PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

GENERIC DRUG NAME / COMPOUND NUMBER: Ozoralizumab (ATN-103) / PF-05230896

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not applicable.

NATIONAL CLINICAL TRIAL NO.: NCT00959036

PROTOCOL NO.: 3242K1-2000-WW (B2271003)

PROTOCOL TITLE:

A Seamless, Phase 1/2, Multiple Ascending Dose, Proof of Concept Study of ATN-103 Administered to Subjects With Active Rheumatoid Arthritis on a Background of Methotrexate

Study Centres:

A total of 52 centres took part in the study and enrolled subjects, including 27 in the United States (US), 9 in the Russian Federation, 5 in Canada, 4 in South Africa (SA), 2 each in Hungary and Serbia, and 1 each in Belgium, Switzerland, and Germany.

Study Initiation and Completion Dates:

03 September 2009 to 12 January 2011

Phase of Development:

Phase 2

Study Objectives:

- Primary Objective: To evaluate the safety and clinical efficacy of multiple ascending doses (MADs) of ozoralizumab administered subcutaneously (SC) to subjects with active rheumatoid arthritis (RA) compared with placebo.

- Secondary Objective: To assess the tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and the optimal treatment frequency regimen for ozoralizumab (administered every 4 weeks [Q4] versus every 8 weeks [Q8]).

METHODS

Study Design:

This was a seamless Phase 1/Phase 2, randomised, stratified, double-blind, placebo-controlled study. The study was designed to commence as a conventional,

sequentially enrolling MAD study before converting to a parallel enrolling, adaptive, proof-of-concept dose-ranging study in subjects with active RA. Each subject participated in the study for approximately 24 weeks. This included a screening period of up to 4 weeks, a 16 week treatment period, and a 4 week follow-up (FU) period.

There were a total of 6 treatment groups:

- Treatment Group 1 (10 mg Q4): ozoralizumab 10 mg every 4 weeks until Week 12.
- Treatment Group 2 (10 mg Q8): ozoralizumab 10 mg every 8 weeks until Week 12 (with placebo given at the intervening 4-Week Visit).
- Treatment Group 3 (30 mg Q4): ozoralizumab 30 mg every 4 weeks until Week 12.
- Treatment Group 4 (80 mg Q4): ozoralizumab 80 mg every 4 weeks until Week 12.
- Treatment Group 5 (80 mg Q8): ozoralizumab 80 mg every 8 weeks until Week 12 (with placebo given at the intervening 4 Week Visit).
- Treatment Group 6 (Placebo Q4): placebo every 4 weeks.

Number of Subjects (Planned and Analysed):

Approximately 240 subjects were planned to be in included in this study (40 subjects per treatment group) in order to achieve 33 completed subjects in each treatment group. A total of 628 subjects were screened of which 374 were screen failures. Therefore, a total of 254 subjects were enrolled including 110 in the US, 49 in the Russian Federation, 48 in SA, 14 in Canada, 13 in Hungary, 10 in Serbia, 7 in Switzerland, 2 in Belgium, and 1 in Germany. Of these, 253 subjects received treatment and were included in the modified intent-to-treat (mITT) and safety populations.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects aged 18-80 years with clinical diagnosis of active RA on a stable background of methotrexate (7.5-25 mg weekly), who met the American College of Rheumatology (ACR) 1987 revised criteria for classification of RA at least 24 weeks prior to screening and ACR functional Class 1 to 3, high-sensitivity C-reactive protein (hs-CRP) concentration ≥8 mg/L (0.8 mg/dL) at Screening were included in the study.

Main Exclusion Criteria: Subjects with any significant health problem other than RA, any clinically significant laboratory abnormalities, any prior use of B cell-depleting therapy, a history or suspicion of (received antibiotics for) a joint prosthesis infection if prosthesis was not removed or replaced, history of cancer or lymphoproliferative disease within previous 5 years, Class 3 or 4 congestive heart failure as defined by the New York Heart Association were excluded from the study. Known or suspected allergy to ATN-103, any type of tumor necrosis factor alpha inhibitor (TNFi), human immunoglobulin (Ig) proteins, or other compounds related to these classes of medications.

Study Treatment:

Each subject was administered a single SC injection of either ozoralizumab or placebo at 4-week intervals for a total of 4 SC injections and participated in only 1 of the following 6 treatment groups (as mentioned above): 10 mg Q4, 10 mg Q8, 30 mg Q4, 80 mg Q4, 80 mg Q8, and placebo Q4.

Each subject remained at the site for a minimum of 60 minutes following administration for monitoring of any hypersensitivity reactions. The treatment period was 16 weeks.

Efficacy Evaluations:

Primary Efficacy Endpoints: The proportion of subjects with at least a 20% improvement from Baseline in ACR (ACR20 response) at Week 16.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints included, but were not limited to:

RA assessments:

- Standardized joint assessment: number of swollen and tender joints. Joint assessors assessed 28 joints for tenderness as follows: 0= no tenderness; 1= any tenderness; JR = joint replacement; NE = not evaluable, and for swelling as follows: 0= no swelling; 1= any swelling; JR = joint replacement; NE = not evaluable.
- Pain visual analog scale (VAS) (0 mm to 100 mm).
- Physician global assessment and patient global assessment on a 0 to 10 scale were completed in a manner that did not bias the Investigator or the Subject.
- Duration of morning stiffness was provided in minutes and up to a maximum of 1440 minutes.
- General health VAS (0 mm to 100 mm) a clinical assessment of the subject's response to therapy.
- Disease Activity Score (DAS) 28 a weighted calculation of the 28-joint count for tenderness and swelling (tenderness scores based on Ritchie Articular Index), hs-CRP, and general health VAS European League Against Rheumatism (EULAR) response as derived from the DAS28.
- ACR20 response (at all scheduled time points except for week 16- week 16 = primary endpoint).
- ACR50 (proportion of subjects with at least a 50% improvement from Baseline in ACR) response (at all scheduled time points).

- ACR70 (proportion of subjects with at least a 70% improvement from Baseline in ACR) response (at all scheduled time points).
- The ACR-N (at all scheduled time points). ACR-N was defined as the lowest of:
    - the percent change from Baseline in the SJC.
    - the percent change from Baseline in TJC.
    - the median of the percent changes from Baseline in the other 5 ACR measures (physician global assessment, patient global assessments, pain VAS, health assessment questionnaire disability index [HAQ-DI], and [hs-CRP]).

Health Outcome Assessments:

- Quality of life as assessed by the HAQ-DI.
- General quality of life as assessed by the SF-36.
- Tiredness scale.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

Pharmacokinetic Evaluations: The following ozoralizumab PK parameters were computed for all dose groups: area under the plasma concentration-time curve (AUC) for first and last dose, terminal elimination half-life ($t_{½}$) for the last dose, accumulation ratio on ozoralizumab AUC exposure between the first and last doses, apparent volume of distribution (V_Z/F), and apparent clearance. The timing of blood sample collection was designed primarily to assess PK exposure after the first dose and last dose for the Q4 week regimens.

Pharmacodynamic Evaluations: Blood levels were measured for PD biomarkers: interleukin (IL)-6, hs-CRP, serum amyloid A, and matrix metalloproteinase-3.

Immunogenicity Assessments: Blood samples for anti-drug antibodies (ADA) were collected and analysed at Baseline, Weeks 4, 8, 16, and 20 for all subjects in the mITT population. Samples collected at Baseline are designated as "baseline" and samples collected at Weeks 4, 8, 16, and 20 are designated as "on-treatment". Blood samples were collected to measure anti-ozoralizumab antibodies at specific time points. Subjects whose blood samples tested positive for antibodies to ozoralizumab also had their blood samples further characterized for neutralizing antibodies (Nabs) to ozoralizumab. A validated assay was used for the detection of anti-ozoralizumab antibodies.

Safety Evaluations:

The safety and tolerability of ozoralizumab was determined using the following assessments: monitoring of adverse events (AEs)/serious adverse events (SAEs) (including injection site reactions [ISRs] and infections), concomitant medications, physical examination findings, vital sign measurements, autoantibody assessments, premature withdrawals, and clinical laboratory determinations.

Statistical Methods:

All statistical tests were 2-sided at alpha level of 0.05 unless stated otherwise. If there were multiple records within a data analysis interval, the last evaluation record within the data analysis interval was used for numeric summary unless stated otherwise.

Measurement of 1 PD parameter, TNF, was not performed due to the inability to develop a TNF assay with samples containing ozoralizumab. Therefore, no analysis was done for this PD parameter.

Analysis of Efficacy Variables: The primary population for the efficacy analysis was the mITT population, defined as all randomised subjects who received at least 1 dose of the Investigational product. The primary efficacy endpoint of the study was the ACR20 response at Week 16.

Categorical variables (eg ACR50 and ACR70), including the primary endpoint were analysed using the Cochran-Mantel-Haenszel test stratified by prior TNFi use status (TNFi naive or prior TNFi use).

For endpoints such as DAS28, patient and physician global assessment, pain VAS, and health outcome assessments considered to be continuous variables, the change from Baseline was analysed using an analysis of covariance (ANCOVA), with treatment and prior TNFi use status (TNFi naive or prior TNFi use) as factors and baseline as a covariate.

Analysis of Safety Variables: Analysis of safety data was based on the safety population, defined as all subjects who received at least 1 dose of the Investigational product. In practice the mITT population and the safety population were the same.

- AEs and Treatment-Emergent AEs (TEAEs): The percentages of subjects experiencing AEs and TEAEs were compared among treatment groups using the Fisher's exact test. p-Values for the overall comparisons as well as for all active versus placebo comparisons were provided.

- Laboratory Evaluations: Laboratory results were summarised both as continuous and categorical endpoints. For continuous endpoints, ANCOVA models with a baseline value as covariate were applied to the change from Baseline values for each study time point. Both within-group and between-group comparisons were conducted. Number, mean, standard deviation, adjusted mean and standard error, median, minimum, maximum) values were reported.

- Autoantibody Analyses: Frequency of positive antibody by time point is provided. p-Values for between treatment comparisons from Fisher's exact test were also given. The frequency of antibody status change from Baseline to each time point was provided. A McNemar test was used to compare the antibody status change before and after treatment.

- Vital Signs: Statistical analysis methods similar to those used for clinical laboratory evaluations were used for vital signs.

Adverse Events of Special Interest:

- Medically Important Infections: Medically important infections (defined as an infection requiring parenteral anti-infective agents and/or hospitalization) were summarised in 2 ways: proportion of subjects with infections and number of infections per subject-year.

  The incidence of infections was summarised in the same manner as AEs/TEAEs.

