Etanercept N = 138	Mean (median) Percent Improvement from Baseline*: Placebo N = 138	Mean (median) Percent Improvement from Baseline*: Etanercept N = 138	P-value†
Nocturnal back pain					
Baseline	60.6 (63.0)	58.5 (62.0)	---	---	
2 weeks	54.9 (60.0)	36.8 (30.0)	-0.9 (5.1)	30.0 (35.9)	< 0.0001
4 weeks	53.5 (56.0)	33.7 (28.5)	-4.9 (3.7)	32.9 (45.7)	< 0.0001
8 weeks	54.8 (58.0)	31.2 (24.5)	2.4 (2.4)	35.6 (55.1)	< 0.0001
12 weeks	53.6 (56.0)	30.5 (22.0)	1.0 (6.3)	41.2 (58.0)	< 0.0001
24 weeks	54.5 (58.0)	30.9 (20.5)	1.3 (2.6)	39.1 (58.4)	< 0.0001
Total back pain					
Baseline	63.5 (66.0)	61.1 (64.0)	---	---	
2 weeks	57.7 (64.0)	40.3 (39.0)	-4.1 (4.2)	26.7 (34.3)	< 0.0001
4 weeks	56.7 (60.0)	38.4 (32.5)	-12.3 (6.9)	29.7 (40.8)	< 0.0001
8 weeks	56.0 (59.0)	35.5 (28.0)	10.1 (11.0)	31.6 (50.9)	< 0.0001
12 weeks	56.3 (56.0)	34.4 (25.5)	1.1 (9.1)	36.9 (53.3)	< 0.0001
24 weeks	57.8 (65.0)	37.1 (32.5)	-1.0 (10.2)	28.6 (46.7)	< 0.0001
Average of nocturnal back pain and total back pain scores					
Baseline	62.1 (65.0)	59.8 (61.8)	---	---	
2 weeks	56.3 (62.5)	38.5 (34.0)	-0.3 (4.9)	29.8 (32.2)	< 0.0001
4 weeks	55.1 (56.0)	36.0 (30.0)	-5.1 (5.9)	33.0 (44.4)	< 0.0001
8 weeks	55.4 (58.5)	33.4 (25.8)	10.1 (6.1)	35.5 (51.0)	< 0.0001
12 weeks	54.9 (56.0)	32.5 (26.3)	6.7 (5.4)	39.9 (54.1)	< 0.0001
24 weeks	56.2 (61.0)	34.0 (26.0)	5.1 (6.0)	34.8 (51.1)	< 0.0001

* One patient in the placebo group had a score of zero at baseline and was not included in the analysis of percent improvement from baseline.

† P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

Table 6.4.3 Bath Ankylosing Spondylitis Functional Index (BASFI): Average of Responses to 10 Questions, Mean (median) Values and Percent Improvement from Baseline

BASFI – average of responses to 10 questions	Mean (median) Values Placebo N = 139	Etanercept N = 138	Mean (median) Percent Improvement from Baseline Placebo N = 139	Etanercept N = 138	P-value*
Baseline	56.3 (58.6)	51.7 (49.5)	—	—	
2 weeks	53.3 (53.7)	41.2 (39.4)	1.8 (2.7)	19.5 (16.4)	0.0005
4 weeks	53.6 (53.6)	37.6 (32.2)	1.8 (0.8)	25.8 (21.7)	< 0.0001
8 weeks	53.7 (54.2)	35.3 (29.4)	1.3 (2.1)	31.2 (28.7)	< 0.0001
12 weeks	53.0 (53.4)	35.0 (29.2)	4.9 (3.3)	33.1 (32.3)	< 0.0001
24 weeks	54.7 (54.7)	36.0 (31.4)	1.9 (-1.0)	30.1 (31.3)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline

Table 6.4.4 Inflammation: Average of Responses to Last 2 Questions on BASDAI Mean (median) Values and Percent Improvement from Baseline

Inflammation – average of last 2 questions on BASDAI	Mean (median) Values Placebo N = 139	Etanercept N = 138	Mean (median) Percent Improvement from Baseline Placebo N = 139	Etanercept N = 138	P-value*
Baseline	64.3 (65.0)	61.4 (60.0)	—	—	
2 weeks	56.8 (58.5)	39.6 (35.5)	8.7 (7.3)	31.7 (31.5)	< 0.0001
4 weeks	55.4 (54.0)	36.4 (30.5)	10.0 (4.3)	38.0 (38.0)	< 0.0001
8 weeks	54.3 (52.0)	32.8 (24.8)	11.1 (11.0)	43.7 (49.5)	< 0.0001
12 weeks	53.3 (49.0)	32.8 (20.8)	13.1 (9.5)	44.8 (55.1)	< 0.0001
24 weeks	56.6 (58.0)	33.4 (25.5)	5.7 (5.0)	43.9 (45.0)	< 0.0001

* P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

Sensitivity analysis

This reviewer conducted sensitivity analyses of ASAS50, ASAS70, and partial remissions in the same way as for ASAS20. The results of the analyses are consistent with the primary analyses, suggesting again that the finding of etanercept efficacy is robust against protocol violations. (Appendix Table 23 and Table 28)

Results of Safety Endpoints

Patient incidence (Proportion of Patients) and event occurrence (Rates per Patient Year) are calculated for each adverse event preferred term by the sponsor and presented below. The analysis of occurrence rate is not very useful because of its impractical assumption that every event is an independent event that occurs any time with equal probability. In another words, a patient on study for a year would have the same chance of experiencing an event as any of 12 patients on study for a month. Moreover, it does not

distinguish early events from late events. Besides, a continuous event can be reported as separate occurrences or as one occurrence for a period of time (eg, headache). These types of reports can obscur the analysis of the occurrence rates. Nevertheless, it is clear from analyses of both patient incidence and event occurrence that significantly more patients in etanercept group complained about injection site reactions and experienced accidental injuries than patients in placebo group.

Table 7.1 Adverse Events of All Intensities in ≥ 5% of Patients in Either Treatment Group

	Proportions of Patients (n [%])*			Rates per Patient-year†		
Event	Placebo N = 139	Etanercept N = 138	P-value‡	Placebo (58.3 pt-yr)	Etanercept (59.2 pt-yr)	P-value**
Any adverse event	105 (76)	99 (72)	0.4976	5.59	6.10	0.2778
Injection site reaction††	13 (9)	41 (30)	< 0.0001	0.36	2.30	< 0.0001
Injection site ecchymosis	23 (17)	29 (21)	0.3597	1.42	1.33	0.7349
Headache	16 (12)	19 (14)	0.5925	0.31	0.32	0.0962
Accidental injury	6 (4)	17 (12)	0.0172	0.10	0.32	0.0163
Diarrhea	13 (9)	11 (8)	0.8314	0.24	0.30	0.6289
Rash	9 (7)	11 (8)	0.6509	0.15	0.24	0.4273
Dizziness	3 (2)	8 (6)	0.1372	0.05	0.17	0.0981
Rhinitis	9 (7)	8 (6)	1.0000	0.15	0.17	1.0000
Abdominal pain	7 (5)	8 (6)	0.7977	0.15	0.17	1.0000
Nausea	7 (5)	7 (5)	1.0000	0.15	0.14	0.9730
Asthenia	7 (5)	5 (4)	0.7694	0.17	0.08	0.2872

* Patients were only counted once for a COSTART term.
† All occurrences of a COSTART term are included.
‡ P-values determined by Fisher's exact test.
** P-values determined by the exact binomial test.
†† Reports of injection site reactions were collected separately.

