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GENERIC DRUG NAME and/or COMPOUND NUMBER: Tofacitinib / CP-690,550

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not applicable

NATIONAL CLINICAL TRIAL NO.: NCT00960440

PROTOCOL NO.: A3921032

PROTOCOL TITLE: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate With Inadequate Response to TNF Inhibitors

Study Centers: This study was conducted at 82 study centers (2 centers in Australia, 3 centers in Austria, 3 centers in Belgium, 4 centers in Brazil, 6 centers in Canada, 5 centers in France, 10 centers in Germany, 1 center in Ireland, 1 center in Italy, 3 centers in Republic of Korea, 7 centers in Spain, 4 centers in Taiwan, and 33 centers in the United States [US]).

Study Initiation and Completion Dates: 12 October 2009 to 17 March 2011

Phase of Development: Phase 3

Study Objectives:

Primary Objectives: To compare the efficacy of CP-690,550, in doses of 5 mg twice daily (BID) and 10 mg BID, vs placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA), in patients with RA on background methotrexate (MTX) who had an inadequate response to a tumor necrosis factor (TNF) inhibitor, as measured by American College of Rheumatology's (ACR) definition for calculating improvement in RA; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures (ACR20) response rates at Month 3; to compare physical function status of patients with active RA on background MTX who had an inadequate response to a TNF inhibitor, after administration of CP-690,550, in doses of 5 mg BID and 10 mg BID, vs placebo, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) response at Month 3; to compare the rate of achieving Disease Activity Score (DAS)28-4 (erythrocyte sedimentation rate [ESR]) <2.6 at Month 3 in patients with active RA on background MTX who had an inadequate response to a TNF inhibitor, after administration of CP-690,550, in doses of 5 mg BID and 10 mg BID, vs placebo; and to compare the safety and tolerability of CP-690,550, in doses of 5 mg BID and 10 mg BID, vs placebo in patients with RA on background MTX who had an inadequate response to a TNF inhibitor.

Secondary Objectives: To compare the efficacy of CP-690,550, in doses of 5 mg BID and 10 mg BID, vs placebo for the treatment of signs and symptoms of RA in patients with RA on background MTX who had an inadequate response to a TNF inhibitor at all other time points as measured by ACR20, ACR definition for calculating improvement in RA, calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures (ACR50), ACR definition for calculating improvement in RA, calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures (ACR70), and DAS28 response rates; to compare the incidence of DAS28 <2.6 and DAS28 ≤3.2 at each visit; and to compare effects on all health outcomes measures in the study at each visit, as appropriate for the specific outcome, compared to baseline. Subject to Investigational Review Board/Independent Ethics Committee approval/favorable opinion, this study included an additional research component involving collection of de-identified biological samples. An additional informed consent document was included as part of this additional research component. Patients may have participated in the main study, even if they chose not to participate in the molecular profiling component.

METHODS

Study Design: This was a Phase 3, randomized, 6-month, double-blind, placebo-controlled, parallel-group study. Patients with rheumatoid arthritis were randomized in a 2:2:1:1 ratio to 1 of the following 4 parallel treatment sequences:

- Treatment Sequence 1: CP-690,550 5 mg BID plus MTX (hereafter referred to as 'CP-690,550 5 mg');
- Treatment Sequence 2: CP-690,550 10 mg BID plus MTX (hereafter referred to as 'CP-690,550 10 mg');
- Treatment Sequence 3: placebo BID → CP-690,550 5 mg BID plus MTX at Month 3 (hereafter referred to as 'placebo → CP-690,550 5 mg'); or
- Treatment Sequence 4: placebo BID → CP-690,550 10 mg BID plus MTX at Month 3 (hereafter referred to as 'placebo → CP-690,550 10 mg').

At the Month 3 visit, all patients randomized to Treatment Sequences 3 or 4 were advanced to the second predetermined treatment in a blinded fashion for the remainder of the 6-month study by the drug allocation system.

Number of Patients (Planned and Analyzed): In total, 396 patients were planned to be enrolled in this study. Three hundred ninety-nine patients were randomized to treatment, 399 (100.0%) received at least 1 dose of study medication, and 311 (77.9%) patients completed the study.

Diagnosis and Main Criteria for Inclusion: Male and female patients at least 18 years of age, with a diagnosis of RA, which was active at the time of the study (based on tender and swollen joint counts), with ongoing treatment with an adequate and stable dose of MTX,

were enrolled in the study. Patients were required to have 1 of the following: ESR >28 mm/hour in the local laboratory and/or C-reactive protein (CRP) >7 mg/L in the central laboratory. Washout periods and discontinuation requirements were specified for disease-modifying antirheumatic drug (DMARDs) and biologic response modifiers before study entry. Exclusionary criteria included active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB). Other exclusion criteria included pregnancy, blood dyscrasias, or any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

Study Treatment: Patients were randomized to 1 of the following treatment sequences: CP-690,550 5 mg BID; CP-690,550 10 mg BID; placebo → CP-690,550 5 mg; or placebo → CP-690,550 10 mg.