- Injection Site Reaction: If an ISR following 1 injection was reported at >1 level of intensity (itching, redness, swelling, pain, and ulceration), the maximum intensity was counted. Summary statistics, including maximum intensity per subject, number of ISRs per subject, number and percentage of subjects with at least 1 ISR, number and percentage of subjects with ISRs by number of ISR, ISRs per injection, and days from first Investigational product administration to first ISR per subject, were reported by treatment group. The incidence of ISRs and ISRs per subject-year was also summarised by intensity of ISR and treatment group. The number of ISRs per subject was also summarised by treatment group and by each injection.

Pharmacokinetic and Pharmacodynamic Analyses:

- Pharmacokinetic Analysis: The following ozoralizumab PK parameters were computed: AUC for first and last dose; elimination half-life for the last dose; accumulation ratio on ozoralizumab AUC exposure between the first and last doses; V_z/F; and apparent clearance.

- Pharmacodynamic Analysis: The change from Baseline in PD parameters was analysed using an ANCOVA with treatment, and TNFi prior use (TNFi naive or prior TNFi use) as factors and baseline as a covariate.

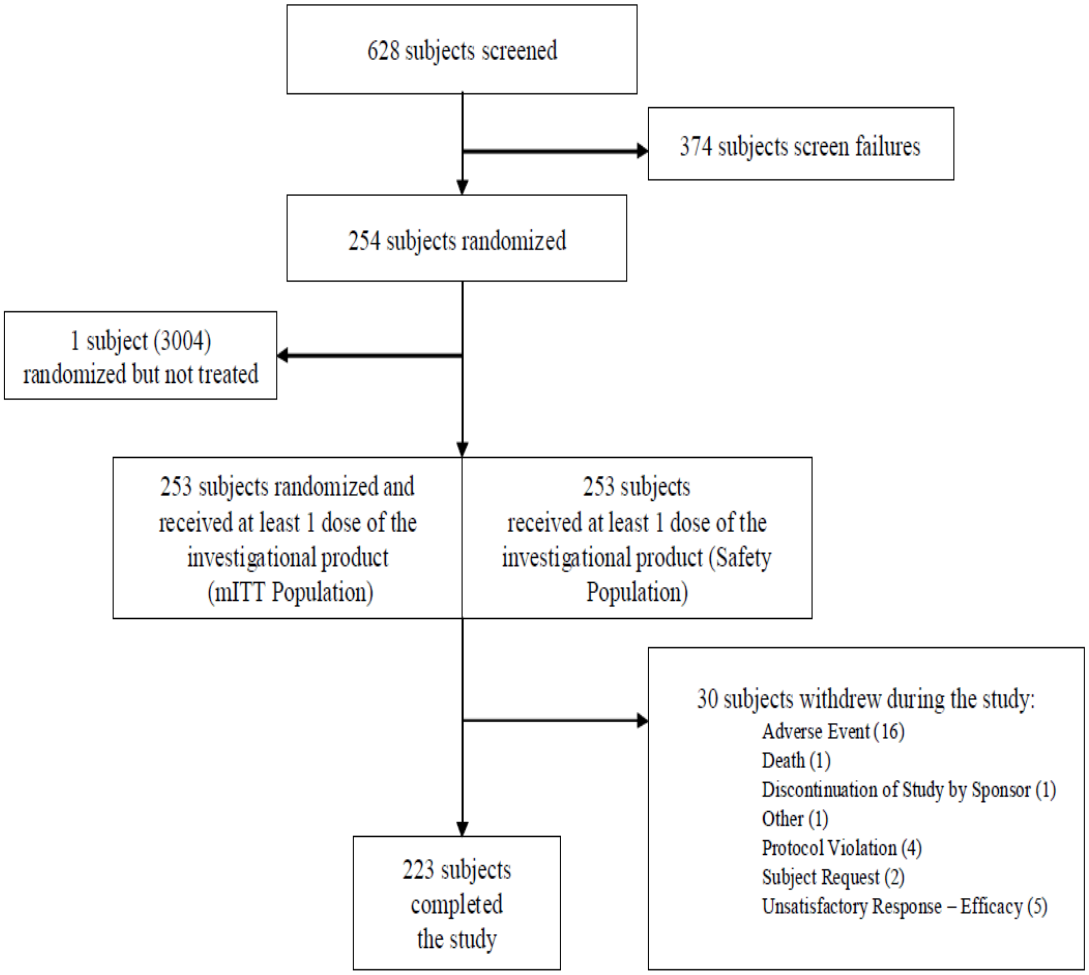
Immunogenicity Analysis: The number and percentage of subjects with positive ADA at Baseline and post dose time points was determined based on ADA-titer above a cut-off threshold and tabulated by dose group and time point. The number and percentage of subjects with positive increase-over-Baseline (IOB) ADA response was tabulated by dose group and time point.

RESULTS

Subject Disposition and Demography:

A total of 254 subjects were randomised and 253 subjects were treated and included in the mITT and safety populations. The number of subjects per treatment group ranged from 40 to 45. One (1) subject, who was randomized to the 30 mg Q4 treatment group, withdrew from the study following a vasovagal episode prior to receiving any Investigational product. Subject disposition is outlined in flow chart Figure 1.

Figure 1. Subject Disposition



mITT = modified intent-to-treat.

Table 1 summarises the primary reasons (n, %) for withdrawal from the study. There were no statistically significant differences in the number of completers and discontinuations in the ozoralizumab treatment groups compared with the placebo group. A total of 30 (11.9%) subjects discontinued from the study.

The safety population (and mITT population) consisted of 203 (80.2%) females and 50 (19.8%) males, with an age range of 18 years to 79 years, and a mean age of 52.1 years. A summary of the subject demography is presented in Table 2.

Table 1. Primary Reasons for Subject Discontinuation From the Study - Safety Population

Conclusion Status Reason	p-Value	Placebo N=45	Ozoralizumab, n (%) 10 mg Q8 N=41	 10 mg Q4 N=42	 30 mg Q4 N=40	 80 mg Q8 N=42	 80 mg Q4 N=43	Total N=253
Total		45 (100.0)	41 (100.0)	42 (100.0)	40 (100.0)	42 (100.0)	43 (100.0)	253 (100.0)
Completed	0.344	38 (84.4)	36 (87.8)	36 (85.7)	36 (90.0)	35 (83.3)	42 (97.7)	223 (88.1)
Discontinued	0.344	7 (15.6)	5 (12.2)	6 (14.3)	4 (10.0)	7 (16.7)	1 (2.3)	30 (11.9)
Adverse event	0.561	2 (4.4)	2 (4.9)	3 (7.1)	3 (7.5)	5 (11.9)	1 (2.3)	16 (6.3)
Death	0.411	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Discontinuation of study by Sponsor	0.411	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Other	0.411	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Protocol violation	0.376	0 (0.0)	2 (4.9)	1 (2.4)	1 (2.5)	0 (0.0)	0 (0.0)	4 (1.6)
Subject request	0.097	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Unsatisfactory response efficacy	0.173	3 (6.7)	1 (2.4)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.0)

p-Value is an overall p-Value.
N = number of subjects in each treatment group; n = number of subjects in each category; Q4 = every 4 weeks; Q8 = every 8 weeks.

Table 2. Demographic Characteristics of the Safety Population

Conclusion Status Reason	Overall p-Value	Placebo N=45	Ozoralizumab 10 mg Q8 N=41	Ozoralizumab 10 mg Q4 N=42	Ozoralizumab 30 mg Q4 N=40	Ozoralizumab 80 mg Q8 N=42	Ozoralizumab 80 mg Q4 N=43	Total N=253
Age (years)	0.224[a]							
Mean ± SD		51.16±13.14	53.76±10.17	55.29±10.45	49.10±13.62	52.64±12.06	50.42±14.12	52.06±12.41
Min, Max		24, 79	31, 74	21, 74	18, 73	27, 76	26, 79	18, 79
Median		50.0	53.0	56.0	52.0	51.5	49.0	52.0
Sex, n (%)	0.170[b]							
Female		35 (77.8)	28 (68.3)	34 (81.0)	31 (77.5)	38 (90.5)	37 (86.0)	203 (80.2)
Male		10 (22.2)	13 (31.7)	8 (19.0)	9 (22.5)	4 (9.5)	6 (14.0)	50 (19.8)

p-Value is an overall p-Value.
Max = maximum; Min = minimum; Q4 = every 4 weeks; Q8 = every 8 weeks; N = number of subjects; n = number of subjects in specified criteria;
SD = standard deviation.
a. One-way analysis of variance with treatment as factor.
b. Chi-square test p-Value (2-tail).

Efficacy Results:

ACR20 Response at Week 16: The primary analysis (last observation carried forward [LOCF]) of the primary efficacy endpoint is presented in Table 3. The number of ACR20 responders at Week 16 was statistically significantly greater in the 80 mg Q4 group than in the placebo group. No other ozoralizumab dosage group showed a significantly greater number of subjects with an ACR20 at Week 16 than in the placebo group.

Table 3. Analyses of ACR20 at Week 16 – mITT Population (LOCF Analysis)

Analysis Treatment (N)	n (%)	p-Value		Placebo Adjusted Difference (CI)
		Ozoralizumab vs placebo	Overall	
Placebo (N=45)	19 (42.2)		0.120	
OZ 10 mg Q8 (N=41)	20 (48.8)	0.390		6.6 (3.6, 19.6)
OZ 10 mg Q4 (N=42)	22 (52.4)	0.130		10.2 (9.3, 24.7)
OZ 30 mg Q4 (N=40)	24 (60.0)	0.122		17.8 (9.4, 25.0)
OZ 80 mg Q8 (N=42)	25 (59.5)	0.101		17.3 (12.2, 27.9)
OZ 80 mg Q4 (N=43)	31 (72.1)	0.006		29.9 (23.5, 38.7)

Stratified (TNFi naive or prior TNFi use) Cochran-Mantel-Haenszel Test.
The minimum risk weighting method proposed by Mehrotra and Railkar was used for calculation of the stratified (TNFi naive or prior TNFi use) CI for the placebo-adjusted difference.
ACR20 = proportion of subjects with at least a 20% improvement from Baseline American College Rheumatology; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; minimum risk; N = number of subjects in mITT population per treatment group; n = number of subjects showing an ACR20 response at Week 16; OZ. = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; TNFi = tumor necrosis factor inhibitor; vs = versus.

ACR20 Response at Week 4, 8, 12 and 20: ACR20 data by study weeks are presented in Table 4. The LOCF analyses showed that the number of ACR20 responders in the ozoralizumab 80 mg Q4 group were statistically significantly greater than in the placebo group at Week 8 and Week 12 as well as at Week 16 as seen in the primary analysis; the number of responders in the 80 mg Q4 group was no longer significantly greater than in the placebo group at FU Week 20.