The sponsor also reported following safety summaries. No deaths occurred during the study or within 30 days following the last dose of study drug. Ten SAEs occurred in 9 patients in the etanercept group and 5 SAEs occurred in 5 patients in the placebo group. Seven patients in the etanercept group and 1 patient in the placebo group discontinued study drug due to adverse events. Sixteen Grade 3 events or infections occurred in 14 patients in the etanercept group, and 3 Grade 3 events occurred in 3 patients in the placebo group during the study.

This reviewer recalcaulted the patient incidence table and presented in descending order in etanercept group (Appendix Table 29). The numbers may be slightly different from the sponsor's because events with missing dates or dates passing the collection timeframe might have been excluded from the sponsor's table. The results of this independent analysis are consistent with the sponsor's analysis. Overall, 72% etanercept treated patients experienced one or more adverse events compared to 76% placebo treated patients on study.

This reviewer also summarized patient incidence for serious adverse events and infectious adverse events. (Appendix Table 30 and Table 31) Overall, more etanercept treated patients experienced serious and/or infectious adverse events than placebo treated patients (7% and 41% vs 4% and 30%, respectively).

Discussion and Conclusion

The results of various efficacy analyses demonstrated that etanercept is effective in treating ankylosing spondylitis. There is a slight tendency in increased risk of serioud adverse events and infectious adverse events.

Study 47687

This study was designed very similarly to study 016.0037. It was a non-IND trial conducted in Europe. This study differs from study 016.0037 in that this study evaluated 12 weeks of etanercept treatment while the later evaluated 12 weeks as well as 24 weeks of etanercept treatment. The efficacy results were consistent between two studies.

Appendix

Independent Statistical Analyses

Table 1. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by randomization stratum

Visit Number	Randomized Strata	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.1 (1.8, 5.2)	<0.001	0.263
	No DMARD	43/ 93 (46.2%)	24/ 95 (25.3%)			
	DMARD	20/ 45 (44.4%)	6/ 44 (13.6%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.1 (1.8, 5.1)	<0.001	0.138
	No DMARD	44/ 93 (47.3%)	26/ 95 (27.4%)			
	DMARD	25/ 45 (55.6%)	8/ 44 (18.2%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.0 (2.4, 6.7)	<0.001	0.551
	No DMARD	55/ 93 (59.1%)	27/ 95 (28.4%)			
	DMARD	27/ 45 (60.0%)	10/ 44 (22.7%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.6)	<0.001	0.273
	No DMARD	54/ 93 (58.1%)	28/ 95 (29.5%)			
	DMARD	29/ 45 (64.4%)	10/ 44 (22.7%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.6 (2.7, 7.6)	<0.001	0.164
	No DMARD	51/ 93 (54.8%)	24/ 95 (25.3%)			
	DMARD	29/ 45 (64.4%)	8/ 44 (18.2%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 2. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Sex

Visit Number	Sex	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.1 (1.8, 5.2)	<0.001	0.814
	Male	49/105 (46.7%)	24/105 (22.9%)			
	Female	14/ 33 (42.4%)	6/ 34 (17.6%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.1 (1.9, 5.2)	<0.001	0.652
	Male	54/105 (51.4%)	28/105 (26.7%)			
	Female	15/ 33 (45.5%)	6/ 34 (17.6%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.0 (2.4, 6.7)	<0.001	0.289
	Male	61/105 (58.1%)	30/105 (28.6%)			
	Female	21/ 33 (63.6%)	7/ 34 (20.6%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.6)	<0.001	0.118
	Male	68/105 (64.8%)	28/105 (26.7%)			
	Female	15/ 33 (45.5%)	10/ 34 (29.4%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.7 (2.8, 7.9)	<0.001	0.533
	Male	66/105 (62.9%)	26/105 (24.8%)			
	Female	14/ 33 (42.4%)	6/ 34 (17.6%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 3. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Race

Visit Number	Race	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.1 (1.8, 5.2)	<0.001	0.980
	Non-Caucasian	4/ 8 (50.0%)	3/ 12 (25.0%)			
	Caucasian	59/130 (45.4%)	27/127 (21.3%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.1 (1.8, 5.1)	<0.001	0.629
	Non-Caucasian	4/ 8 (50.0%)	2/ 12 (16.7%)			
	Caucasian	65/130 (50.0%)	32/127 (25.2%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.0 (2.4, 6.7)	<0.001	0.756
	Non-Caucasian	4/ 8 (50.0%)	3/ 12 (25.0%)			
	Caucasian	78/130 (60.0%)	34/127 (26.8%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.6)	<0.001	0.072
	Non-Caucasian	7/ 8 (87.5%)	2/ 12 (16.7%)			
	Caucasian	76/130 (58.5%)	36/127 (28.3%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.7 (2.8, 7.9)	<0.001	0.710
	Non-Caucasian	5/ 8 (62.5%)	4/ 12 (33.3%)			
	Caucasian	75/130 (57.7%)	28/127 (22.0%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 4. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Age

Visit Number	Age (years)	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	2.9 (1.7, 5.0)	<0.001	0.406
	<34	17/ 31 (54.8%)	7/ 38 (18.4%)			
	34 to <42	15/ 37 (40.5%)	7/ 25 (28.0%)			
	42 to <50	23/ 41 (56.1%)	9/ 35 (25.7%)			
	50+	8/ 29 (27.6%)	7/ 41 (17.1%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.0 (1.8, 5.0)	<0.001	0.511
	<34	18/ 31 (58.1%)	8/ 38 (21.1%)			
	34 to <42	17/ 37 (45.9%)	7/ 25 (28.0%)			
	42 to <50	23/ 41 (56.1%)	9/ 35 (25.7%)			
	50+	11/ 29 (37.9%)	10/ 41 (24.4%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.0 (2.4, 6.7)	<0.001	0.341
	<34	20/ 31 (64.5%)	11/ 38 (28.9%)			
	34 to <42	21/ 37 (56.8%)	6/ 25 (24.0%)			
	42 to <50	28/ 41 (68.3%)	8/ 35 (22.9%)			
	50+	13/ 29 (44.8%)	12/ 41 (29.3%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.7)	<0.001	0.550
	<34	23/ 31 (74.2%)	12/ 38 (31.6%)			
	34 to <42	24/ 37 (64.9%)	6/ 25 (24.0%)			
	42 to <50	23/ 41 (56.1%)	10/ 35 (28.6%)			
	50+	13/ 29 (44.8%)	10/ 41 (24.4%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.8 (2.8, 8.2)	<0.001	0.868
	<34	22/ 31 (71.0%)	12/ 38 (31.6%)			
	34 to <42	20/ 37 (54.1%)	5/ 25 (20.0%)			
	42 to <50	25/ 41 (61.0%)	7/ 35 (20.0%)			
	50+	13/ 29 (44.8%)	8/ 41 (19.5%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 5. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Body Weight at Baseline