Efficacy Evaluations: The primary efficacy endpoints were as follows:

- ACR20 responder rate at the Month 3 visit;
- Change from baseline in the HAQ-DI at the Month 3 visit; and
- Rate of patients achieving a DAS28-4(ESR) <2.6 at the Month 3 visit.

The secondary efficacy endpoints were as follows:

- Signs and symptoms of RA, as measured by ACR20 responder rates vs placebo analyzed at all time points other than Month 3; ACR50 and ACR70 responder rates at all time points; and incidence and response rates of DAS28-3(CRP) and DAS28-4(ESR).
- Physical function and patient reported outcomes, as measured by HAQ-DI; Patient Assessment of Arthritis Pain; Patient Global Assessment of Arthritis; Physician Global Assessment of Arthritis; Short Form-36 (SF-36) (Version 2, Acute); Medical Outcome Study Sleep Scale (MOS-SS); Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale; self-report questionnaire (quality of life instrument) developed by the European Quality of Life (EuroQoL) Group (EQ-5D); RA Healthcare Resource Utilization (HCRU) Questionnaire; and Work Limitations Questionnaire (WLQ).

Pharmacogenomic Evaluations: Anonymized samples for molecular profiling were collected; study-specific nonanonymized pharmacogenomic testing was not performed.

Safety Evaluations: Safety was assessed by the reporting of adverse events (AEs), physical examinations, vital signs measurements (blood pressure [BP], heart rate, temperature, and weight), electrocardiograms (ECGs), and clinical laboratory results in all patients who received at least 1 dose of study drug. Investigators and Sponsor clinicians reviewed individual patient data throughout the conduct of the study to ensure the patients' well-being.

Statistical Methods: This study was designed to address the primary study objectives based on 3 primary endpoints. In order to preserve Type I error, each objective was assessed sequentially, using a gate-keeping or step-down approach, where statistical significance could be claimed for the endpoint only if the previous endpoint in the sequence met the requirements for significance. Additionally (for the primary analyses), as there were 2 doses within each endpoint, the gate-keeping or step-down approach was to be applied, ie, the highest dose (CP-690,550 10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint was significant; the low dose (5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint were significant.

Analysis sets used for this study were as follows:

- The full analysis set (FAS) included all patients who were randomized to the study and received at least 1 dose of the randomized study drug (CP-690,550) or placebo. The primary analysis population for this study was defined by the FAS of patients.

- FAS patients who had a protocol deviation thought to affect the efficacy analysis were excluded from the Per Protocol (PP) efficacy analysis. Protocol deviations that would have excluded patients from the PP set were defined before the randomization blind was broken.

- The safety analysis set was defined as those patients who received at least 1 dose of the study drug (CP-690,550) or placebo.

The proposed sequence of primary endpoints was signs and symptoms as measured by ACR20 response rate at Month 3, physical function as measured by the mean change from baseline in HAQ-DI at Month 3, and the rate of patients achieving DAS28-4(ESR) <2.6 at Month 3. The normal approximation for the difference in binomial proportions was used to test the superiority of each dose of CP-690,550 to placebo with respect to rates of patients achieving ACR20 and DAS28-4(ESR) <2.6.

The HAQ-DI was expressed as a change from baseline. The analysis was done using a mixed-effect repeated-measure model that included the fixed effects of treatment, visit (Week 2, Month 1, and Month 3), treatment by visit interaction, geographic region (US, Europe/Canada, Latin America, Rest of World), and the baseline value as a covariate. Patients were a random effect and compound symmetry was assumed. In addition, change in HAQ-DI from baseline after Month 3 was also analyzed for descriptive purposes; and the mixed effect model with repeated measures was applied as well to evaluate the effect following Month 3.

The ACR50 and ACR70 response variables, as well as all ACR20 responses for other time points, were analyzed in a similar manner as described for the ACR20 in the primary analysis. An analysis that used last observation carried forward (LOCF) rather than nonresponder imputation (NRI) was also performed to support the robustness of the results.

All the safety data were summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations as follows:

- AEs were summarized according to the Sponsor's standards;
- Safety laboratory tests were summarized according to the Sponsor's standards; special attention was given to the following safety criteria: neutrophil counts, serum creatinine levels, platelet counts, liver tests, events of anemia, hyperlipidemia and hypertension;
- Any cardiovascular safety endpoints as adjudicated by the Cardiovascular Safety Endpoint Adjudication Committee were summarized;
- Any potentially malignant tumor, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD) over-read by the central pathologists was summarized;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, were summarized. (This was done by written narratives);
- Abnormal changes in physical examination compared with baseline were summarized;
- Change from baseline in vital signs (BP, heart rate, temperature, and weight measurements) was summarized.

AEs were displayed for the period of time from baseline to Month 3 (that is, AEs that occurred up to Month 3), and Month 3 to the end of treatment period (that is, AEs that occurred after Month 3).