Table 4. Analysis of ACR 20 Response (mITT Population, LOCF, CMH)

Timepoint	Treatment	N	n (%)	p-Value		Placebo-Adjusted Difference and its CI (30% Percentile, 80% Percentile) (OZ - Placebo)	
				OZ vs Palcebo	Overall		
Week 4	Placebo	45	10 (22.2)		0.009		
	OZ 10 mg Q8	41	9 (22.0)	0.980		-0.3	(-5.3, 8.8)
	OZ 10 mg Q4	42	19 (45.2)	0.031		23.0	(16.5, 31.8)
	OZ 30 mg Q4	40	21 (52.5)	0.005		30.3	(23.0, 38.1)
	OZ 80 mg Q8	42	17 (40.5)	0.088		18.3	(11.2, 25.3)
	OZ 80 mg Q4	43	20 (46.5)	0.018		24.3	(18.2, 33.3)
Week 8	Placebo	45	15 (33.3)		0.040		
	OZ 10 mg Q8	41	15 (36.6)	0.700		3.3	(-1.7, 13.9)
	OZ 10 mg Q4	42	19 (45.2)	0.223		11.9	(7.5, 23.3)
	OZ 30 mg Q4	40	20 (50.0)	0.141		16.7	(8.7, 24.5)
	OZ 80 mg Q8	42	23 (54.8)	0.048		21.4	(15.7, 31.4)
	OZ 80 mg Q4	43	28 (65.1)	0.003		31.8	(25.2, 40.7)
Week 12	Placebo	45	20 (44.4)		0.044		
	OZ 10 mg Q8	41	20 (48.8)	0.548		4.3	(0.8, 16.8)
	OZ 10 mg Q4	42	23 (54.8)	0.197		10.3	(8.4, 24.2)
	OZ 30 mg Q4	40	24 (60.0)	0.183		15.6	(7.2, 22.8)
	OZ 80 mg Q8	42	29 (69.0)	0.019		24.6	(19.8, 35.2)
	OZ 80 mg Q4	43	32 (74.4)	0.005		30.0	(24.0, 39.0)
Week 20 FU	Placebo	45	17 (37.8)		0.115		
	OZ 10 mg Q8	41	10 (24.4)	0.231		-13.4	(-17.6, -2.7)
	OZ 10 mg Q4	42	15 (35.7)	0.808		-2.1	(-4.1, 11.1)
	OZ 30 mg Q4	40	20 (50.0)	0.306		12.2	(3.2, 18.5)
	OZ 80 mg Q8	42	15 (35.7)	0.922		-2.1	(-6.5, 9.0)
	OZ 80 mg Q4	43	24 (55.8)	0.102		18.0	(11.4, 27.2)

Stratified (TNFi naive or prior TNFi use) Cochran-Mantel-Haenszel Test.
The minimum risk weighting method proposed by Mehrotra and Railkar was used for calculation of the stratified (TNFi naive or prior TNFi use) CI for the placebo-adjusted difference.
ACR 20 = proportion of subjects with at least a 20% improvement from Baseline in American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FU = follow-up; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects in specific category; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; TNFi = tumor necrosis factor inhibitor; vs = versus.

ACR50 Response at Week 4, 8, 12, 16 and 20: ACR50 data are presented in Table 5. The number of ACR50 responders (LOCF analyses) in the 80 mg Q4 group was significantly greater than the number in the placebo group at Week 16 but not at other weeks.

Table 5. Analysis of ACR 50 Response (mITT Population, LOCF, CMH)

Timepoint	Treatment	N	n (%)	p-Value		Placebo-Adjusted Difference and its CI (30% Percentile, 80% Percentile) (Ozoralizumab - Placebo)	
				Ozoralizumab vs Palcebo	Overall		
Week 4	Placebo	45	3 (6.7)		0.115		
	OZ 10 mg Q8	41	2 (4.9)	0.876		-1.8	(-5.8, 5.8)
	OZ 10 mg Q4	42	6 (14.3)	0.302		7.6	(3.1, 13.0)
	OZ 30 mg Q4	40	8 (20.0)	0.078		13.3	(8.3, 19.6)
	OZ 80 mg Q8	42	8 (19.0)	0.094		12.4	(7.7, 18.7)
	OZ 80 mg Q4	43	3 (7.0)	1.000		0.3	(-4.5, 6.6)
Week 8	Placebo	45	7 (15.6)		0.089		
	OZ 10 mg Q8	41	4 (9.8)	0.494		-5.8	(-9.1, 2.1)
	OZ 10 mg Q4	42	5 (11.9)	0.609		-3.7	(-8.5, 3.0)
	OZ 30 mg Q4	40	13 (32.5)	0.078		16.9	(9.5, 23.2)
	OZ 80 mg Q8	42	10 (23.8)	0.364		8.3	(2.5, 15.5)
	OZ 80 mg Q4	43	11 (25.6)	0.267		10.0	(3.4, 16.3)
Week 12	Placebo	45	8 (17.8)		0.123		
	OZ 10 mg Q8	41	13 (31.7)	0.076		13.9	(12.7, 25.2)
	OZ 10 mg Q4	42	10 (23.8)	0.381		6.0	(4.4, 17.0)
	OZ 30 mg Q4	40	17 (42.5)	0.015		24.7	(18.2, 32.5)
	OZ 80 mg Q8	42	17 (40.5)	0.021		22.7	(18.0, 32.1)
	OZ 80 mg Q4	43	13 (30.2)	0.193		12.5	(6.6, 18.7)
Week 16	Placebo	45	8 (17.8)		0.388		
	OZ 10 mg Q8	41	10 (24.4)	0.299		6.6	(6.2, 17.6)
	OZ 10 mg Q4	42	9 (21.4)	0.494		3.7	(3.1, 15.2)
	OZ 30 mg Q4	40	13 (32.5)	0.139		14.7	(10.3, 27.5)
	OZ 80 mg Q8	42	13 (31.0)	0.157		13.2	(8.4, 21.9)
	OZ 80 mg Q4	43	16 (37.2)	0.047		19.4	(14.3, 28.5)
Week 20 Follow-up	Placebo	45	8 (17.8)		0.215		
	OZ 10 mg Q8	41	3 (7.3)	0.238		-10.5	(-17.9, -3.0)
	OZ 10 mg Q4	42	4 (9.5)	0.481		-8.3	(-13.8, 2.1)
	OZ 30 mg Q4	40	10 (25.0)	0.485		7.2	(1.1, 17.8)
	OZ 80 mg Q8	42	10 (23.8)	0.436		6.0	(3.0, 15.9)
	OZ 80 mg Q4	43	11 (25.6)	0.414		7.8	(3.6, 15.5)

Stratified (TNFi naive or prior TNFi use) Cochran-Mantel-Haenszel Test. The minimum risk weighting method proposed by Mehrotra and Railkar is used for calculation of the stratified (TNFi naive or prior TNFi use) CI for the placebo-adjusted difference.
ACR 50 = proportion of subjects with at least a 50% improvement from Baseline in American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects in specific category; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; TNFi = tumor necrosis factor inhibitor; vs = versus.

ACR70 Response at Week 4, 8, 12, 16 and 20: ACR70 data are presented in Table 6. With the exception of the 30 mg Q4 group at Week 8, no statistically significant differences in ACR70 response rates compared to the placebo group were seen at any week for any treatment group.

Table 6. Analysis of ACR 70 Response (mITT Population, LOCF, CMH)

Timepoint	Treatment	N	n (%)	p-Value		Placebo-Adjusted Difference and its CI (30% Percentile, 80% Percentile) (Ozoralizumab - Placebo)	
				Ozoralizumab vs Palcebo	Overall		
Week 4	Placebo	45	0 (0.0)		0.291		
	OZ 10 mg Q8	41	0 (0.0)			0.0	
	OZ 10 mg Q4	42	2 (4.8)	0.246		4.8	(6.8, 19.2)
	OZ 30 mg Q4	40	3 (7.5)	0.070		7.5	(5.8, 14.6)
	OZ 80 mg Q8	42	2 (4.8)	0.157		4.8	(1.8, 7.7)
	OZ 80 mg Q4	43	1 (2.3)	0.317		2.3	(0.6, 6.2)
Week 8	Placebo	45	1 (2.2)		0.044		
	OZ 10 mg Q8	41	0 (0.0)	0.382		-2.2	(-5.4, 0.4)
	OZ 10 mg Q4	42	3 (7.1)	0.249		4.9	(2.4, 9.9)
	OZ 30 mg Q4	40	6 (15.0)	0.039		12.8	11.0, 23.0)
	OZ 80 mg Q8	42	2 (4.8)	0.531		2.5	(-0.4, 6.5)
	OZ 80 mg Q4	43	1 (2.3)	1.000		0.1	(-3.0, 4.3)
Week 12	Placebo	45	4 (8.9)		0.813		
	OZ 10 mg Q8	41	5 (12.2)	0.496		3.3	(1.9, 10.9)
	OZ 10 mg Q4	42	7 (16.7)	0.298		7.8	(3.9, 14.7)
	OZ 30 mg Q4	40	7 (17.5)	0.274		8.6	(4.4, 18.7)
	OZ 80 mg Q8	42	7 (16.7)	0.279		7.8	(3.8, 15.0)
	OZ 80 mg Q4	43	5 (11.6)	0.700		2.7	(-0.8, 9.5)
Week 16	Placebo	45	4 (8.9)		0.290		
	OZ 10 mg Q8	41	5 (12.2)	0.496		3.3	(1.9, 10.9)
	OZ 10 mg Q4	42	2 (4.8)	0.536		-4.1	(-5.6, 2.5)
	OZ 30 mg Q4	40	8 (20.0)	0.167		11.1	(7.4, 22.1)
	OZ 80 mg Q8	42	8 (19.0)	0.184		10.2	(5.6, 16.9)
	OZ 80 mg Q4	43	5 (11.6)	0.700		2.7	(-0.8, 9.5)
Week 20 FU	Placebo	45	6 (13.3)		0.478		
	OZ 10 mg Q8	41	2 (4.9)	0.265		-8.5	(-15.2, -2.0)
	OZ 10 mg Q4	42	1 (2.4)	0.112		-11.0	(-18.5, -6.3)
	OZ 30 mg Q4	40	4 (10.0)	0.563		-3.3	(-10.6, 3.1)
	OZ 80 mg Q8	42	4 (9.5)	0.644		-3.8	(-5.5, 4.4)
	OZ 80 mg Q4	43	2 (4.7)	0.135		-8.7	(-16.6, -4.4)

Stratified (TNFi naive or prior TNFi use) Cochran-Mantel-Haenszel Test.
The minimum risk weighting method proposed by Mehrotra and Railkar is used for calculation of the stratified (TNFi naive or prior TNFi use) CI for the placebo-adjusted difference.
ACR 70 = proportion of subjects with at least a 70% improvement from Baseline in American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FU = follow-up; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects in specific category; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; TNFi = tumor necrosis factor inhibitor; vs = versus.