Visit Number	Baseline Weight(kg)	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.0 (1.8, 5.2)	<0.001	0.114
	Missing	0/ 1 (0.0%)	0/ 1 (0.0%)			
	<68	14/ 29 (48.3%)	6/ 33 (18.2%)			
	68 to <80	22/ 45 (48.9%)	4/ 26 (15.4%)			
	80 to <93	15/ 32 (46.9%)	6/ 40 (15.0%)			
	93+	12/ 31 (38.7%)	14/ 39 (35.9%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.1 (1.9, 5.3)	<0.001	0.938
	Missing	1/ 1 (%)	0/ 1 (0.0%)			
	<68	15/ 29 (51.7%)	8/ 33 (24.2%)			
	68 to <80	21/ 45 (46.7%)	5/ 26 (19.2%)			
	80 to <93	16/ 32 (50.0%)	9/ 40 (22.5%)			
	93+	16/ 31 (51.6%)	12/ 39 (30.8%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.1 (2.5, 6.9)	<0.001	0.308
	Missing	0/ 1 (0.0%)	0/ 1 (0.0%)			
	<68	18/ 29 (62.1%)	6/ 33 (18.2%)			
	68 to <80	24/ 45 (53.3%)	8/ 26 (30.8%)			
	80 to <93	18/ 32 (56.3%)	13/ 40 (32.5%)			
	93+	22/ 31 (71.0%)	10/ 39 (25.6%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	3.8 (2.3, 6.3)	<0.001	0.893
	Missing	1/ 1 (%)	0/ 1 (0.0%)			
	<68	16/ 29 (55.2%)	9/ 33 (27.3%)			
	68 to <80	28/ 45 (62.2%)	9/ 26 (34.6%)			
	80 to <93	18/ 32 (56.3%)	10/ 40 (25.0%)			
	93+	20/ 31 (64.5%)	10/ 39 (25.6%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.5 (2.7, 7.6)	<0.001	0.374
	Missing	1/ 1 (%)	0/ 1 (0.0%)			
	<68	19/ 29 (65.5%)	5/ 33 (15.2%)			
	68 to <80	25/ 45 (55.6%)	6/ 26 (23.1%)			
	80 to <93	16/ 32 (50.0%)	11/ 40 (27.5%)			
	93+	19/ 31 (61.3%)	10/ 39 (25.6%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 6. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Duration of Disease at Baseline

Visit Number	Duration of AS (years)	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.2 (1.9, 5.4)	<0.001	0.247
	<2.25	13/ 34 (38.2%)	8/ 35 (22.9%)			
	2.25 to <8.75	18/ 34 (52.9%)	9/ 35 (25.7%)			
	8.75 to <16.25	17/ 38 (44.7%)	2/ 31 (6.5%)			
	16.25+	15/ 32 (46.9%)	11/ 38 (28.9%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.0 (1.8, 5.1)	<0.001	0.312
	<2.25	14/ 34 (41.2%)	9/ 35 (25.7%)			
	2.25 to <8.75	14/ 34 (41.2%)	9/ 35 (25.7%)			
	8.75 to <16.25	24/ 38 (63.2%)	6/ 31 (19.4%)			
	16.25+	17/ 32 (53.1%)	10/ 38 (26.3%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.0 (2.4, 6.7)	<0.001	0.169
	<2.25	20/ 34 (58.8%)	13/ 35 (37.1%)			
	2.25 to <8.75	17/ 34 (50.0%)	9/ 35 (25.7%)			
	8.75 to <16.25	25/ 38 (65.8%)	4/ 31 (12.9%)			
	16.25+	20/ 32 (62.5%)	11/ 38 (28.9%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.6)	<0.001	0.080
	<2.25	20/ 34 (58.8%)	16/ 35 (45.7%)			
	2.25 to <8.75	19/ 34 (55.9%)	8/ 35 (22.9%)			
	8.75 to <16.25	25/ 38 (65.8%)	4/ 31 (12.9%)			
	16.25+	19/ 32 (59.4%)	10/ 38 (26.3%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.7 (2.8, 8.0)	<0.001	0.278
	<2.25	21/ 34 (61.8%)	14/ 35 (40.0%)			
	2.25 to <8.75	17/ 34 (50.0%)	7/ 35 (20.0%)			
	8.75 to <16.25	23/ 38 (60.5%)	4/ 31 (12.9%)			
	16.25+	19/ 32 (59.4%)	7/ 38 (18.4%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 7. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Global Assessment at Baseline

Visit Number	Baseline Patient Global	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.0 (1.8, 5.0)	<0.001	0.124
	Missing	0/ 2 (0.0%)	0/ 3 (0.0%)			
	<50	11/ 35 (31.4%)	9/ 32 (28.1%)			
	50 to <65	12/ 27 (44.4%)	8/ 38 (21.1%)			
	65 to <75	19/ 37 (51.4%)	8/ 32 (25.0%)			
	75+	21/ 37 (56.8%)	5/ 34 (14.7%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.2 (1.9, 5.3)	<0.001	0.353
	Missing	0/ 2 (0.0%)	0/ 2 (0.0%)			
	<50	13/ 35 (37.1%)	8/ 32 (25.0%)			
	50 to <65	15/ 27 (55.6%)	11/ 39 (28.2%)			
	65 to <75	20/ 36 (55.6%)	10/ 32 (31.3%)			
	75+	21/ 38 (55.3%)	5/ 34 (14.7%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.5 (2.7, 7.6)	<0.001	0.563
	Missing	0/ 5 (0.0%)	0/ 1 (0.0%)			
	<50	18/ 32 (56.3%)	9/ 32 (28.1%)			
	50 to <65	19/ 28 (67.9%)	13/ 39 (33.3%)			
	65 to <75	21/ 36 (58.3%)	9/ 32 (28.1%)			
	75+	24/ 37 (64.9%)	6/ 35 (17.1%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.2 (2.5, 7.0)	<0.001	0.262
	Missing	0/ 5 (0.0%)	0/ 5 (0.0%)			
	<50	18/ 32 (56.3%)	8/ 31 (25.8%)			
	50 to <65	18/ 28 (64.3%)	13/ 37 (35.1%)			
	65 to <75	20/ 36 (55.6%)	10/ 31 (32.3%)			
	75+	27/ 37 (73.0%)	7/ 35 (20.0%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.9 (2.9, 8.5)	<0.001	0.326
	Missing	0/ 13 (0.0%)	0/ 18 (0.0%)			
	<50	15/ 29 (51.7%)	9/ 27 (33.3%)			
	50 to <65	19/ 27 (70.4%)	10/ 35 (28.6%)			
	65 to <75	20/ 33 (60.6%)	6/ 29 (20.7%)			
	75+	26/ 36 (72.2%)	7/ 30 (23.3%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 8. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Investigator Global Assessment at Baseline