Serious AE (SAE) presentations were derived from a combination of data contained within the clinical study database and the corporate safety database. The corporate safety database was a separate, centralized, AE monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the sponsor. The clinical study database was based on information provided from the Case Report Forms/Data Collection Tools. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

RESULTS

Patient Disposition and Demography: Table 1 summarizes patient disposition. Three hundred ninety-nine patients were randomized to treatment, 399 (100.0%) received at least 1 dose of study medication, and 311 (77.9%) patients completed the study. The CP-690,550 5 mg sequence had the highest rate of completion (80.5%), and the placebo → CP-690,550 10 mg sequence had the highest rate of patients who discontinued (27.3%). A total of 32 (8.0%) patients withdrew due to AEs (18 of the patients had AEs considered related to

study drug and 14 patients had AEs considered not related). One patient (who received placebo → CP-690,550 10 mg) died due to pulmonary embolism.

Table 1. Patient Disposition

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 589				
Assigned to Study Treatment	133	134	66	66
Treated	133	134	66	66
Completed	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)
Discontinued	26 (19.5)	31 (23.1)	13 (19.7)	18 (27.3)
Patient Died	0	0	0	1 (1.5)
Related to Study Drug	10 (7.5)	12 (9.0)	6 (9.1)	8 (12.1)
Adverse event	8 (6.0)	7 (5.2)	3 (4.5)	0
Lack of efficacy	2 (1.5)	5 (3.7)	3 (4.5)	8 (12.1)
Not Related to Study Drug	16 (12.0)	19 (14.2)	7 (10.6)	9 (13.6)
Adverse event	4 (3.0)	5 (3.7)	1 (1.5)	4 (6.1)
Other	1 (0.8)	1 (0.7)	1 (1.5)	0
Protocol violation	2 (1.5)	8 (6.0)	3 (4.5)	4 (6.1)
Patient no longer willing to participate in study	9 (6.8)	5 (3.7)	2 (3.0)	1 (1.5)

Information related to study discontinuations is from the patient summary page of the Case Report Form.
Abbreviations: BID = twice daily, No. = number

The majority of the treated patients were female (335 /399, 84.0%) and white (332/399, 83.2%). The mean age of all patients was 55.0 years (range 20 years to 84 years). The mean weight was 79.1 kg (range kg 43.0 to 188.0 kg), and mean body mass index was 29.5 kg/m^2 (range 16.9 kg/m^2 to 70.8 kg/m^2). The characteristics of the patients in each of the treatment sequences were similar to one another and to the overall study population (Table 2). The mean time from diagnosis of RA to enrollment in the study ranged from 11.2 years to 13.0 years across the 4 treatment sequences; the overall duration of RA since diagnosis for all patients ranged from 0.4 years to 55.0 years.

Table 2. Demographic Characteristics

Page 1 of 3						
Demographic Characteristic Parameter	**CP-690,550 5 mg BID**			**CP-690,550 10 mg BID**		
	Male N=20	**Female N=113**	**Total N=133**	**Male N=18**	**Female N=116**	**Total N=134**
Age (years), n (%):						
18-44	3 (15.0)	16 (14.2)	19 (14.3)	0	23 (19.8)	23 (17.2)
45-64	13 (65.0)	71 (62.8)	84 (63.2)	14 (77.8)	71 (61.2)	85 (63.4)
≥65	4 (20.0)	26 (23.0)	30 (22.6)	4 (22.2)	22 (19.0)	26 (19.4)
Mean (SD)	53.8 (12.2)	55.7 (11.4)	55.4 (11.5)	57.3 (6.9)	54.7 (11.8)	55.1 (11.3)
Range	29-72	20-83	20-83	46-65	21-84	21-84
Race, n (%):						
White	17 (85.0)	91 (80.5)	108 (81.2)	16 (88.9)	96 (82.8)	112 (83.6)
Black	2 (10.0)	9 (8.0)	11 (8.3)	1 (5.6)	6 (5.2)	7 (5.2)
Asian	1 (5.0)	10 (8.8)	11 (8.3)	0	8 (6.9)	8 (6.0)
Other	0	3 (2.7)	3 (2.3)	1 (5.6)	6 (5.2)	7 (5.2)
Weight (kg):						
Mean (SD)	87.7 (18.6)	75.8 (21.3)	77.6 (21.3)	90.0 (20.8)	77.0 (19.5)	78.8 (20.1)
Range	55.5-130.2	45.4-188.0	45.4-188.0	56.0-125.2	43.0-139.7	43.0-139.7
Body mass index (kg/m^2):						
Mean (SD)	27.9 (5.1)	29.4 (7.8)	29.2 (7.5)	28.8 (5.8)	29.5 (6.9)	29.4 (6.8)
Range	18.5-41.0	18.3-70.8	18.3-70.8	19.6-37.8	16.9-50.2	16.9-50.2
Height (cm):						
Mean (SD)	177.1 (8.1)	160.4 (7.9)	162.9 (9.9)	176.3 (7.4)	161.3 (7.2)	163.4 (8.8)
Range	165.0-197.0	140.0-185.4	140.0-197.0	157.0-188.0	138.0-180.0	138.0-188.0

Body mass index computed as $weight/(height/100)^2$

Abbreviations: BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, SD = standard deviation