ACR-N Response at Week 4, 8, 12, 16 and 20: The LOCF analyses of ACR-N are presented in Table 7. At Week 16, statistically significant results were shown for both the 80 mg Q4 and the 80 mg Q8 treatment groups compared to the placebo group.

Table 7. Analysis of ACR-N (%) by Timepoint – mITT Population - LOCF

Timepoint[a]	Treatment	N	LOCF Mean	Adjusted Mean (SE)	Diff of Adjusted Mean (95% CI) (Ozoralizumab - Placebo)	p-Value (Ozoralizumab Versus Placebo)
Week 4	Placebo	45	5.6	7.0 (7.6)		
	OZ 10 mg Q8	41	6.4	7.2 (7.8)	0.2 (-20.9, 21.3)	0.985
	OZ 10 mg Q4	42	12.2	12.8 (7.7)	5.8 (-15.2, 26.8)	0.588
	OZ 30 mg Q4	40	5.6	7.3 (8.1)	0.3 (-20.9, 21.5)	0.980
	OZ 80 mg Q8	42	18.8	19.8 (7.7)	12.8 (-8.1, 33.8)	0.228
	OZ 80 mg Q4	43	15.6	17.2 (7.8)	10.3 (-10.5, 31.0)	0.332
Week 8	Placebo	45	11.4	10.3 (7.3)		
	OZ 10 mg Q8	41	2.7	2.2 (7.5)	-8.2 (-28.5, 12.2)	0.429
	OZ 10 mg Q4	42	20.5	20.2 (7.4)	9.8 (-10.4, 30.1)	0.341
	OZ 30 mg Q4	40	12.9	11.7 (7.8)	1.3 (-19.1, 21.8)	0.897
	OZ 80 mg Q8	42	23.7	23.0 (7.5)	12.6 (-7.5, 32.8)	0.219
	OZ 80 mg Q4	43	31.3	30.2 (7.5)	19.8 (-0.2, 39.9)	0.052
Week 12	Placebo	45	16.0	12.1 (6.6)		
	OZ 10 mg Q8	41	16.7	14.6 (6.7)	2.6 (-15.6, 20.8)	0.780
	OZ 10 mg Q4	42	23.2	21.7 (6.6)	9.7 (-8.5, 27.8)	0.294
	OZ 30 mg Q4	40	24.9	20.3 (7.0)	8.2 (-10.1, 26.5)	0.376
	OZ 80 mg Q8	42	30.6	27.7 (6.7)	15.6 (-2.4, 33.7)	0.090
	OZ 80 mg Q4	43	33.9	29.5 (6.7)	17.4 (-0.5, 35.4)	0.057
Week 16	Placebo	45	8.1	5.7 (6.4)		
	OZ 10 mg Q8	41	21.4	20.2 (6.5)	14.4 (-3.3, 32.1)	0.109
	OZ 10 mg Q4	42	20.7	19.8 (6.4)	14.1 (-3.5, 31.7)	0.117
	OZ 30 mg Q4	40	18.6	15.8 (6.8)	10.1 (-7.7, 27.8)	0.265
	OZ 80 mg Q8	42	29.5	27.7 (6.5)	22.0 (4.4, 39.5)	0.014*
	OZ 80 mg Q4	43	35.4	32.7 (6.5)	26.9 (9.5, 44.3)	0.003**
Week 20 FU	Placebo	45	11.3	7.6 (7.0)		
	OZ 10 mg Q8	41	-1.7	-3.6 (7.2)	-11.2 (-30.7, 8.3)	0.258
	OZ 10 mg Q4	42	4.2	2.8 (7.1)	-4.8 (-24.2, 14.6)	0.629
	OZ 30 mg Q4	40	8.7	4.2 (7.5)	-3.3 (-22.9, 16.2)	0.737
	OZ 80 mg Q8	42	12.1	9.3 (7.1)	1.7 (-17.6, 21.0)	0.860
	OZ 80 mg Q4	43	18.2	13.9 (7.2)	6.3 (-12.8, 25.5)	0.515

Statistical significance at the 0.05 and 0.01 levels are denoted by * and ** respectively.
Adjusted means account for imbalance among treatments with respect to all other effects in model.
Comparisons between treatments were based on analysis of variance (unadjusted for multiplicity).
Standard model of analysis: value = treatment stratum.
The numeric ACR (ACR-N) is defined as the lowest percentage improvement from Baseline of 3 measures: tender joint count, swollen joint count, and the median percent improvement from Baseline among the remaining 5 core measures.
CI = confidence interval; diff = difference; FU = follow-up; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error.
a. All analyses were done independently by data analysis interval using data with non-missing baseline values.

Disease Activity Score (DAS28): DAS28 data are presented in Table 8. At Week 16, the adjusted mean decreases from Baseline were statistically significantly greater in the 30 mg Q4, 80 mg Q8, and 80 mg Q4 groups than in the placebo group. The adjusted mean decreases from Baseline were also statistically significantly greater in the 30 mg Q4 group than in the placebo group at Weeks 4 and 12, and at Weeks 4, 8 and 12 in the 80 mg Q8 and 80 mg Q4 groups.

Table 8. Analysis of DAS28 at Week 16 – mITT Population (LOCF Analysis)

Timepoint[a] Treatment (N)	Baseline	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)[b]	Difference Adj Mean Change (95% CI) Ozoralizumab vs Placebo	p-Value ozoralizumab vs Placebo[c]
Week 16						
Placebo (N=45)	6.17	4.91	1.27	1.20 (0.2)		
OZ 10 mg Q8 (N=41)	6.12	4.42	1.70	1.70 (0.2)	0.50 (-0.1, 1.1)	0.085
OZ 10 mg Q4 (N=42)	6.10	4.49	1.60	1.63 (0.2)	0.43 (-0.1, 1.0)	0.141
OZ 30 mg Q4 (N=40)	6.10	4.01	2.09	2.04 (0.2)	0.84 (0.3, 1.4)	0.005*
OZ 80 mg Q8 (N=42)	6.25	4.32	1.93	1.85 (0.2)	0.65 (0.1, 1.2)	0.025**
OZ 80 mg Q4 (N=43)	6.59	4.13	2.46	2.18 (0.2)	0.98 (0.4, 1.5)	<0.001***

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
Adj = adjusted; CI = confidence interval; DAS = Disease Activity Score; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; vs = versus.

a. All analyses were done independently by data analysis interval using data with non-missing baseline values.

b. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.

c. Statistical significance at the 0.01, 0.05 and 0.001 levels are denoted by *, **, and *** respectively (ozoralizumab vs placebo).

European League Against Rheumatism (EULAR): EULAR data are presented in Table 9. The proportion of subjects in the 80 mg Q4 group who had a good or moderate EULAR response at Week 16 (90.7%; p=0.022) was statistically significantly greater than that in the placebo group (60%); None of the other groups showed a statistically significant difference compared to placebo at Week 16. The proportion of subjects in the 80 mg Q4 group who had a good or moderate EULAR response was also statistically significantly greater than that in the placebo group at FU Week 20 (p=0.033), but not at any other week.

Table 9. Analysis of EULAR Response at Week 16– mITT Population (LOCF Analysis)

EULAR Response	Placebo	Ozoralizumab, n (%)				
	N=45 n (%)	10 mg Q8 N=41	10 mg Q4 N=42	30 mg Q4 N=40	80 mg Q8 N=42	80 mg Q4 N=43
Good	9 (20.0)	8 (19.5)	5 (11.9)	15 (37.5)	10 (23.8)	10 (23.3)
Moderate	18 (40.0)	19 (46.3)	25 (59.5)	15 (37.5)	22 (52.4)	29 (67.4)
None	18 (40.0)	14 (34.1)	12 (28.6)	10 (25.0)	10 (23.8)	4 (9.3)
p-Value vs placebo		0.595	0.608	0.066	0.173	0.022

Stratified (TNFi naive or prior TNFi use) Cochran-Mantel-Haenszel Test.
EULAR = European League Against Rheumatism; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; n = subjects with good, moderate, or none as EULAR response; Q4 = every 4 weeks; Q8 = every 8 weeks; TNFi = tumor necrosis factor inhibitor; vs = versus.

Standardized Joint Assessment at Week 16:

Tender Joints Count: In the LOCF analyses, the adjusted mean decreases in number of tender joints at Week 16 compared to Baseline in the 10 mg Q8 and 80 mg Q4 groups were statistically significantly greater than those seen in the placebo group (6.0). Decreases seen in other groups were not statistically significantly different than that seen in the placebo group (Table 10). The change in the 80 mg Q4 group reflects a decrease in the LOCF mean number of tender joints from 19.9 at Baseline to 7.7 at Week 16. At other weeks, the adjusted mean decreases in the number of tender joints in the 80 mg Q4 group were not statistically significantly different from that seen in the placebo group.

Table 10. Analysis of Tender Joints at Week 16 – mITT Population (LOCF Analysis)

Analysis[a] Treatment (N)	Baseline	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)[b]	Difference Adjusted Mean Change (95% CI) OZ vs Placebo	p-Value OZ vs Placebo[c]
Week 16						
Placebo (N=45)	17.3	10.8	6.4	6.0 (1.1)		
OZ 10 mg Q8 (N=41)	16.2	7.0	9.2	9.6 (1.1)	3.6 (0.6, 6.6)	0.020*
OZ 10 mg Q4 (N=42)	16.1	8.4	7.8	8.3 (1.1)	2.3 (-0.7, 5.3)	0.134
OZ 30 mg Q4 (N=40)	16.9	8.4	8.5	8.2 (1.2)	2.1 (-0.9, 5.2)	0.166
OZ 80 mg Q8 (N=42)	18.1	8.7	9.4	8.7 (1.1)	2.6 (-0.4, 5.6)	0.085
OZ 80 mg Q4 (N=43)	19.9	7.7	12.1	10.2 (1.1)	4.1 (1.1, 7.1)	0.007**

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity). Standard model of analysis: change = baseline treatment stratum. Prorated total number of tender joints = 28*total number of joints with tender score >0/number of non-missing joints.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; vs = versus.

a. All analyses were done independently by data analysis interval using data with non-missing baseline values.
b. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
c. Statistical significance at the 0.05 and 0.01 levels are denoted by * and ** respectively.

Swollen Joints Count: In the LOCF analyses, the adjusted decreases in swollen joints at Week 16 compared to Baseline in all ozoralizumab treatment groups (8.4-8.6) other than the 10 mg Q4 group (7.8) were statistically significantly greater than that seen in the placebo group (6.0) (Table 11). The adjusted decrease in the 80 mg Q4 group (8.6) reflected a decrease in the mean LOCF number of swollen joints from 16.0 at Baseline to 6.1 at Week 16. At other weeks, the adjusted mean decreases in the number of swollen joints in the 80 mg Q4 group were not statistically significantly different from that seen in the placebo group.