Visit Number	Baseline Doctor Global	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.1 (1.8, 5.3)	<0.001	0.425
	Missing	0/ 2 (0.0%)	0/ 3 (0.0%)			
	<45	18/ 38 (47.4%)	10/ 30 (33.3%)			
	45 to <57	17/ 27 (63.0%)	8/ 35 (22.9%)			
	57 to <70	15/ 36 (41.7%)	8/ 37 (21.6%)			
	70+	13/ 35 (37.1%)	4/ 34 (11.8%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.1 (1.9, 5.3)	<0.001	0.817
	Missing	0/ 2 (0.0%)	0/ 2 (0.0%)			
	<45	24/ 40 (60.0%)	11/ 30 (36.7%)			
	45 to <57	17/ 27 (63.0%)	9/ 35 (25.7%)			
	57 to <70	16/ 35 (45.7%)	8/ 38 (21.1%)			
	70+	12/ 34 (35.3%)	6/ 34 (17.6%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.4 (2.6, 7.4)	<0.001	0.522
	Missing	0/ 5 (0.0%)	0/ 1 (0.0%)			
	<45	26/ 40 (65.0%)	10/ 30 (33.3%)			
	45 to <57	19/ 26 (73.1%)	9/ 35 (25.7%)			
	57 to <70	19/ 34 (55.9%)	12/ 38 (31.6%)			
	70+	18/ 33 (54.5%)	6/ 35 (17.1%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.2 (2.5, 7.0)	<0.001	0.850
	Missing	0/ 5 (0.0%)	0/ 5 (0.0%)			
	<45	26/ 40 (65.0%)	11/ 29 (37.9%)			
	45 to <57	18/ 26 (69.2%)	10/ 34 (29.4%)			
	57 to <70	19/ 34 (55.9%)	9/ 36 (25.0%)			
	70+	20/ 33 (60.6%)	8/ 35 (22.9%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	5.0 (2.9, 8.7)	<0.001	0.805
	Missing	0/ 13 (0.0%)	0/ 18 (0.0%)			
	<45	28/ 36 (77.8%)	11/ 27 (40.7%)			
	45 to <57	17/ 26 (65.4%)	7/ 32 (21.9%)			
	57 to <70	18/ 32 (56.3%)	9/ 32 (28.1%)			
	70+	17/ 31 (54.8%)	5/ 30 (16.7%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 9. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient Back Pain at Baseline

Visit Number	Baseline BackPain	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.0 (1.8, 5.0)	<0.001	0.028
	Missing	0/ 2 (0.0%)	0/ 3 (0.0%)			
	<50	13/ 39 (33.3%)	9/ 27 (33.3%)			
	50 to <63	16/ 32 (50.0%)	11/ 37 (29.7%)			
	63 to <76	19/ 34 (55.9%)	7/ 35 (20.0%)			
	76+	15/ 31 (48.4%)	3/ 37 (8.1%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.2 (1.9, 5.3)	<0.001	0.523
	Missing	0/ 2 (0.0%)	0/ 2 (0.0%)			
	<50	19/ 39 (48.7%)	6/ 27 (22.2%)			
	50 to <63	15/ 33 (45.5%)	12/ 37 (32.4%)			
	63 to <76	21/ 33 (63.6%)	10/ 36 (27.8%)			
	76+	14/ 31 (45.2%)	6/ 37 (16.2%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.2 (2.5, 6.9)	<0.001	0.087
	Missing	0/ 5 (0.0%)	0/ 1 (0.0%)			
	<50	22/ 36 (61.1%)	11/ 27 (40.7%)			
	50 to <63	17/ 33 (51.5%)	12/ 37 (32.4%)			
	63 to <76	23/ 33 (69.7%)	8/ 37 (21.6%)			
	76+	20/ 31 (64.5%)	6/ 37 (16.2%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.2 (2.5, 7.0)	<0.001	0.172
	Missing	0/ 5 (0.0%)	0/ 5 (0.0%)			
	<50	19/ 37 (51.4%)	9/ 26 (34.6%)			
	50 to <63	20/ 32 (62.5%)	13/ 36 (36.1%)			
	63 to <76	24/ 33 (72.7%)	9/ 36 (25.0%)			
	76+	20/ 31 (64.5%)	7/ 36 (19.4%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.8 (2.8, 8.2)	<0.001	0.059
	Missing	0/ 13 (0.0%)	0/ 18 (0.0%)			
	<50	19/ 33 (57.6%)	10/ 24 (41.7%)			
	50 to <63	18/ 29 (62.1%)	11/ 32 (34.4%)			
	63 to <76	24/ 32 (75.0%)	7/ 34 (20.6%)			
	76+	19/ 31 (61.3%)	4/ 31 (12.9%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 10. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient BASFI at Baseline

Visit Number	Baseline BASFI	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.0 (1.7, 5.1)	<0.001	0.238
	Missing	0/ 2 (0.0%)	0/ 4 (0.0%)			
	<39	19/ 34 (55.9%)	9/ 33 (27.3%)			
	39 to <53	20/ 42 (47.6%)	6/ 24 (25.0%)			
	53 to <70	13/ 30 (43.3%)	13/ 40 (32.5%)			
	70+	11/ 30 (36.7%)	2/ 38 (5.3%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.2 (1.9, 5.4)	<0.001	0.307
	Missing	0/ 2 (0.0%)	0/ 2 (0.0%)			
	<39	23/ 35 (65.7%)	9/ 34 (26.5%)			
	39 to <53	22/ 42 (52.4%)	6/ 24 (25.0%)			
	53 to <70	13/ 28 (46.4%)	15/ 41 (36.6%)			
	70+	11/ 31 (35.5%)	4/ 38 (10.5%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.4 (2.6, 7.4)	<0.001	0.451
	Missing	0/ 5 (0.0%)	0/ 1 (0.0%)			
	<39	25/ 34 (73.5%)	11/ 34 (32.4%)			
	39 to <53	23/ 41 (56.1%)	8/ 24 (33.3%)			
	53 to <70	18/ 29 (62.1%)	13/ 41 (31.7%)			
	70+	16/ 29 (55.2%)	5/ 39 (12.8%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.7)	<0.001	0.340
	Missing	0/ 6 (0.0%)	0/ 6 (0.0%)			
	<39	23/ 34 (67.6%)	12/ 32 (37.5%)			
	39 to <53	27/ 41 (65.9%)	9/ 24 (37.5%)			
	53 to <70	15/ 28 (53.6%)	12/ 40 (30.0%)			
	70+	18/ 29 (62.1%)	5/ 37 (13.5%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.8 (2.7, 8.4)	<0.001	0.156
	Missing	0/ 13 (0.0%)	0/ 18 (0.0%)			
	<39	23/ 31 (74.2%)	12/ 27 (44.4%)			
	39 to <53	26/ 40 (65.0%)	7/ 23 (30.4%)			
	53 to <70	15/ 27 (55.6%)	11/ 37 (29.7%)			
	70+	16/ 27 (59.3%)	2/ 34 (5.9%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 11. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient BASDAI at Baseline