Table 2. Demographic Characteristics (continued)

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Demographic Characteristic Parameter	**Placebo → CP-690,550 5 mg BID**			**Placebo → CP-690,550 10 mg BID**		
	Male N=13	**Female N=53**	**Total N=66**	**Male N=13**	**Female N=53**	**Total N=66**
Age (years) n (%):						
18-44	4 (30.8)	9 (17.0)	13 (19.7)	1 (7.7)	8 (15.1)	9 (13.6)
45-64	8 (61.5)	32 (60.4)	40 (60.6)	9 (69.2)	37 (69.8)	46 (69.7)
≥65	1 (7.7)	12 (22.6)	13 (19.7)	3 (23.1)	8 (15.1)	11 (16.7)
Mean (SD)	50.7 (10.9)	55.2 (11.8)	54.3 (11.7)	54.2 (9.9)	54.6 (11.4)	54.5 (11.0)
Range	34-69	31-82	31-82	40-72	22-80	22-80
Race n (%):						
White	12 (92.3)	47 (88.7)	59 (89.4)	11 (84.6)	42 (79.2)	53 (80.3)
Black	0	1 (1.9)	1 (1.5)	1 (7.7)	7 (13.2)	8 (12.1)
Asian	1 (7.7)	3 (5.7)	4 (6.1)	1 (7.7)	3 (5.7)	4 (6.1)
Other	0	2 (3.8)	2 (3.0)	0	1 (1.9)	1 (1.5)
Weight (kg):						
Mean (SD)	102.6 (35.3)	74.9 (22.8)	80.4 (27.7)	81.4 (14.9)	81.8 (21.9)	81.7 (20.6)
Range	47.0-175.1	45.5-134.7	45.5-175.1	63.0-110.0	49.7-163.3	49.7-163.3
Body Mass Index (kg/m^2):						
Mean (SD)	32.3 (10.4)	29.2 (7.9)	29.8 (8.4)	26.7 (4.5)	30.6 (8.1)	29.9 (7.6)
Range	17.7-53.8	19.1-50.4	17.7-53.8	19.4-37.6	19.6-54.6	19.4-54.6
Height (cm):						
Mean (SD)	177.5 (6.9)	159.6 (7.4)	163.1 (10.2)	174.4 (5.5)	163.2 (7.0)	165.5 (8.1)
Range	163.0-185.4	142.7-180.0	142.7-185.4	166.0-185.0	147.0-174.0	147.0-185.0

Body mass index computed as $weight/(height/100)^2$

Abbreviations: BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, SD = standard deviation

Table 2. Demographic Characteristics (continued)

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Demographic Characteristic Parameter	**All Placebo**			**Total**		
	Male N=26	**Female N=106**	**Total N=132**	**Male N=64**	**Female N=335**	**Total N=399**
Age (years) n (%):						
18-44	5 (19.2)	17 (16.0)	22 (16.7)	8 (12.5)	56 (16.7)	64 (16.0)
45-64	17 (65.4)	69 (65.1)	86 (65.2)	44 (68.8)	211 (63.0)	255 (63.9)
≥65	4 (15.4)	20 (18.9)	24 (18.2)	12 (18.8)	68 (20.3)	80 (20.1)
Mean (SD)	52.4 (10.3)	54.9 (11.5)	54.4 (11.3)	54.2 (10.2)	55.1 (11.6)	55.0 (11.3)
Range	34-72	22-82	22-82	29-72	20-84	20-84
Race n (%):						
White	23 (88.5)	89 (84.0)	112 (84.8)	56 (87.5)	276 (82.4)	332 (83.2)
Black	1 (3.8)	8 (7.5)	9 (6.8)	4 (6.3)	23 (6.9)	27 (6.8)
Asian	2 (7.7)	6 (5.7)	8 (6.1)	3 (4.7)	24 (7.2)	27 (6.8)
Other	0	3 (2.8)	3 (2.3)	1 (1.6)	12 (3.6)	13 (3.3)
Weight (kg):						
Mean (SD)	92.0 (28.7)	78.3 (22.5)	81.0 (24.3)	90.1 (23.5)	77.0 (21.1)	79.1 (22.0)
Range	47.0-175.1	45.5-163.3	45.5-175.1	47.0-175.1	43.0-188.0	43.0-188.0
Body Mass Index (kg/m^2):						
Mean (SD)	29.5 (8.3)	29.9 (8.0)	29.8 (8.0)	28.8 (6.7)	29.6 (7.6)	29.5 (7.4)
Range	17.7-53.8	19.1-54.6	17.7-54.6	17.7-53.8	16.9-70.8	16.9-70.8
Height (cm):						
Mean (SD)	175.9 (6.3)	161.4 (7.4)	164.3 (9.3)	176.4 (7.1)	161.0 (7.5)	163.5 (9.3)
Range	163.0-185.4	142.7-180.0	142.7-185.4	157.0-197.0	138.0-185.4	138.0-197.0

Body mass index computed as $weight/(height/100)^2$

Abbreviations: BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, SD = standard deviation

Efficacy Results:

Statistical significance of the efficacy primary objectives was determined using the step-down procedure. The ACR20 response rates at Month 3 were statistically significantly different for both CP-690,550 doses compared with placebo. Improvements over time were observed for ACR50 and ACR70. The differences from placebo for mean changes from baseline in HAQ-DI at Month 3 were also statistically significantly different for both CP-690,550 doses. The rates of patients achieving a DAS28-4(ESR) <2.6 at Month 3 was significantly different from placebo for the CP-690,550 5 mg and 10 mg treatment sequences.