Table 11. Analysis of Swollen Joints at Week 16 – mITT Population (LOCF Analysis)

Analysis[a] Treatment (N)	Baseline	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)[b]	Difference Adjusted Mean Change (95% CI) OZ vs Placebo	p-Value OZ vs Placebo[c]
Week 16						
Placebo (N=45)	13.4	7.6	5.8	6.0 (0.8)		
OZ 10 mg Q8 (N=41)	13.8	5.4	8.4	8.4 (0.8)	2.4 (0.2, 4.6)	0.029*
OZ 10 mg Q4 (N=42)	12.1	5.3	6.8	7.8 (0.8)	1.8 (-0.4, 4.0)	0.105
OZ 30 mg Q4 (N=40)	13.3	5.0	8.3	8.6 (0.8)	2.6 (0.4, 4.8)	0.023*
OZ 80 mg Q8 (N=42)	14.4	5.6	8.8	8.5 (0.8)	2.5 (0.3, 4.6)	0.027*
OZ 80 mg Q4 (N=43)	16.0	6.1	10.0	8.6 (0.8)	2.6 (0.5, 4.8)	0.018*

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
Prorated total number of tender joints = 28*total number of joints with tender score >0/number of non-missing joints.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q8 = every 8 weeks; Q4 = every 4 weeks; SE = standard error; vs = versus.

a. All analyses were done independently by data analysis interval using data with non-missing baseline values.
b. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
c. Statistical significance at the 0.05 level is denoted by ∗.

Pain VAS: Analyses of pain VAS (0-100 mm scale) data for Week 16 are presented in Table 12. At Week 16, the LOCF adjusted mean changes from Baseline in the 80 mg Q8 and 80 mg Q4 groups were statistically significantly greater than that in the placebo group. The adjusted decrease in the 80 mg Q4 group reflected a decrease in the unadjusted mean LOCF score from 69.3 mm at Baseline to 35.9 mm at Week 16. The LOCF adjusted mean changes from Baseline in the 80 mg Q4 group were also statistically significantly greater than that in the placebo group at Week 8.

Table 12. Analysis of Pain VAS[a] at Week 16 – mITT Population (LOCF Analysis)

Analysis[a] Treatment (N)	Baseline (mm)	LOCF Mean (mm)	LOCF Mean Change (%) From Baseline (mm)	Adjusted Mean Change (mm) (SE)[c]	Difference Adjusted Mean Change OZ vs Placebo (mm) (95% CI)	p-Value OZ vs Placebo[d]
Week 16						
Placebo (N=45)	60.7	50.1	10.6	9.0 (3.7)		
OZ 10 mg Q8 (N=41)	64.6	46.2	18.3	15.4 (3.8)	6.3 (-4.0, 16.6)	0.228
OZ 10 mg Q4 (N=42)	61.0	43.8	17.2	16.9 (3.7)	7.0 (-2.4, 18.1)	0.133
OZ 30 mg Q4 (N=40)	58.2	40.5	17.8	17.5 (4.0)	8.4 (-1.9, 18.8)	0.111
OZ 80 mg Q8 (N=42)	57.0	35.4	21.6	23.1 (3.8)	14.0 (3.8, 24.3)	0.007**
OZ 80 mg Q4 (N=43)	69.3	35.9	33.4	25.9 (3.9)	16.9 (6.7, 27.1)	0.001**

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity). Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 =every 8 weeks; SE = standard error; VAS = visual analog scale; vs = versus.

a. Measured on 0 to 100 mm scale. Pain VAS: No Pain (0 mm); Severe Pain (100 mm).
b. All analyses were done independently by data analysis interval using data with non-missing baseline values.
c. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
d. Statistical significance at the 0.01 level is denoted by ** (ozoralizumab vs placebo).

General Health VAS: Analyses of LOCF General Health VAS data for Week 16 are presented in Table 13. The LOCF adjusted mean changes in this from Baseline to Week 16 in the 30 mg Q4, 80 mg Q8, and 80 mg Q4 groups were statistically significantly greater than that in the placebo group. The adjusted decrease in the 80 mg Q4 group reflected a decrease in the unadjusted mean LOCF score from 73.0 mm at Baseline to 42.1 mm at Week 16.

Table 13. Analysis of General Health VAS (0-100 mm)[a] at Week 16 – mITT Population (LOCF Analysis)

Analysis[a] Treatment (N)	Baseline (mm)	LOCF Mean (mm)	LOCF Mean Change (%) From Baseline (mm)	Adjusted Mean Change (mm) (SE)[c]	Difference Adjusted Mean Change OZ vs Placebo (mm) (95% CI)	p-Value OZ vs Placebo[d]
Week 16						
Placebo (N=45)	63.5	49.5	14.0	13.3 (3.6)		
OZ 10 mg Q8 (N=41)	66.5	48.4	18.0	16.7 (3.6)	3.4 (-6.4, 13.3)	0.493
OZ 10 mg Q4 (N=42)	67.0	47.0	20.1	18.8 (3.6)	5.5 (-4.3, 15.4)	0.269
OZ 30 mg Q4 (N=40)	65.0	38.8	26.2	24.1 (3.8)	10.8 (0.9, 20.7)	0.033*
OZ 80 mg Q8 (N=42)	64.9	40.6	24.3	23.4 (3.6)	10.1 (0.3, 19.8)	0.044*
OZ 80 mg Q4 (N=43)	73.0	42.1	30.9	23.8 (3.7)	10.5 (0.7, 20.3)	0.036*

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat;
N = number of subjects in mITT population per treatment group; OZ. = ozoralizumab; Q4 = every 4 weeks;
Q8 = every 8 weeks; SE = standard error; VAS = visual analog scale; vs = versus.

a. General Health VAS: Very Well (0 mm); Extremely Bad (100 mm).
b. All analyses were done independently by data analysis interval using data with non-missing baseline values.
c. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
d. Statistical significance at the 0.05 level is denoted by * (ozoralizumab vs placebo).

Physician Global Assessment of Disease Activity: Analyses of the LOCF physician global assessment of disease activity data are presented in Table 14. In the LOCF analyses, the adjusted mean decreases in physician global assessments at Week 16 compared to Baseline were statistically significantly greater than that seen in the placebo group in all ozoralizumab treatment groups. The adjusted decrease in the 80 mg Q4 group (3.4) reflected a decrease in the unadjusted mean LOCF score from 7.5 at Baseline to 3.5 at Week 16.

Table 14. Analysis of Physician Global Assessment of Disease Activity (0 to 10 Scale)[a] at Week 16 – mITT Population (LOCF Analysis)

Analysis[b] Treatment (N)	Baseline (mm)	LOCF Mean (mm)	LOCF Mean Change (%) From Baseline (mm)	Adjusted Mean Change (mm) (SE)[c]	Difference Adjusted Mean Change OZ vs Placebo (mm) (95% CI)	p-Value OZ vs Placebo[d]
Week 16						
Placebo (N=45)	6.9	4.8	2.1	1.9 (0.3)		
OZ 10 mg Q8 (N=41)	7.0	3.9	3.1	2.9 (0.3)	1.0 (0.1, 1.9)	0.036*
OZ 10 mg Q4 (N=42)	6.7	3.9	2.8	2.9 (0.3)	1.0 (0.1, 1.9)	0.036*
OZ 30 mg Q4 (N=40)	6.4	3.4	3.0	3.2 (0.4)	1.2 (0.3, 2.2)	0.011*
OZ 80 mg Q8 (N=42)	7.2	3.5	3.7	3.3 (0.3)	1.4 (0.5, 2.3)	0.004**
OZ 80 mg Q4 (N=43)	7.5	3.5	4.0	3.4 (0.3)	1.4 (0.5, 2.4)	0.003**

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab: Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; vs = versus.

a. Physician global assessment: (0) no disease activity; (10) extreme disease activity.
b. All analyses were done independently by data analysis interval using data with non-missing baseline values.
c. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
d. Statistical significance at the 0.05 and 0.01 levels are denoted by * and ** respectively.

Patient Global Assessment of Disease Activity: Analyses of the LOCF patient global assessment of disease activity data are presented in Table 15. In the LOCF analyses, the adjusted mean decreases in patient global assessments at Week 16 compared to Baseline in the 80 mg Q8 and 80 mg Q4 groups was statistically significantly greater than that seen in the placebo group. The adjusted decrease in the 80 mg Q4 group reflected a decrease in the unadjusted mean LOCF score from 7.6 at Baseline to 4.5 at Week 16.

Table 15. Analysis of Patient Global Assessment of Disease Activity (0 to 10 Scale)[a] at Week 16 – mITT Population (LOCF Analysis)

Analysis[b] Treatment (N)	Baseline (mm)	LOCF Mean (mm)	LOCF Mean Change (%) From Baseline (mm)	Adjusted Mean Change (mm) (SE)[c]	Difference Adjusted Mean Change OZ vs Placebo (mm) (95% CI)	p-Value OZ vs Placebo[d]
Week 16						
Placebo (N=45)	7.0	5.5	1.5	1.3 (0.4)		
OZ 10 mg Q8 (N=41)	7.3	5.0	2.2	2.0 (0.4)	0.7 (-0.3, 1.7)	0.174
OZ 10 mg Q4 (N=42)	7.1	5.0	2.0	2.0 (0.4)	0.7 (-0.3, 1.6)	0.184
OZ 30 mg Q4 (N=40)	6.9	4.6	2.2	2.1 (0.4)	0.8 (-0.2, 1.8)	0.122
OZ 80 mg Q8 (N=42)	7.2	4.5	2.7	2.5 (0.4)	1.1 (0.2, 2.1)	0.020*
OZ 80 mg Q4 (N=43)	7.6	4.5	3.1	2.5 (0.4)	1.2 (0.2, 2.1)	0.017*

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity). Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; vs = versus.

a. Patient global assessment: (0) no disease activity; (10) extreme disease activity.
b. All analyses were done independently by data analysis interval using data with non-missing baseline values.
c. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
d. Statistical significance at the 0.05 level is denoted by *.

Duration of Morning Stiffness: Data for duration of morning stiffness (minutes) are provided in Table 16. The adjusted mean change from Baseline to Week 16 for the 80 mg Q8 group was statistically significantly greater than that in the placebo group; the adjusted mean changes seen in the other ozoralizumab treatment groups were not significantly different from those in the placebo group.