Visit Number	Baseline BASDAI	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.3 (1.9, 5.7)	<0.001	0.994
	Missing	0/ 2 (0.0%)	0/ 4 (0.0%)			
	<47	14/ 39 (35.9%)	4/ 28 (14.3%)			
	47 to <63	16/ 34 (47.1%)	7/ 34 (20.6%)			
	63 to <80	16/ 28 (57.1%)	11/ 35 (31.4%)			
	80+	17/ 35 (48.6%)	8/ 38 (21.1%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.3 (2.0, 5.6)	<0.001	0.546
	Missing	0/ 2 (0.0%)	0/ 2 (0.0%)			
	<47	19/ 40 (47.5%)	4/ 29 (13.8%)			
	47 to <63	20/ 34 (58.8%)	8/ 34 (23.5%)			
	63 to <80	15/ 27 (55.6%)	13/ 36 (36.1%)			
	80+	15/ 35 (42.9%)	9/ 38 (23.7%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.7 (2.8, 7.9)	<0.001	0.926
	Missing	0/ 5 (0.0%)	0/ 1 (0.0%)			
	<47	21/ 40 (52.5%)	7/ 29 (24.1%)			
	47 to <63	22/ 32 (68.8%)	10/ 35 (28.6%)			
	63 to <80	19/ 27 (70.4%)	12/ 36 (33.3%)			
	80+	20/ 34 (58.8%)	8/ 38 (21.1%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.4 (2.6, 7.4)	<0.001	0.296
	Missing	0/ 6 (0.0%)	0/ 6 (0.0%)			
	<47	20/ 40 (50.0%)	8/ 26 (30.8%)			
	47 to <63	23/ 32 (71.9%)	11/ 34 (32.4%)			
	63 to <80	17/ 26 (65.4%)	12/ 35 (34.3%)			
	80+	23/ 34 (67.6%)	7/ 38 (18.4%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	5.4 (3.1, 9.4)	<0.001	0.312
	Missing	0/ 13 (0.0%)	0/ 18 (0.0%)			
	<47	19/ 37 (51.4%)	5/ 23 (21.7%)			
	47 to <63	24/ 30 (80.0%)	7/ 31 (22.6%)			
	63 to <80	17/ 26 (65.4%)	13/ 35 (37.1%)			
	80+	20/ 32 (62.5%)	7/ 32 (21.9%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 12. Study 016.0037 Analysis of ASAS20 Responders in mITT Population Stratified by Patient DMARD Use on Study

Visit Number	ConMed DMARD	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	63/138 (45.7%)	30/139 (21.6%)	3.1 (1.8, 5.2)	<0.001	0.577
	No	44/ 94 (46.8%)	23/ 96 (24.0%)			
	Yes	19/ 44 (43.2%)	7/ 43 (16.3%)			
4	All	69/138 (50.0%)	34/139 (24.5%)	3.1 (1.9, 5.1)	<0.001	0.464
	No	46/ 94 (48.9%)	25/ 96 (26.0%)			
	Yes	23/ 44 (52.3%)	9/ 43 (20.9%)			
8	All	82/138 (59.4%)	37/139 (26.6%)	4.1 (2.4, 6.8)	<0.001	0.620
	No	57/ 94 (60.6%)	28/ 96 (29.2%)			
	Yes	25/ 44 (56.8%)	9/ 43 (20.9%)			
12	All	83/138 (60.1%)	38/139 (27.3%)	4.0 (2.4, 6.6)	<0.001	0.323
	No	56/ 94 (59.6%)	29/ 96 (30.2%)			
	Yes	27/ 44 (61.4%)	9/ 43 (20.9%)			
24	All	80/138 (58.0%)	32/139 (23.0%)	4.6 (2.7, 7.7)	<0.001	0.322
	No	53/ 94 (56.4%)	24/ 96 (25.0%)			
	Yes	27/ 44 (61.4%)	8/ 43 (18.6%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 13. Study 016.0037 Analysis of ASAS20 Responders
Adjusted for randomization stratum
(Excluding patients with protocol violations for 'conduct')

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	65/111 (58.6%)	34/120 (28.3%)	3.6 (2.1, 6.1)	<0.001	0.355
24	63/111 (56.8%)	26/120 (21.7%)	4.7 (2.6, 8.3)	<0.001	0.181

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 14. Study 016.0037 Analysis of ASAS20 Responders
Adjusted for randomization stratum
(Treating patients with protocol violations for 'conduct' as nonresponders)

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	65/138 (47.1%)	34/139 (24.5%)	2.7 (1.6, 4.6)	<0.001	0.320
24	63/138 (45.7%)	26/139 (18.7%)	3.6 (2.1, 6.2)	<0.001	0.171

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 15. Study 016.0037 Analysis of ASAS50 Responders in mITT Population Stratified by randomization stratum

Visit Number	Randomized Strata	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	33/138 (23.9%)	10/139 (7.2%)	4.0 (1.9, 8.5)	<0.001	0.073
	No DMARD	20/ 93 (21.5%)	9/ 95 (9.5%)			
	DMARD	13/ 45 (28.9%)	1/ 44 (2.3%)			
4	All	48/138 (34.8%)	12/139 (8.6%)	5.6 (2.8, 11)	<0.001	0.062
	No DMARD	31/ 93 (33.3%)	11/ 95 (11.6%)			
	DMARD	17/ 45 (37.8%)	1/ 44 (2.3%)			
8	All	59/138 (42.8%)	17/139 (12.2%)	5.3 (2.9, 9.8)	<0.001	0.142
	No DMARD	38/ 93 (40.9%)	14/ 95 (14.7%)			
	DMARD	21/ 45 (46.7%)	3/ 44 (6.8%)			
12	All	62/138 (44.9%)	18/139 (12.9%)	5.4 (3.0, 9.9)	<0.001	0.260
	No DMARD	40/ 93 (43.0%)	14/ 95 (14.7%)			
	DMARD	22/ 45 (48.9%)	4/ 44 (9.1%)			
24	All	58/138 (42.0%)	14/139 (10.1%)	6.4 (3.4, 12)	<0.001	0.238
	No DMARD	34/ 93 (36.6%)	10/ 95 (10.5%)			
	DMARD	24/ 45 (53.3%)	4/ 44 (9.1%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 16. Study 016.0037 Analysis of ASAS70 Responders in mITT Population Stratified by randomization stratum

Visit Number	Randomized Strata	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	16/138 (11.6%)	3/139 (2.2%)	5.9 (1.7, 21)	0.002	0.147
	No DMARD	9/ 93 (9.7%)	3/ 95 (3.2%)			
	DMARD	7/ 45 (15.6%)	0/ 44 (0.0%)			
4	All	32/138 (23.2%)	5/139 (3.6%)	7.8 (3.0, 20)	<0.001	0.052
	No DMARD	18/ 93 (19.4%)	5/ 95 (5.3%)			
	DMARD	14/ 45 (31.1%)	0/ 44 (0.0%)			
8	All	32/138 (23.2%)	7/139 (5.0%)	5.7 (2.4, 13)	<0.001	0.646
	No DMARD	20/ 93 (21.5%)	5/ 95 (5.3%)			
	DMARD	12/ 45 (26.7%)	2/ 44 (4.5%)			
12	All	40/138 (29.0%)	10/139 (7.2%)	5.2 (2.5, 11)	<0.001	0.277
	No DMARD	25/ 93 (26.9%)	8/ 95 (8.4%)			
	DMARD	15/ 45 (33.3%)	2/ 44 (4.5%)			
24	All	39/138 (28.3%)	7/139 (5.0%)	7.3 (3.2, 17)	<0.001	0.198
	No DMARD	24/ 93 (25.8%)	6/ 95 (6.3%)			
	DMARD	15/ 45 (33.3%)	1/ 44 (2.3%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 17. Study 016.0037 Analysis of Partial Remission (Y/N) in mITT Population Stratified by randomization stratum