Statistical significance of the efficacy primary objectives was determined using the step-down procedure. For secondary analyses, statistical significance was determined by nominal p-value ≤0.05.

Primary Efficacy Results

ACR20 Response Rates at Month 3: Both CP-690,550 doses, 5 mg and 10 mg, demonstrated statistically significant (p-values of 0.0024 and <0.0001, respectively) and clinically meaningful reductions in signs and symptoms of RA over placebo as measured by ACR20 at Month 3 (Table 3).

Table 3. Normal Approximation to ACR20 Response Rates at Month 3 (FAS, NRI, Difference From Placebo)

Treatment	N	n	%	Difference From Placebo			
				Difference	95% CI for Difference		P-Value
					Lower	Upper	
CP-690,550 5 mg BID	132	55	41.67	17.23	6.06	28.41	0.0024
CP-690,550 10 mg BID	133	64	48.12	23.69	12.45	34.92	<0.0001
Placebo	131	32	24.43				

Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Changes from Baseline in HAQ-DI at Month 3: Both CP-690,550 doses demonstrated statistically significant (p-values <0.0001) and clinically meaningful improvements in physical function over placebo as measured by the HAQ-DI at Month 3 (Table 4).

Table 4. Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, NRI, Differences From Placebo)

Treatment	N	LS Mean	Differences From Placebo			
			Difference	95% CI for Difference		P-value
				Lower	Upper	
CP-690,550 5 mg BID	117	-0.43	-0.25	-0.36	-0.15	<0.0001
CP-690,550 10 mg BID	125	-0.46	-0.28	-0.38	-0.17	<0.0001
Placebo	118	-0.18				

Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS = least squares, N = number of patients, NRI = nonresponder imputation

Rate of Patients Achieving DAS28-4(ESR) <2.6 Versus Placebo at Month 3: The rates of patients achieving DAS28-4(ESR) <2.6 at Month 3 for CP-690,550 5 mg (8 [6.72%] patients) and CP-690,550 10 mg (14 [11.20%] patients) were statistically significantly different from placebo (p-values = 0.0496 and 0.0017, respectively) (Table 5).

Table 5. Summary of Patients Achieving DAS28-4(ESR) <2.6 at Month 3 (FAS, NRI, Comparisons to Placebo)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	119	8	6.72	5.05	0.00	10.10	0.0496
CP-690,550 10 mg BID	125	14	11.20	9.53	3.54	15.51	0.0017
Placebo	120	2	1.67				

Abbreviations: BID = twice daily, CI = confidence interval, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Secondary Efficacy Results

ACR20 Response Rates at All Time Points: ACR20 response rates were higher for patients in the CP-690,550 5 mg and 10 mg sequences at Month 3 compared with patients in the placebo → CP-690,550 5 mg and placebo → CP-690,550 10 mg sequences at Month 3. ACR20 response rates for the placebo → CP-690,550 5 mg and placebo → CP-690,550 10 mg sequences improved between Months 3 and 6 (ie, after advancing to CP-690,550). By Month 6, ACR20 response rates for patients (FAS, NRI) in the CP-690,550 5 mg and 10 mg sequences were 51.5% and 54.9%, respectively, compared with 45.5% and 40.0% for patients in the placebo → CP-690,550 5 mg and placebo → CP-690,550 10 mg sequences, respectively.

ACR50 Response Rates at All Time Points: At Week 2, the difference from placebo in response rate was statistically significant for the CP-690,550 5 mg sequence (6.1%; p-value = 0.0183). A Month 1, the difference from placebo was statistically significant for the CP-690,550 10 mg sequence (11.2%; p-value = 0.0040). At Month 3, the differences

from placebo for both CP-690,550 treatments (5 and 10 mg) were statistically significant (18.1%, p-value = <0.0001; 19.4%, p-value = <0.0001; respectively).

Patients in the CP-690,550 5 mg and 10 mg treatment sequences showed separation from the placebo → CP-690,550 treatment sequences by Week 2. Patients randomized to placebo treatment showed clear improvements in ACR50 response rates after switching to CP-690,550 treatment at Month 3.

ACR70 Response Rates at All Time Points: The percentages of patients treated with CP-690,550 5 mg and 10 mg who achieved ACR70 at Month 1 were statistically significant compared with placebo (7.6%; p-value = 0.0010; 6.8%; p-value = 0.0018; respectively). Patients in the CP-690,550 treatment sequences began to show response by Week 2, and response rates generally increased through Month 6. ACR70 response rates for the placebo → CP-690,550 treatment sequences remained very low through Month 3, and then increased between Month 3 and Month 6 (ie, after advancing to CP-690,550). By Month 6, the ACR70 response rates for the CP-690,550 treatment sequences remained slightly higher than for the placebo → CP-690,550 treatment sequences.