Table 16. Analysis of Duration (Minutes) of Morning Stiffness at Week 16 – mITT Population (LOCF Analysis)

Analysis[a] Treatment (N)	Baseline (min)	LOCF Mean (min)	LOCF Mean Change (%) From Baseline (min)	Adjusted Mean Change (min) (SE)[b]	Difference Adjusted Mean Change OZ vs Placebo (min) (95% CI)	p-Value OZ vs Placebo[c]
Week 16						
Placebo (N=45)	358.9	267.6	91.3	111.1 (57.9)		
OZ 10 mg Q8 (N=41)	464.3	174.5	289.8	254.7 (59.3)	143.6 (-17.5, 304.6)	0.080
OZ 10 mg Q4 (N=42)	432.3	290.3	142.0	135.1 (58.4)	23.9 (-136.4, 184.2)	0.769
OZ 30 mg Q4 (N=40)	302.7	142.7	160.0	212.1 (61.9)	101.0 (-60.5, 262.5)	0.219
OZ 80 mg Q8 (N=42)	466.4	117.3	349.1	304.0 (59.1)	192.9 (33.2, 352.6)	0.018*
OZ 80 mg Q4 (N=43)	629.0	239.8	389.2	216.0 (60.3)	104.9 (-55.4, 265.1)	0.199

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; vs = versus.

a. All analyses were done independently by data analysis interval using data with non-missing baseline values.
b. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
c. Statistical significance at the 0.05 level is denoted by * (ozoralizumab vs placebo).

Health Assessment Questionnaire Disability Index: HAQ-DI data are presented in Table 17. The mean HAQ-DI score at Baseline in the various treatment groups ranged from 1.5 to 1.8. The adjusted mean change from Baseline to Week 16 for the 80 mg Q4 group was statistically significantly greater than that in the placebo group; the adjusted mean changes seen in the other ozoralizumab treatment groups at Week 16 were not significantly different from those in the placebo group. The adjusted decrease in the 80 mg Q4 group reflected a decrease in the unadjusted mean LOCF score from 1.8 at Baseline to 1.2 at Week 16.

Table 17. Analysis of HAQ-DI at Week 16 – mITT Population (LOCF Analysis)

Analysis[a] Treatment (N)	Baseline	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)[b]	Difference Adjusted Mean Change OZ vs Placebo(95% CI)	p-Value OZ vs Placebo[c]
Week 16						
Placebo (N=45)	1.6	1.2	0.3	0.3 (0.1)		
OZ 10 mg Q8 (N=41)	1.7	1.3	0.3	0.3 (0.1)	-0.0 (-0.2, 0.2)	0.950
OZ 10 mg Q4 (N=42)	1.5	1.1	0.4	0.4 (0.1)	0.0 (-0.2, 0.3)	0.658
OZ 30 mg Q4 (N=40)	1.5	1.1	0.4	0.4 (0.1)	0.1 (-0.1, 0.3)	0.361
OZ 80 mg Q8 (N=42)	1.5	1.1	0.3	0.4 (0.1)	0.0 (-0.2, 0.3)	0.765
OZ 80 mg Q4 (N=43)	1.8	1.2	0.6	0.5 (0.1)	0.2 (0.0, 0.4)	0.041*

Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; HAQ-DI = Health Assessment Questionnaire Disability Index; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; vs = versus.

a. All analyses were done independently by data analysis interval using data with non-missing baseline values.
b. Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
c. Statistical significance at the 0.05 level is denoted by * (ozoralizumab vs placebo).

Short Form-36: Data on the short form (SF)-36 domains are presented in Table 18. There were no statistically significant differences between the placebo group and any of the ozoralizumab treatment groups in the mean adjusted change from Baseline at Week 16 in either the Standardized Mental Component or the Standardized Physical Component. Similarly, there were no statistically significant differences between the placebo group and any of the ozoralizumab treatment groups in the mean adjusted change from Baseline at Week 16 in any of the individual domains with the exceptions of Bodily Pain and Vitality. At Week 16, the adjusted mean decreases from Baseline in the Bodily Pain Domain score in the 80 mg Q8 and 80 mg Q4 groups were statistically significantly greater than that in the placebo group. At Week 16, the adjusted mean decrease from Baseline in the vitality score in the 10 mg Q8 group was statistically significantly smaller than that in the placebo group.

Table 18. Analysis of SF-36: Week 16 – LOCF mITT Population

Timepoint[a] SF-36 Component Treatment (N)	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)	Difference Adjusted Mean Change (95% CI) OZ vs Placebo	p-Value OZ vs Placebo
Week 16					
Physical functioning					
Placebo (N=45)	48.9	10.4 (48.8)	11.4 (3.4)		
OZ 10 mg Q8 (N=41)	36.3	7.8 (50.5)	5.5 (3.4)	-6.0 (-15.4, 3.4)	0.212
OZ 10 mg Q4 (N=42)	43.3	7.4 (51.0)	8.1 (3.4)	-3.3 (-12.6, 6.0)	0.483
OZ 30 mg Q4 (N=40)	44.3	15.3 (98.2)	12.3 (3.6)	0.9 (-8.5, 10.3)	0.851
OZ 80 mg Q8 (N=42)	47.0	12.7 (51.5)	12.4 (3.4)	1.0 (-8.3, 10.2)	0.838
OZ 80 mg Q4 (N=43)	45.9	15.1 (76.8)	13.0 (3.4)	1.5 (-7.7, 10.7)	0.746
Role-physical					
Placebo (N=45)	53.5	12.8 (70.3)	12.6 (3.3)		
OZ 10 mg Q8 (N=41)	41.3	12.0 (59.4)	8.5 (3.4)	-4.1 (-13.3, 5.1)	0.383
OZ 10 mg Q4 (N=42)	48.7	9.1 (39.8)	9.5 (3.3)	-3.1 (-12.2, 5.9)	0.500
OZ 30 mg Q4 (N=40)	52.0	14.4 (77.4)	12.8 (3.5)	0.2 (-8.9, 9.4)	0.960
OZ 80 mg Q8 (N=42)	54.5	15.0 (38.9)	14.8 (3.3)	2.2 (-6.8, 11.2)	0.631
OZ 80 mg Q4 (N=43)	55.8	22.1 (89.7)	19.2 (3.4)	6.6 (-2.4, 15.6)	0.149
Bodily pain					
Placebo (N=45)	42.5	16.8 (64.4)	13.8 (2.8)		
OZ 10 mg Q8 (N=41)	42.0	14.2 (48.0)	12.9 (2.9)	-0.9 (-8.7, 6.9)	0.818
OZ 10 mg Q4 (N=42)	46.7	12.7 (50.4)	14.5 (2.8)	0.7 (-7.1, 8.6)	0.851
OZ 30 mg Q4 (N=40)	50.4	20.0 (65.3)	18.9 (3.0)	5.1 (-2.7, 13.0)	0.198
OZ 80 mg Q8 (N=42)	54.4	24.6 (83.2)	23.9 (2.9)	10.1 (2.4, 17.9)	0.011*
OZ 80 mg Q4 (N=43)	50.8	24.3 (99.3)	21.4 (2.9)	7.7 (0.0, 15.3)	0.050*
General Health Perceptions					
Placebo (N=45)	49.2	7.5 (17.9)	7.2 (2.4)		
OZ 10 mg Q8 (N=40)	44.9	3.2 (27.4)	3.3 (2.5)	-3.9 (-10.7, 2.9)	0.259
OZ 10 mg Q4 (N=42)	50.0	7.2 (27.7)	7.7 (2.5)	0.5 (-6.2, 7.3)	0.874
OZ 30 mg Q4 (N=40)	52.6	10.0 (73.6)	9.9 (2.6)	2.7 (-4.1, 9.5)	0.437
OZ 80 mg Q8 (N=42)	51.6	12.4 (57.1)	11.5 (2.5)	4.3 (-2.4, 11.0)	0.209
OZ 80 mg Q4 (N=43)	46.4	11.6 (64.1)	8.9 (2.5)	1.7 (-5.0, 8.4)	0.612
Vitality					
Placebo (N=45)	49.0	15.0 (61.7)	12.7 (2.8)		
OZ 10 mg Q8 (N=41)	40.7	4.9 (40.5)	4.2 (2.9)	-8.1 (-16.4, 0.1)	0.053
OZ 10 mg Q4 (N=42)	43.6	8.2 (44.8)	7.7 (2.8)	-4.2 (-12.5, 4.1)	0.325
OZ 30 mg Q4 (N=40)	53.9	13.9 (75.6)	13.4 (3.0)	0.8 (-7.5, 9.1)	0.851
OZ 80 mg Q8 (N=42)	45.1	12.8 (66.0)	10.4 (2.8)	-1.2 (-9.4, 6.9)	0.768
OZ 80 mg Q4 (N=43)	49.0	17.7 (80.9)	14.2 (2.9)	0.9 (-7.1, 8.8)	0.830
Social functioning					
Placebo (N=45)	61.1	12.5 (50.1)	11.0 (3.4)		
OZ 10 mg Q8 (N=41)	54.6	10.7 (50.1)	7.9 (3.5)	-3.2 (-12.6, 6.2)	0.506
OZ 10 mg Q4 (N=42)	58.3	3.9 (27.7)	5.7 (3.4)	-5.3 (-14.7, 4.0)	0.262
OZ 30 mg Q4 (N=40)	65.9	21.9 (86.0)	18.3 (3.6)	7.2 (-2.2, 16.7)	0.132
OZ 80 mg Q8 (N=42)	64.0	14.3 (44.4)	13.6 (3.4)	2.6 (-6.7, 11.9)	0.586
OZ 80 mg Q4 (N=43)	60.8	8.1 (33.3)	8.2 (3.5)	-2.9 (-12.1, 6.4)	0.543
Role-emotional					
Placebo (N=45)	66.5	8.5 (28.1)	12.6 (3.7)		
OZ 10 mg Q8 (N=41)	55.3	12.9 (67.0)	9.6 (3.8)	-3.0 (-13.4, 7.5)	0.576
OZ 10 mg Q4 (N=42)	54.8	5.8 (22.5)	5.7 (3.7)	-6.9 (-17.2, 3.4)	0.189
OZ 30 mg Q4 (N=40)	59.0	12.3 (56.7)	10.9 (3.9)	-1.7 (-12.1, 8.7)	0.745
OZ 80 mg Q8 (N=42)	65.5	16.5 (32.9)	16.3 (3.8)	3.7 (-6.5, 14.0)	0.475
OZ 80 mg Q4 (N=43)	60.7	13.4 (38.6)	12.3 (3.8)	-0.3 (-10.5, 9.9)	0.950
Mental health index					
Placebo (N=45)	64.3	7.2 (31.1)	7.5 (2.6)		
OZ 10 mg Q8 (N=41)	60.9	3.2 (11.2)	3.6 (2.7)	-3.8 (-11.2, 3.5)	0.305
OZ 10 mg Q4 (N=42)	64.6	7.1 (18.2)	7.5 (2.7)	0.1 (-7.2, 7.4)	0.985
OZ 30 mg Q4 (N=40)	63.0	6.3 (21.3)	6.3 (2.8)	-1.1 (-8.5, 6.3)	0.767