Visit Number	Randomized Strata	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
2	All	15/138 (10.9%)	4/139 (2.9%)	4.1 (1.3, 13)	0.009	0.988
	No DMARD	11/ 93 (11.8%)	3/ 95 (3.2%)			
	DMARD	4/ 45 (8.9%)	1/ 44 (2.3%)			
4	All	25/138 (18.1%)	6/139 (4.3%)	4.9 (1.9, 12)	<0.001	0.274
	No DMARD	15/ 93 (16.1%)	5/ 95 (5.3%)			
	DMARD	10/ 45 (22.2%)	1/ 44 (2.3%)			
8	All	25/138 (18.1%)	6/139 (4.3%)	4.9 (1.9, 12)	<0.001	0.480
	No DMARD	17/ 93 (18.3%)	5/ 95 (5.3%)			
	DMARD	8/ 45 (17.8%)	1/ 44 (2.3%)			
12	All	29/138 (21.0%)	11/139 (7.9%)	3.1 (1.5, 6.5)	0.002	0.225
	No DMARD	18/ 93 (19.4%)	9/ 95 (9.5%)			
	DMARD	11/ 45 (24.4%)	2/ 44 (4.5%)			
24	All	24/138 (17.4%)	5/139 (3.6%)	5.7 (2.1, 15)	<0.001	0.578
	No DMARD	16/ 93 (17.2%)	4/ 95 (4.2%)			
	DMARD	8/ 45 (17.8%)	1/ 44 (2.3%)			

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 18. Study 016.0037 Analysis of % Change from Baseline Patient Global Assessment in mITT Population

Visit Number	Statistics	TNFR:Fc25	Placebo	Difference (95%CI)	pValue (Wilcoxon)
2	N	136	135		
	Mean+/-SD	31.2 +/- 40.3	7.6 +/- 41.1		
	Q1,Median,Q3	6.1, 27.9, 66.9	-7.9, 9.6, 31.9	21.6 (12.5, 31.3)	<0.001
4	N	134	136		
	Mean+/-SD	37.3 +/- 46.5	5.4 +/- 45.5		
	Q1,Median,Q3	14.3, 44.0, 75.0	-16.3, 5.5, 35.3	34.6 (23.4, 44.5)	<0.001
8	N	132	137		
	Mean+/-SD	40.5 +/- 45.9	6.3 +/- 49.4		
	Q1,Median,Q3	14.2, 54.3, 76.4	-14.9, 4.9, 33.8	38.0 (27.6, 48.1)	<0.001
12	N	132	132		
	Mean+/-SD	42.5 +/- 47.6	11.9 +/- 43.5		
	Q1,Median,Q3	14.1, 51.8, 84.4	-6.6, 9.3, 34.3	35.4 (23.9, 46.2)	<0.001
24	N	124	121		
	Mean+/-SD	44.6 +/- 46.3	11.6 +/- 41.9		
	Q1,Median,Q3	13.3, 55.4, 82.5	-15.5, 10.4, 37.3	36.6 (24.9, 48.6)	<0.001

Note: Hodges-Lehman 95% confidence interval for between group difference in median.
Wilcoxon rank-sum test between group difference.

Table 19. Study 016.0037 Analysis of % Change from Baseline Doctor Global Assessment in mITT Population

Visit Number	Statistics	TNFR:Fc25	Placebo	Difference (95%CI)	pValue (Wilcoxon)
2	N	134	133		
	Mean+/-SD	15.2 +/- 62.8	3.8 +/- 49.1		
	Q1,Median,Q3	0.0, 20.9, 45.9	-7.0, 5.5, 23.2	12.5 (4.7, 21.2)	0.002
4	N	136	135		
	Mean+/-SD	19.1 +/- 68.1	6.8 +/- 37.6		
	Q1,Median,Q3	-2.5, 22.9, 56.5	-11.1, 5.2, 27.9	16.4 (7.7, 25.6)	<0.001
8	N	133	136		
	Mean+/-SD	31.3 +/- 59.0	8.9 +/- 54.2		
	Q1,Median,Q3	12.3, 40.0, 62.5	-6.7, 10.6, 35.8	24.2 (14.7, 33.7)	<0.001
12	N	133	133		
	Mean+/-SD	35.0 +/- 60.6	11.7 +/- 53.7		
	Q1,Median,Q3	16.7, 46.0, 68.6	-2.3, 14.5, 36.1	26.9 (17.3, 36.0)	<0.001
24	N	125	121		
	Mean+/-SD	32.2 +/- 76.2	8.1 +/- 68.4		
	Q1,Median,Q3	5.1, 49.2, 71.7	-9.2, 17.6, 42.9	25.2 (13.4, 36.9)	<0.001

Note: Hodges-Lehman 95% confidence interval for between group difference in median.
Wilcoxon rank-sum test between group difference.

Table 20. Study 016.0037 Analysis of % Change from Baseline Back Pain Score in mITT Population

Visit Number	Statistics	TNFR:Fc25	Placebo	Difference (95%CI)	pValue (Wilcoxon)
2	N	136	134		
	Mean+/-SD	30.3 +/- 75.6	-0.3 +/-114.3		
	Q1,Median,Q3	4.7, 32.6, 71.1	-10.2, 5.5, 31.6	25.9 (16.5, 35.8)	<0.001
4	N	136	136		
	Mean+/-SD	33.8 +/- 87.4	-5.2 +/-128.3		
	Q1,Median,Q3	5.4, 46.6, 75.7	-11.2, 6.5, 36.4	31.4 (20.0, 42.4)	<0.001
8	N	133	137		
	Mean+/-SD	37.7 +/- 91.0	10.2 +/- 42.6		
	Q1,Median,Q3	11.3, 54.5, 78.4	-11.6, 6.3, 38.3	35.6 (24.9, 46.3)	<0.001
12	N	133	132		
	Mean+/-SD	41.8 +/- 70.0	7.6 +/- 76.8		
	Q1,Median,Q3	14.7, 57.7, 81.0	-12.6, 5.8, 42.7	37.9 (27.0, 48.3)	<0.001
24	N	125	121		
	Mean+/-SD	41.7 +/- 78.1	7.3 +/- 66.5		
	Q1,Median,Q3	14.5, 56.3, 84.4	-12.8, 8.0, 34.9	38.4 (27.3, 49.4)	<0.001

Note: Hodges-Lehman 95% confidence interval for between group difference in median.
Wilcoxon rank-sum test between group difference.

Table 21. Study 016.0037 Analysis of % Change from Baseline BASFI in mITT Population

Visit Number	Statistics	TNFR:Fc25	Placebo	Difference (95%CI)	pValue (Wilcoxon)
2	N	136	135		
	Mean+/-SD	19.8 +/- 36.9	1.9 +/- 45.9		
	Q1,Median,Q3	-3.4, 17.3, 44.6	-8.3, 3.3, 23.1	12.6 (5.4, 20.9)	<0.001
4	N	136	137		
	Mean+/-SD	26.1 +/- 41.6	1.8 +/- 44.4		
	Q1,Median,Q3	0.3, 22.0, 56.8	-12.6, 1.3, 20.8	21.7 (12.8, 31.1)	<0.001
8	N	133	138		
	Mean+/-SD	32.2 +/- 39.5	1.3 +/- 53.1		
	Q1,Median,Q3	4.2, 29.2, 61.7	-16.1, 2.2, 26.9	27.0 (17.6, 36.7)	<0.001
12	N	132	133		
	Mean+/-SD	34.3 +/- 41.0	7.7 +/- 38.4		
	Q1,Median,Q3	2.8, 35.3, 71.2	-13.2, 5.3, 29.6	27.1 (17.1, 37.5)	<0.001
24	N	125	121		
	Mean+/-SD	33.7 +/- 42.1	7.8 +/- 36.1		
	Q1,Median,Q3	4.4, 37.0, 68.3	-15.5, 2.0, 28.2	27.9 (18.1, 38.1)	<0.001

Note: Hodges-Lehman 95% confidence interval for between group difference in median.
Wilcoxon rank-sum test between group difference.