Health Assessment Questionnaire – Disability Index (HAQ-DI): The results for the CP-690,550 5 mg and CP-690,550 10 mg patients demonstrated statistically significantly decreased HAQ-DI scores (improvements) at Month 3 compared with placebo. Patients who received CP-690,550 10 mg experienced greater improvement compared with CP-690,550 5 mg and achieved statistically significantly lower HAQ-DI scores beginning at Week 2. Decreases from baseline in HAQ-DI scores were noted in the CP-690,550 treatment sequences as early as Week 2 that continued through Month 6.

Rates of at Least 0.22 Improvements in HAQ-DI: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significantly greater rates of improvement compared with placebo at Month 3. In the CP-690,550 treatment sequences, the proportions of patients increased through approximately Month 3. By Month 6, the rates of patients with at least 0.22 improvement in HAQ-DI were similar for all treatment sequences.

DAS28-4(ESR): Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant improvements from baseline in DAS28-4(ESR) at Month 3 compared with placebo. The decrease from baseline was larger for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg. The CP-690,550 treatment sequences had a numerically greater decrease from baseline at Month 3 compared with the placebo → CP-690,550 treatment sequences. An initial decrease from baseline was noted for the placebo → CP-690,550 treatment sequences; after Month 3 (ie, after advancing to CP-690,550), a further decrease was observed.

Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significantly greater response rates of patients achieving DAS28-4(ESR) ≤3.2 compared with placebo at Month 3. Patients in the CP-690,550 treatment sequences showed a response by Month 3; the response rates continued to increase through Month 6. A smaller proportion of patients in the placebo → CP-690,550 treatment sequences achieved DAS28-4(ESR) ≤3.2 by Month 3.

Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significantly greater response rates of patients achieving DAS28-4(ESR) <2.6 compared with placebo at Month 3. Rates were similar for all treatment sequences at Month 6, except for the placebo → CP-690,550 10 mg treatment sequence which remained relatively low.

The number of patients in the CP-690,550 5 mg treatment sequence with 0 active joints (ie, tender or swollen) increased from 3 at Month 3 to 7 at Month 6; the number of patients in the CP-690,550 10 mg treatment sequence with 0 active joints increased from 6 at Month 3 to 8 at Month 6.

Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significantly greater response rates with DAS28-4(ESR) response ('good' or 'moderate') compared with placebo at Month 3. A response was noted at Month 3 for patients who received placebo. Approximately three-fourths of patients in the CP-690,550 treatment sequences achieved DAS28-4(ESR) response by Month 3 (ie, 70% and 78% for CP-690,550 5 mg and 10 mg, respectively); the response rates were relatively stable at Month 6. A smaller proportion of patients in the placebo → CP-690,550 treatment sequences achieved DAS28-4(ESR) response by Month 3.

ESR: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases from baseline in ESR at Month 3 compared with placebo. The CP-690,550 treatment sequences had statistically significant (p-value <0.0001) decreases from baseline in ESR at Month 3; while the values remained stable through Month 6, the decrease remained statistically significant from baseline (p-value <0.0001). The placebo → CP-690,550 5 mg treatment sequence had a smaller decrease at Month 3.

DAS28-3(CRP):

Patients who received CP-690,550 had statistically significant decreases from baseline in DAS28-3(CRP) compared with placebo by Week 2 that continued through Month 3. Changes from baseline were greater for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg. Patients in the CP-690,550 treatment sequences had pronounced decreases from baseline by Week 2 that continued through Month 6. Decreases in the CP-690,550 10 mg sequence were larger than those in the CP-690,550 5 mg sequence.

Patients in the CP-690,550 treatment sequences began to achieve DAS28-3(CRP) ≤3.2 by Week 2; response rates increased through Month 6. The response rates were higher in the CP-690,550 10 mg sequence than in the CP-690,550 5 mg sequence. After Month 3 (ie, after advancing to CP-690,550) there was an increase in the proportion of patients in the placebo → CP-690,550 treatment sequences who achieved DAS28-3(CRP) ≤3.2.

Patients who received CP-690,550 10 mg had statistically significantly improved DAS28-3(CRP) <2.6 response rates for Week 2 through Month 3 compared with placebo; the response rate for patients who received CP-690,550 5 mg was statistically significant compared with placebo at Months 1 and 3. The response rates were numerically greater for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg.

The percentages of patients in the CP-690,550 treatment sequences who achieved DAS28-3(CRP) <2.6 increased at each time point through Month 4.5, with a slight decrease from Months 4.5 to 6 for the CP-690,550 10 mg treatment sequence. Patients in the CP-690,550 10 mg sequence achieved DAS28-3(CRP) <2.6 at a greater frequency than patients in the CP-690,550 5 mg sequence. The percentages of patients in the placebo → CP-690,550 treatment sequences who achieved DAS28-3(CRP) <2.6 remained near baseline levels (ie, 0% - 6%) prior to Month 3. After Month 3 (ie, after advancing to CP-690,550), there was an increase in the percentage of patients in the placebo → CP-690,550 treatment sequences who achieved DAS28-3(CRP) <2.6.

Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant improvements in DAS28-3(CRP) response rates compared with placebo from Week 2 through Month 3. A large percentage of patients in the CP-690,550 5 mg treatment sequence showed response by Week 2, with response rates increasing through approximately Month 4.5 and then plateauing through Month 6. An initial response was noted for patients in the placebo → CP-690,550 treatment sequences; after Month 3 (ie, after advancing to CP-690,550), the response rates increased.

CRP: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases from baseline in CRP concentrations compared with placebo from Week 2 through Month 3. The decreases from baseline were observed as early as Week 2 for the CP-690,550 treatment sequences; the values stabilized through Month 6. Mean CRP values for the placebo → CP-690,550 treatment sequences were unchanged through Month 3; upon initiation of CP-690,550 treatment after Month 3 there was a steep decline in CRP levels from baseline.

Patient Global Assessment of Arthritis: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases (improvements) in Patient Global Assessment of Arthritis from baseline compared with placebo at Week 2 through Month 3. The decreases from baseline were greater for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg. The CP-690,550 treatment sequences demonstrated decreases (improvements) from baseline beginning at Week 2; the decreases continued through Month 6.

Physician Global Assessment of Arthritis: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases from baseline in Physician Global Assessment of Arthritis compared with placebo at Week 2 through Month 3. The CP-690,550 treatment sequences demonstrated decreases from baseline beginning at Week 2; the decreases continued through Month 6. An initial decrease in Physician Global Assessment of Arthritis was noted for the placebo → CP-690,550 treatment sequences.

Pain: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases in pain from baseline compared with placebo at Week 2 through Month 3. The CP-690,550 treatment sequences demonstrated decreases (improvements) from baseline beginning at Week 2; the decreases continued through Month 6.

Tender Joint Counts: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases from baseline in tender joint counts compared with placebo at Week 2 through Month 3. The decreases from baseline were slightly larger for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg.

The CP-690,550 treatment sequences demonstrated decreases from baseline in tender joint counts beginning at Week 2; the decreases continued through Month 6. The changes from baseline were statistically significant at each time point for the CP-690,550 treatment sequences compared with placebo. An initial decrease in tender joint counts was noted for patients in the placebo → CP-690,550 treatment sequences; after Month 3 (ie, after advancing to CP-690,550), there was a continued decrease.

Swollen Joint Counts: Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant decreases from baseline in swollen joint counts compared with placebo at Week 2 through Month 3. The decreases from baseline were slightly larger for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg.

The CP-690,550 treatment sequences demonstrated decreases from baseline in swollen joint counts beginning at Week 2; the decreases continued through Month 6. An initial decrease in swollen joint counts was noted for patients in the placebo → CP-690,550 treatment sequences; after Month 3 (ie, after advancing to CP-690,550), there was a continued decrease.

SF-36 (Version 2, Acute): Treatment with CP-690,550 (5 mg or 10 mg) resulted in statistically significant improvements from baseline in all SF-36 domains and component summary scores compared with placebo at Month 3. Score improvements for Physical Function, Role Physical, Social Function, Bodily Pain, Mental Health, Role Emotional, Vitality, General Health, Mental Component, and Physical Component for patients who received CP-690,550 10 mg were greater than for those who received CP-690,550 5 mg.

Patients in both CP-690,550 treatment sequences had increases (improvements) from baseline in each of the SF-36 domain scores at Month 3; the increases continued or remained stable through Month 6. An initial increase from baseline in each of the SF-36 domain scores was noted for patients in the placebo → CP-690,550 treatment sequences between baseline and Month 3; after Month 3 (ie, after advancing to CP-690,550), there was a continued increase.

Increases (improvements) from baseline were noted in each of the CP-690,550 sequences and in the placebo → CP-690,550 10 mg sequence for the SF-36 mental component at Month 3; the greatest improvement was noted in the placebo → CP-690,550 10 mg sequence at Month 6. Increases (improvements) were also noted in the SF-36 physical component scores in each of the treatment sequences at Month 3 and Month 6, with larger increases in the CP-690,550 treatment sequences compared with the placebo → CP-690,550 sequences.

MOS Sleep Scale (MOS-SS): Treatment with CP-690,550 5 mg resulted in statistically significant improvements from baseline compared with placebo in the Somnolence, Snoring, and Sleep Disturbance subscales at Month 3. Treatment with CP-690,550 10 mg resulted in

statistically significant improvements from baseline compared with placebo in Sleep Disturbance at Month 3.

In general, the MOS-SS subscale scores showed improvement from baseline. In the CP-690,550 treatment sequences, the MOS-SS subscale scores with the most consistent improvements were Overall Sleep, Sleep Problem Summary, Sleep Disturbance, and Adequacy Scores, where statistically significant improvements were observed for the 5 mg and 10 mg BID groups at both 3 and 6 months.