Table 18. Analysis of SF-36: Week 16 – LOCF mITT Population

Timepoint[a] SF-36 Component Treatment (N)	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)	Difference Adjusted Mean Change (95% CI) OZ vs Placebo	p-Value OZ vs Placebo
OZ 80 mg Q8 (N=42)	66.0	10.8 (30.4)	10.3 (2.7)	2.8 (-4.4, 10.1)	0.443
OZ 80 mg Q4 (N=43)	66.1	11.2 (31.5)	10.6 (2.7)	3.1 (-4.1, 10.4)	0.394
Standardized physical component					
Placebo (N=45)	36.6	5.3 (21.1)	4.7 (1.1)		
OZ 10 mg Q8 (N=40)	33.5	4.0 (13.7)	3.2 (1.2)	-1.5 (-4.7, 1.7)	0.350
OZ 10 mg Q4 (N=42)	36.5	3.8 (13.8)	4.1 (1.2)	-0.5 (-3.7, 2.6)	0.733
OZ 30 mg Q4 (N=40)	37.9	6.8 (28.0)	6.0 (1.2)	1.3 (-1.8, 4.5)	0.403
OZ 80 mg Q8 (N=42)	38.1	6.4 (22.6)	6.1 (1.2)	1.5 (-1.7, 4.6)	0.361
OZ 80 mg Q4 (N=43)	37.4	8.0 (31.3)	6.7 (1.2)	2.0 (-1.1, 5.1)	0.203
Standardized mental component					
Placebo (N=45)	45.1	4.6 (23.8)	4.8 (1.5)		
OZ 10 mg Q8 (N=40)	42.5	3.4 (16.3)	3.2 (1.6)	-1.6 (-5.9, 2.6)	0.450
OZ 10 mg Q4 (N=42)	42.5	2.8 (11.6)	2.8 (1.5)	-2.0 (-6.2, 2.2)	0.357
OZ 30 mg Q4 (N=40)	44.5	5.3 (16.0)	5.0 (1.6)	0.2 (-4.0, 4.4)	0.927
OZ 80 mg Q8 (N=42)	44.9	6.4 (24.2)	5.9 (1.5)	1.1 (-3.1, 5.3)	0.613
OZ 80 mg Q4 (N=43)	44.2	5.2 (19.6)	4.8 (1.6)	0.0 (-4.1, 4.2)	0.999

Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
Statistical significance at the .05 level is denoted by *.Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
CI = confidence interval; HAQ-DI = Health Assessment Questionnaire Disability Index; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of subjects in mITT population per treatment group;
OZ = ozoralizumab; Q4 = every 4 weeks; Q8 = every 8 weeks; SE = standard error; SF-36 = 36-item short form health survey; vs = versus.
d. All analyses were done independently by data analysis interval using data with non-missing baseline values.

The Tiredness Scale: Data on the Tiredness Scale are presented in Table 19. At Week 16, none of the ozoralizumab treatment groups showed an adjusted mean change from Baseline that was statistically significantly different from that in the placebo group.

Table 19. Analysis of Tiredness (0 to 10 Scale) at Week 16 – LOCF mITT Population

Treatment (N)	LOCF Mean	LOCF Mean Change (%) From Baseline	Adjusted Mean Change (SE)[b]	Difference Adjusted Mean Change (95% CI) OZ vs Placebo	p-Value OZ vs Placebo
Placebo (N=45)	5.7	1.4 (23.0)	1.1 (0.3)		
OZ 10 mg Q8 (N=41)	5.7	1.4 (14.3)	1.2 (0.3)	0.1 (-0.8, 1.0)	0.820
OZ 10 mg Q4 (N=42)	5.7	1.2 (14.9)	1.1 (0.3)	0.0 (-0.9, 1.0)	0.939
OZ 30 mg Q4 (N=40)	4.7	2.1 (28.4)	1.9 (0.4)	0.8 (-0.2, 1.7)	0.112
OZ 80 mg Q8 (N=42)	5.5	1.4 (17.5)	1.2 (0.3)	0.1 (-0.8, 1.1)	0.773
OZ 80 mg Q4 (N=43)	5.4	1.6 (20.3)	1.3 (0.3)	0.2 (-0.7, 1.1)	0.655

All analyses were done independently by data analysis interval using data with non-missing baseline values.
Adjusted means of 'change' account for imbalance among treatments with respect to all other effects in model.
Comparisons between treatments were based on analysis of covariance (unadjusted for multiplicity).
Standard model of analysis: change = baseline treatment stratum.
Tiredness Scale: (0) Not tired at all; (10) As tired as you can imagine.
CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat;
N = number of subjects in mITT population per treatment group; OZ = ozoralizumab; Q4 = every 4 weeks;
Q8 = every 8 weeks; SE = standard error; vs = versus.

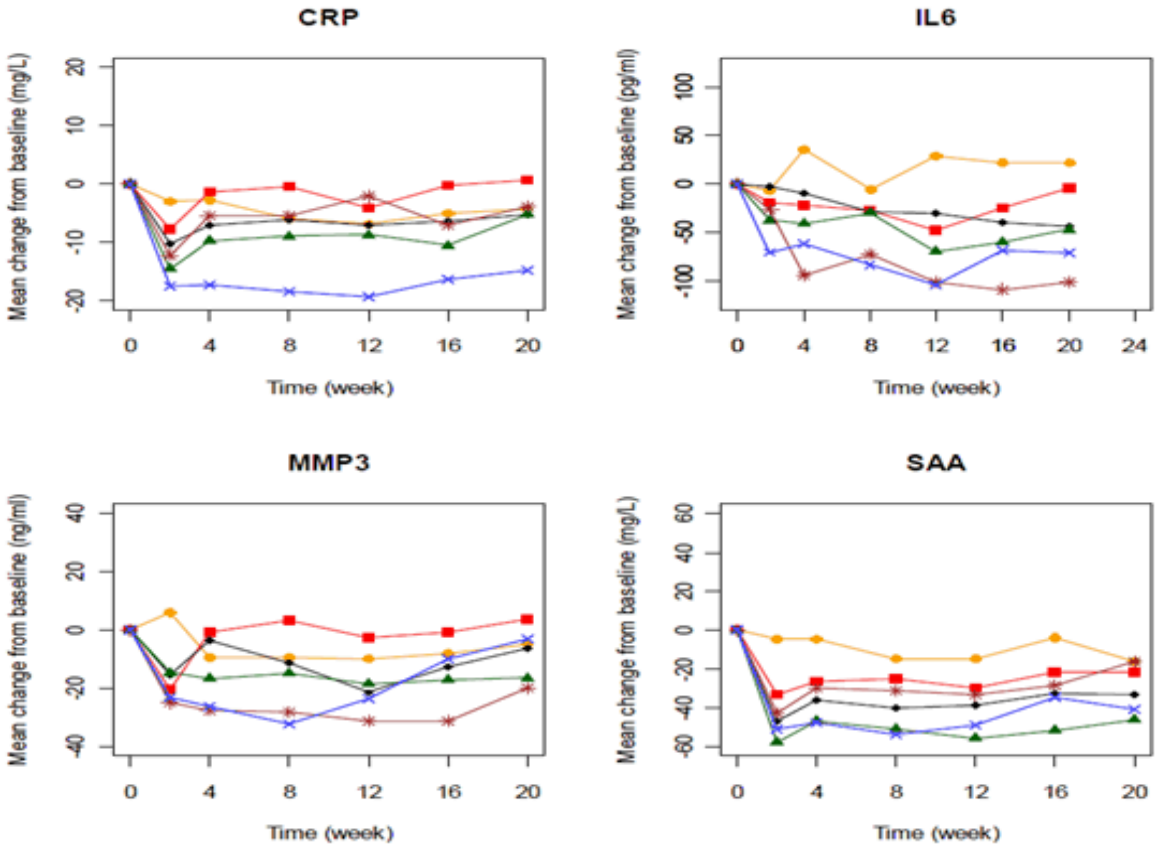
Pharmacokinetic, Pharmacodynamic, and/or Other Results:

Pharmacokinetics Results: Following the first SC injection, ozoralizumab was absorbed with a mean T_{max} ranging between 66 hours and 135 hours (2.8 and 5.6 days), and a mean $t_{½}$ ranging between 5.7 days and 13.2 days. The apparent oral dose clearance values of ozoralizumab ranged between 12 mL/h and 22 mL/h, and V_z/F values of ozoralizumab ranged between 2.9 L and 6.7 L.

The C_{max} and AUC of ozoralizumab after the first dose increased in a dose proportional manner from 10 mg to 80 mg Q4. Following the last SC injection of ozoralizumab the mean T_{max} ranged between 108 hours and 159 hours (4.5 days and 6.6 days), and the mean $t_{½}$ ranged between 9.3 days and 11.5 days. The mean accumulation ratio ranged between 0.89 and 1.48.

Pharmacodynamics Results: Overall, there was a mean reduction in all PD levels at the first post-dose time point (Week 2) in all active-treatment groups. In contrast, mean PD levels fluctuated in the placebo treatment group. Due to significant variability in PD levels, a clear dose-response relationship was not clearly demonstrated in all cases. However, further investigation may better define whether an individual dose-response relationship may be present in ≥1PD markers. Mean change from Baseline for each of the 4 PD markers is presented in Figure 2.

Figure 2. Mean Change From Baseline for Pharmacodynamic Markers CRP, IL6, MMP3, and SAA



CRP = C-reactive protein; IL 6 = interleukin-6; MMP 3 = matrix metalloproteinase-3; SAA = serum amyloid A.

Immunogenicity Results: Five (5) of 203 (2%) ozoralizumab treated subjects tested positive for Nabs with 1 subject at 2 occasions. Presence of ADAs or Nabs did not appear to alter PK of ozoralizumab.

Safety Results:

The overall AE profile by treatment group is summarised in Table 20.

Table 20. Number (%) of Subjects With Adverse Events – Safety Population

Category of AEs Relationship to Treatment	Overall p-Value[a]	Placebo N=45	Ozoralizumab, n (%)					Total N=253
			10 mg Q8 N=41	10 mg Q4 N=42	30 mg Q4 N=40	80 mg Q8 N=42	80 mg Q4 N=43	
All adverse events	0.824	20 (44.4)	23 (56.1)	24 (57.1)	20 (50.0)	24 (57.1)	23 (53.5)	134 (53.0)
TEAEs	0.623	18 (40.0)	23 (56.1)	21 (50.0)	19 (47.5)	24 (57.1)	23 (53.5)	128 (50.6)
Related	--	6 (13.3)	7 (17.1)	4 (9.5)	3 (7.5)	6 (14.3)	8 (18.6)	34 (13.4)
Not related	--	12 (26.7)	16 (39.0)	17 (40.5)	16 (40.0)	18 (42.9)	15 (34.9)	94 (37.2)
Serious adverse events	0.446	2 (4.4)	3 (7.3)	2 (4.8)	2 (5.0)	4 (9.5)	0 (0.0)	13 (5.1)
Severe adverse events								
Related	--	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)	2 (4.8)	0 (0.0)	4 (1.6)
Not related	--	2 (4.4)	2 (4.9)	1 (2.4)	0 (0.0)	3 (7.1)	0 (0.0)	8 (3.2)
AEs leading to withdrawal	0.561	2 (4.4)	2 (4.9)	3 (7.1)	3 (7.5)	5 (11.9)	1 (2.3)	16 (6.3)
Deaths	0.411	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
AEs of special interest								
Infections	0.719	8 (17.8)	10 (24.4)	13 (31.0)	10 (25.0)	15 (35.7)	8 (18.6)	64 (25.3)
Serious infections	0.087	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.5)	3 (7.1)	0 (0.0)	5 (2.0)
Medically important infections	--	0 (0.0)	2 (4.9)	0 (0.0)	1 (2.5)	3 (7.1)	0 (0.0)	6 (2.4)

AEs = adverse events; N = total number of subjects in each treatment group; n = number of subjects; Q4 = every 4 weeks; Q8 = every 8 weeks; TEAEs = treatment-emergent adverse events.
a. Overall p-value refers to number of subjects' data. Fisher's Exact Test p-value (2-Tail).