Table 22. Study 016.0037 Analysis of % Change from Baseline BASDAI in mITT Population

Visit Number	Statistics	TNFR:Fc25	Placebo	Difference (95%CI)	pValue (Wilcoxon)
2	N	136	135		
	Mean+/-SD	32.1 +/- 40.2	9.0 +/- 37.2		
	Q1,Median,Q3	5.1, 32.5, 61.4	-6.2, 8.2, 31.1	23.0 (13.8, 31.6)	<0.001
4	N	136	137		
	Mean+/-SD	38.5 +/- 43.9	10.1 +/- 39.8		
	Q1,Median,Q3	8.5, 38.3, 76.8	-10.4, 5.6, 36.3	27.9 (18.3, 38.1)	<0.001
8	N	133	138		
	Mean+/-SD	44.8 +/- 41.6	11.2 +/- 47.5		
	Q1,Median,Q3	14.8, 52.4, 78.8	-7.0, 11.5, 40.0	32.5 (22.8, 42.3)	<0.001
12	N	132	133		
	Mean+/-SD	46.1 +/- 43.1	15.8 +/- 42.0		
	Q1,Median,Q3	14.2, 57.0, 82.1	-5.4, 11.5, 45.3	30.7 (21.0, 41.4)	<0.001
24	N	125	121		
	Mean+/-SD	46.8 +/- 42.1	10.2 +/- 46.4		
	Q1,Median,Q3	14.0, 50.9, 85.2	-9.2, 10.1, 34.7	36.9 (26.5, 47.8)	<0.001

Note: Hodges-Lehman 95% confidence interval for between group difference in median.
Wilcoxon rank-sum test between group difference.

Table 23. Study 016.0037 Analysis of ASAS50 Responders
Adjusted for randomization stratum
(Excluding patients with protocol violations for 'conduct')

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	46/111 (41.4%)	15/120 (12.5%)	4.9 (2.5, 9.5)	<0.001	0.469
24	41/111 (36.9%)	10/120 (8.3%)	6.4 (3.0, 14)	<0.001	0.324

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 24. Study 016.0037 Analysis of ASAS70 Responders
Adjusted for randomization stratum
(Excluding patients with protocol violations for 'conduct')

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	27/111 (24.3%)	7/120 (5.8%)	5.2 (2.1, 12)	<0.001	0.566
24	29/111 (26.1%)	6/120 (5.0%)	6.6 (2.6, 17)	<0.001	0.250

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 25. Study 016.0037 Analysis of Partial Remission (Y/N)
Adjusted for randomization stratum
(Excluding patients with protocol violations for 'conduct')

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	21/111 (18.9%)	8/120 (6.7%)	3.3 (1.4, 7.7)	0.005	0.554
24	17/111 (15.3%)	4/120 (3.3%)	5.3 (1.7, 16)	0.002	0.943

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 26. Study 016.0037 Analysis of ASAS50 Responders
Adjusted for randomization stratum
(Treating patients with protocol violations for 'conduct' as nonresponders)

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	46/138 (33.3%)	15/139 (10.8%)	4.1 (2.2, 7.8)	<0.001	0.435
24	41/138 (29.7%)	10/139 (7.2%)	5.4 (2.6, 11)	<0.001	0.328

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 27. Study 016.0037 Analysis of ASAS70 Responders
Adjusted for randomization stratum
(Treating patients with protocol violations for 'conduct' as nonresponders)

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	27/138 (19.6%)	7/139 (5.0%)	4.6 (1.9, 11)	<0.001	0.534
24	29/138 (21.0%)	6/139 (4.3%)	5.8 (2.3, 14)	<0.001	0.235

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 28. Study 016.0037 Analysis of Partial Remission (Y/N)
Adjusted for randomization stratum
(Treating patients with protocol violations for 'conduct' as nonresponders)

Visit Number	TNFR:Fc25	Placebo	OR (95%CI) for Response	pValue (CMH)	pValue (Breslow-Day)
12	29/138 (21.0%)	11/139 (7.9%)	3.1 (1.5, 6.5)	0.002	0.225
24	24/138 (17.4%)	5/139 (3.6%)	5.7 (2.1, 15)	<0.001	0.578

Note: Cochran-Mantel-Haenszel (CMH) test for between group difference.
Breslow-Day test for homogenious treatment effect across strata.

Table 29. Study 016.0037 All Adverse Events in Safety Population
Patient incidence in descrease order

(Including all AEs with date missing or >= date of 1st dose)

Preferred Term	TNFR:Fc25 N=138	Placebo N=139
Any SAE	99 (71.7%)	105 (75.5%)
HEM INJECT SITE	29 (21.0%)	23 (16.5%)
HEADACHE	19 (13.8%)	16 (11.5%)
INJURY ACCID	17 (12.3%)	6 (4.3%)
DIARRHEA	11 (8.0%)	13 (9.4%)
RASH	11 (8.0%)	9 (6.5%)
RHINITIS	8 (5.8%)	9 (6.5%)
PAIN ABDO	8 (5.8%)	7 (5.0%)
DIZZINESS	8 (5.8%)	3 (2.2%)
NAUSEA	7 (5.1%)	7 (5.0%)
ASTHENIA	5 (3.6%)	7 (5.0%)
DYSPEPSIA	5 (3.6%)	2 (1.4%)
COUGH INC	5 (3.6%)	1 (0.7%)
ECCHYMOSIS	4 (2.9%)	6 (4.3%)
VOMIT	4 (2.9%)	4 (2.9%)
PAIN	4 (2.9%)	3 (2.2%)
PRURITUS	4 (2.9%)	3 (2.2%)
THROAT IRRITATION	4 (2.9%)	2 (1.4%)
BONE FRACT SPONTAN	4 (2.9%)	
PARESTHESIA	3 (2.2%)	4 (2.9%)
HEM GI	3 (2.2%)	3 (2.2%)
FEVER	3 (2.2%)	2 (1.4%)
SINUSITIS	3 (2.2%)	2 (1.4%)
SEASONAL ALLERGY	3 (2.2%)	1 (0.7%)
DEPRESSION	2 (1.4%)	3 (2.2%)
EDEMA PERIPH	2 (1.4%)	3 (2.2%)
IRITIS	2 (1.4%)	3 (2.2%)
PAIN BONE	2 (1.4%)	3 (2.2%)
HYPERTENS	2 (1.4%)	2 (1.4%)
SKIN DIS	2 (1.4%)	2 (1.4%)
SPASM GENERAL	2 (1.4%)	2 (1.4%)
DYSURIA	2 (1.4%)	1 (0.7%)
LYMPHADENO	2 (1.4%)	1 (0.7%)
TREMOR	2 (1.4%)	1 (0.7%)
WEIGHT INC	2 (1.4%)	1 (0.7%)
ABDO ENLARGE	2 (1.4%)	
ARTHRALGIA	2 (1.4%)	
FLATUL	2 (1.4%)	
MIGRAINE	2 (1.4%)	
SJOGRENS SYNDROME	2 (1.4%)	
URTICARIA	2 (1.4%)	
UVEITIS	1 (0.7%)	5 (3.6%)
MYALGIA	1 (0.7%)	4 (2.9%)
PAIN BACK	1 (0.7%)	3 (2.2%)
RECTAL DIS	1 (0.7%)	3 (2.2%)
CONJUNCTIVITIS	1 (0.7%)	2 (1.4%)