Adverse Events: Table 21 summarises the incidence of TEAEs by treatment group reported by ≥5% of subjects. There was no statistically significant imbalance among the treatment groups in the overall incidence of TEAEs. The most commonly reported TEAEs were upper respiratory tract infections and urinary tract infections. The only specific TEAEs showing a significant imbalance among the groups were contusion (4 cases) tonsillitis (2 cases) and weight increase (2 cases), for which the imbalance reflected a small number of cases being concentrated in only 1 or 2 treatment groups. In most cases, TEAEs were mild to moderate in severity.

Withdrawals due to Adverse Events: AEs leading to withdrawal are summarised in Table 22. AEs led to withdrawal from the study in 16 subjects, only 1 from the 80 mg Q4 group. Urinary tract infection (2 subjects) was the only AE resulting in the withdrawal of >1 subject. There was no significant imbalance among the treatment groups.

Deaths: One (1) subject died during this study. The subject, who was in the 10 mg Q4 group and had a long history of depression and a previous suicide attempt, committed suicide by gunshot. The subject's suicide was not thought to be related to the study medication.

Table 21. Number (%) of Subjects (>5%) in Any Treatment Group Reporting Treatment-Emergent Adverse Events-Safety Population

System Organ Class[a] Adverse Event	Overall p-Value[b]	Placebo N=45	Ozoralizumab, n (%)					Total N=253
			10 mg Q8 N=41	10 mg Q4 N=42	30 mg Q4 N=40	80 mg Q8 N=42	80 mg Q4 N=43	
Any adverse event	0.623	18 (40.0)	23 (56.1)	21 (50.0)	19 (47.5)	24 (57.1)	23 (53.5)	128 (50.6)
Infections and infestations								
Sinusitis	0.242	2 (4.4)	1 (2.4)	0 (0.0)	3 (7.5)	1 (2.4)	0 (0.0)	7 (2.8)
Upper respiratory tract infection	0.387	1 (2.2)	4 (9.8)	1 (2.4)	4 (10.0)	2 (4.8)	1 (2.3)	13 (5.1)
Urinary tract infection	0.709	2 (4.4)	3 (7.3)	2 (4.8)	0 (0.0)	2 (4.8)	2 (4.7)	11 (4.3)
Vascular disorders								
Hypertension	0.723	3 (6.7)	0 (0.0)	2 (4.8)	1 (2.5)	2 (4.8)	1 (2.3)	9 (3.6)
General disorders and administration site conditions								
Pyrexia	0.316	1 (2.2)	3 (7.3)	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	6 (2.4)
Edema peripheral	0.083	0 (0.0)	3 (7.3)	1 (2.4)	0 (0.0)	1 (2.4)	0 (0.0)	5 (2.0)
Injury, poisoning, and procedural complications								
Contusion	0.033*	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	3 (7.1)	0 (0.0)	4 (1.6)

* Statistical significance.

N = total number of subjects in each treatment group; n = number of subjects; Q4 = every 4 weeks; Q8 = every 8 weeks.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

b. Overall p-value: refers to number of subjects data. Fisher's Exact Test p-value (2-Tail).

Table 22. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Study – Safety Population

System Organ Class Preferred Term	Overall p-Value	Placebo N=45	Ozoralizumab, n (%)					Total N=253
			10 mg Q8 N=41	10 mg Q4 N=42	30 mg Q4 N=40	80 mg Q8 N=42	80 mg Q4 N=43	
Any adverse event	0.591	2 (4.4)	2 (4.9)	3 (7.1)	3 (7.5)	5 (11.9)	1 (2.3)	16 (6.3)
Blood and lymphatic system disorders								
Lymphadenopathy	0.652	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Gastrointestinal disorders								
Diverticulum	0.652	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Periodontitis	0.652	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Infections and infestations								
Abscess	0.652	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Bronchopneumonia	0.158	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.4)
Cellulitis	0.652	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Pneumonia	0.652	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Staphylococcal infection	0.652	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Tuberculosis	0.652	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Urinary tract infection	0.320	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	1 (2.4)	0 (0.0)	2 (0.8)
Metabolism and nutrition disorders								
Hypoglycemia	1.000	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders								
Systemic lupus erythematosus	0.320	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Renal and urinary disorders								
Haematuria	1.000	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Nephrolithiasis	0.652	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders								
Idiopathic pulmonary fibrosis	0.320	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pneumonitis	0.158	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders								
Dermatitis allergic	0.822	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.4)

Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.
Overall p-value refers to the number of subjects' data. Fisher's exact test p-value (2-tail).
N = total number of subjects in each treatment group; n = number of subjects; Q4 = every 4 weeks; Q8 = every 8 weeks.

Serious Adverse Events: SAEs are summarised in Table 23. SAEs were reported in 13 subjects, none in the 80 mg Q4 group; no event was reported as an SAE in >1 subject. Six (6) of the SAEs were considered by the Investigator to be related to the Investigational product and 12 of the SAEs were considered by the Investigator not to be related.

Table 23. Summary of Subjects With Serious Adverse Events

Treatment Subject Serial Number	System Organ Class	Adverse Event	Treatment Related
Placebo			
1	Metabolism and nutrition	Hypokalemia	No
2	Metabolism and nutrition	Hypoglycemia	No
	Metabolism and nutrition	Hypoglycemia	No
	Injury, poisoning, and procedural complications	Right sacrum fracture	No
	Injury, poisoning, and procedural complications	Right pubic fracture	No
Ozoralizumab 10 mg Q8			
3	Infections and infestations	Pyelonephritis	No
4	Cardiac disorders	Atrial fibrillation	No
5	Respiratory, thoracic, and mediastinal disorders	Idiopathic fibrosing alveolitis	Yes
Ozoralizumab 10 mg Q4			
6	Psychiatric disorders	Death by suicide	No
7	Respiratory, thoracic, and mediastinal disorders	Chronic Obstructive Pulmonary Disease	No
Ozoralizumab 30 mg Q4			
8	Infections and infestations	Bronchopneumonia	No
9	Respiratory, thoracic, and mediastinal disorders	Acute pneumonitis	Yes
Ozoralizumab 80 mg Q8			
10	Infections and infestations	Diverticulitis	No
11	Infections and infestations	Pneumonia	Yes
	Infections and infestations	Left arm cellulitis	Yes
	Infections and infestations	Left arm abscess	Yes
12	Infections and infestations	Pleural tuberculosis	Yes
13	Renal and urinary disorders	Right ureteropelvic junction kidney stone	No

Q4 = every 4 weeks; Q8 = every 8 weeks.

Adverse Events of Special Interest: Treatment-emergent infections were reported in 22.5% of subjects; the most common infections were upper respiratory infections (5.1%) and urinary tract infection (4.3%). Medically important infections were reported in 2.4% of subjects, none in the 80 mg Q4 group. Infections reported as SAEs occurred in 2.0% of subjects, none in the 80 mg Q4 group. There was 1 report of tuberculosis. There were no statistically significant imbalances among the groups in infections overall, or in serious infections. The only specific infection for which there was a significant imbalance among the groups was tonsillitis, which occurred in 2 subjects in the 30 mg Q4 group only.

ISRs were reported in 3 subjects, occurring after the first injection only in 2 subjects and after the third and fourth injections in the other. All resolved spontaneously.

Clinical Laboratory Results: Few subjects had laboratory results reported as AEs. No AEs on blood chemistry or hematological parameters were identified.

Vital Signs Results: There was a statistically significantly imbalance among the treatment groups in potential clinical importance (PCI) increases in body weight (≥5%). A total of 20 (7.9%) subjects had a PCI increase in weight during the on-treatment period. Overall, 14 subjects had a PCI decrease (≥5%) in weight during the study period but there was no significantly imbalance among the treatment groups.

PCI increases in systolic blood pressure (BP) were seen in 2 subjects (0.8%) as were PCI increases in diastolic BP. PCI decreases in systolic BP were seen in 2 subjects (0.8%) while a PCI decrease in diastolic BP was seen in 1 subject. At Week 16, there were no statistically significantly imbalances between the treatment groups for any of the vital sign parameters.

Autoantibody Results: Statistically significant differences were shown for antinuclear antibodies (30 mg Q4 group) and anti-cardiolipin IgM (10 mg Q8 and 10 mg Q4 groups). There were no statistically significant differences shown for anti-double-stranded deoxyribonucleic acid and anti-cardiolipin IgG.

CONCLUSIONS:

Only the ozoralizumab 80 mg Q4 group showed a statistically significantly higher response rate than the placebo group for the primary efficacy endpoint of the ACR20 at Week 16 with 72% of subjects in the 80 mg Q4 group showing a ACR20 response compared to 42% in the placebo group.

The response rate in the 80 mg Q4 treatment group was also statistically significantly higher than in the placebo group at Week 16 for the ACR50 but not for the ACR70.

Statistically significant better results in the 80 mg Q4 group compared to the placebo group were seen at Week 16 for the DAS28, EULAR response, number of tender joints, number of swollen joints, the pain VAS, the general health VAS, the physician's global assessment of disease activity, and the patient's global assessment of disease activity. Statistically significant better results compared to the placebo group at Week 16 were seen for other treatment groups in several of the secondary efficacy parameters, but none with the same consistency as with the 80 mg Q4 group.

In this study, treatment with ozoralizumab appeared to be generally well tolerated. There were no dose-dependent increases in SAEs, TEAEs, withdrawals due to AEs, or infections. No dose limiting toxicity was identified. SAEs were reported in 13 subjects, none in the 80 mg Q4 group; no event was reported as an SAE in >1 subject. The only death in the study was the result of a suicide in a subject with longstanding depression and a previous suicide attempt; the suicide was not felt to be drug-related by the Investigator or the Sponsor.