Table 29. (cont'd) Study 016.0037 All Adverse Events in Safety Population
Patient incidence in descrease order
(Including all AEs with date missing or >= date of 1st dose)

Preferred Term	TNFR:Fc25 N=138	Placebo N=139
CONSTIP	1 (0.7%)	2 (1.4%)
INSOMNIA	1 (0.7%)	2 (1.4%)
PSORIASIS	1 (0.7%)	2 (1.4%)
VASODILAT	1 (0.7%)	2 (1.4%)
VERTIGO	1 (0.7%)	2 (1.4%)
ALLERG REACT	1 (0.7%)	1 (0.7%)
ASTHMA	1 (0.7%)	1 (0.7%)
CHILLS	1 (0.7%)	1 (0.7%)
COLITIS	1 (0.7%)	1 (0.7%)
DERM CONTACT	1 (0.7%)	1 (0.7%)
DIABETES MELL	1 (0.7%)	1 (0.7%)
EYE DIS	1 (0.7%)	1 (0.7%)
ILEITIS	1 (0.7%)	1 (0.7%)
PAIN INJECT SITE	1 (0.7%)	1 (0.7%)
SYNCOPE	1 (0.7%)	1 (0.7%)
ULCER MOUTH	1 (0.7%)	1 (0.7%)
URIN RETENT	1 (0.7%)	1 (0.7%)
VESTIBUL DIS	1 (0.7%)	1 (0.7%)
ACNE	1 (0.7%)	
AMBLYOPIA	1 (0.7%)	
APPETITE INC	1 (0.7%)	
ARTHRITIS	1 (0.7%)	
COLITIS ULCER	1 (0.7%)	
CONVULS GRAND MAL	1 (0.7%)	
CRAMPS LEG	1 (0.7%)	
DEHYDRAT	1 (0.7%)	
DREAM ABNORM	1 (0.7%)	
DRY MOUTH	1 (0.7%)	
EPISTAXIS	1 (0.7%)	
GASTROENTERITIS	1 (0.7%)	
GI DIS	1 (0.7%)	
HEM RECTAL	1 (0.7%)	
HEMATURIA	1 (0.7%)	
HERNIA	1 (0.7%)	
HYPERTROPHY SKIN	1 (0.7%)	
JOINT DIS	1 (0.7%)	
JOINT SWELLING	1 (0.7%)	
NAIL DIS	1 (0.7%)	
NERVOUSNESS	1 (0.7%)	
NEURALGIA	1 (0.7%)	
OBSTRUCT INTEST	1 (0.7%)	
PAIN NECK	1 (0.7%)	
PERICARDITIS	1 (0.7%)	
SLEEP DIS	1 (0.7%)	
STOMATITIS	1 (0.7%)	
STOMATITIS ULCER	1 (0.7%)	

Table 29. (cont'd) Study 016.0037 All Adverse Events in Safety
Patient incidence in descrease order
(Including all AEs with date missing or >= date of 1st dose)

Preferred Term	TNFR:Fc25 N=138	Placebo N=139
STOOL ABNORM	1 (0.7%)	
TENOSYNOVITIS	1 (0.7%)	
THINKING ABNORM	1 (0.7%)	
TWITCH	1 (0.7%)	
VASC DIS	1 (0.7%)	
VISION ABNORM	1 (0.7%)	
ANXIETY		4 (2.9%)
EDEMA FACE		3 (2.2%)
PAIN CHEST		3 (2.2%)
CONJUNCTIV ALLERGIC		2 (1.4%)
DYSPNEA		2 (1.4%)
GOUT		2 (1.4%)
SOMNOLENCE		2 (1.4%)
BREAST FIBROCYST		1 (0.7%)
BURSITIS		1 (0.7%)
DYSMENORRHEA		1 (0.7%)
ESOPHAGITIS		1 (0.7%)
HEMATEMESIS		1 (0.7%)
HYPERTONIA		1 (0.7%)
IMPOTENCE		1 (0.7%)
KIDNEY CALCULUS		1 (0.7%)
MELENA		1 (0.7%)
MENS DIS		1 (0.7%)
OSTEOPOROSIS		1 (0.7%)
PROSTAT DIS		1 (0.7%)
RASH VESIC BULL		1 (0.7%)
SKIN DISCOLOR		1 (0.7%)
SKIN DRY		1 (0.7%)
SPLENOMEGALY		1 (0.7%)
STUPOR		1 (0.7%)
SUICIDE ATTEMPT		1 (0.7%)
TASTE PERVERS		1 (0.7%)
TINNITUS		1 (0.7%)
ULCER STOMACH		1 (0.7%)
URETHRITIS		1 (0.7%)
WEIGHT DEC		1 (0.7%)

Table 30. Study 016.0037 Serious Adverse Events in Safety Population
Patient incidence in descrease order

Preferred Term	TNFR:Fc25 N=138	Placebo N=139
Any SAE	9 (6.5%)	5 (3.6%)
BONE FRACT SPONTAN	3 (2.2%)	
CELLULITIS	1 (0.7%)	
COLITIS	1 (0.7%)	
FEVER	1 (0.7%)	
INFECT	1 (0.7%)	
LYMPHADENO	1 (0.7%)	
OBSTRUCT INTEST	1 (0.7%)	
RASH	1 (0.7%)	
INJURY ACCID		2 (1.4%)
INFECT VIRAL		1 (0.7%)
PAIN CHEST		1 (0.7%)
SUICIDE ATTEMPT		1 (0.7%)

Table 31. Study 016.0037 Infectious Adverse Events in Safety Population Patient incidence in descrease order

Preferred Term	TNFR:Fc25 N=138	Placebo N=139
Any SAE	57 (41.3%)	42 (30.2%)
UPPER RESP INFECT	28 (20.3%)	16 (11.5%)
FLU SYND	5 (3.6%)	10 (7.2%)
PHARYNGITIS	5 (3.6%)	1 (0.7%)
RHINITIS	4 (2.9%)	1 (0.7%)
BRONCHITIS	3 (2.2%)	1 (0.7%)
INFECT	3 (2.2%)	1 (0.7%)
SINUSITIS	2 (1.4%)	1 (0.7%)
GINGIVITIS	2 (1.4%)	
INFECT URIN TRACT	1 (0.7%)	2 (1.4%)
TOOTH CARIES	1 (0.7%)	2 (1.4%)
CELLULITIS	1 (0.7%)	1 (0.7%)
CHOLECYST	1 (0.7%)	
COLITIS	1 (0.7%)	
CYSTITIS	1 (0.7%)	
DERM FUNG	1 (0.7%)	
FURUNCULOSIS	1 (0.7%)	
LARYNGITIS	1 (0.7%)	
MONILIA VAGINA	1 (0.7%)	
PNEUMONIA	1 (0.7%)	
URETHRITIS	1 (0.7%)	
VAGINITIS	1 (0.7%)	
GASTROENTERITIS		4 (2.9%)
HERPES SIMPLEX		3 (2.2%)
ABSCESS PERIODONT		2 (1.4%)
OTITIS MED		2 (1.4%)
CONJUNCTIVITIS		1 (0.7%)
ENTERITIS		1 (0.7%)
INFECT FUNG		1 (0.7%)