The CP-690,550 10 mg treatment sequence had a greater mean change from baseline in the MOS-SS Sleep Quantity Score at Month 3 compared with the CP-690,550 5 mg treatment sequence.

There were small LS mean changes from baseline in the MOS-SS Sleep Quantity subscale at Month 3, which were statistically significant for the CP-690,550 10 mg BID treatment group. Over the full 6-month treatment period, the CP-690,550 10 mg BID treatment sequence had statistically significant increases in the MOS-SS Sleep Quantity subscale beginning at Week 2 and continuing through Month 6.

The percentages of patients who received CP-690,550 and achieved optimal sleep on the MOS-SS Optimal Sleep subscale were not statistically significantly different from placebo at Month 3, and the proportions were comparable when assessed by treatment sequence through Month 6.

FACIT Fatigue Scale: Patients who received CP-690,550 5 mg and CP-690,550 10 mg showed statistically significant improvements from baseline in the FACIT Fatigue Scale at Month 3 compared with placebo. All 4 treatment sequences had greater changes from baseline at Month 6 compared with Month 3. After Month 3 (ie, after advancing to CP-690,550), patients in the placebo → CP-690,550 treatment sequences had marked increases in FACIT Fatigue Scale scores.

EQ-5D: CP-690,550 treatment (5 mg or 10 mg) resulted in statistically significant improvements in the utility score compared with placebo at Months 1 and 3; changes were numerically greater for patients who received CP-690,550 10 mg compared with CP-690,550 5 mg.

The mean changes from baseline for the CP-690,550 5 mg and 10 mg BID treatment sequences were statistically significant beginning at Month 1 and continued through Month 6. Utility score increases in the CP-690,550 10 mg sequence were slightly greater than the increases in the CP-690,550 5 mg sequence. After Month 3 (ie, after advancing to CP-690,550), health state profile scores in the placebo → CP-690,550 treatment groups increased and were approaching the values of the CP-690,550 5 mg and 10 mg BID groups by Month 6.

Work Limitations Questionnaire: There were statistically significant differences between treatment with each of the CP-690,550 doses and placebo at Month 3 for the Time Management, Mental/Interpersonal Demands (10 mg only), Output Demands, and Work Loss Index subscales of the Work Limitations Questionnaire.

Safety Results:

Adverse Events: From baseline to Month 3, the 3 most frequently experienced AEs by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) (Version [v] 13.1) overall were infections and infestations (CP-690,550 5 mg: 18.0%; CP-690,550 10 mg: 21.6%; placebo: 19.7%), gastrointestinal disorders (CP-690,550 5 mg: 18.0%; CP-690,550 10 mg: 18.7%; placebo: 15.9%), and musculoskeletal and connective tissue disorders (CP-690,550 5 mg: 9.0%; CP-690,550 10 mg: 9.7%; placebo: 17.4%). The proportion of patients with AEs in each category was similar across the 3 treatments up to Month 3. From baseline to Month 3, some AEs occurred more frequently in the specific treatment groups as follows: CP-690,550 5 mg (eg, diarrhea, upper respiratory tract infection), CP-690,550 10 mg (eg, nasopharyngitis, headache), and placebo (eg, nausea, arthralgia). With the exception of diarrhea for CP-690,550 5 mg (8/133, 6.0%), nausea for placebo (9/132, 6.8%), and headache for CP-690,550 10 mg (8/134, 6.0%), all other AEs occurred in less than 5% of the patients in their respective treatment groups (Table 6).

From baseline to Month 3, the most commonly experienced treatment-emergent AEs (TEAEs) by MedDRA preferred term for the CP-690,550 5 mg dose were diarrhea (8/133 patients, 6.0%), and nasopharyngitis, upper respiratory tract infection, and urinary tract infection (each with 5/133 patients, 3.8%). The most commonly experienced TEAEs by preferred term for the CP-690,550 10 mg dose were headache (8/134 patients, 6.0%), nasopharyngitis (6/134 patients, 4.5%), and diarrhea (5/134 patients, 3.7%). The most commonly experienced TEAEs by preferred term for placebo were nausea (9/132 patients, 6.8%) and diarrhea, arthralgia, and cough (each with 5/132 patients, 3.8%).

Table 6. Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥2% of Patients in Any Treatment Group, Baseline to Month 3); All Causalities

System Organ Class[a] Preferred Term[a]	CP-690,550 5 mg BID (N=133) n (%)	CP-690,550 10 mg BID (N=134) n (%)	Placebo (N=132) n (%)
No. patients with an event	71 (53.4)	76 (56.7)	75 (56.8)
Gastrointestinal disorders			
Abdominal pain upper	3 (2.3)	1 (0.7)	0
Constipation	4 (3.0)	3 (2.2)	1 (0.8)
Diarrhea	8 (6.0)	5 (3.7)	5 (3.8)
Nausea	4 (3.0)	2 (1.5)	9 (6.8)
General disorders and administration site conditions			
Fatigue	1 (0.8)	3 (2.2)	0
Infections and infestations			
Nasopharyngitis	5 (3.8)	6 (4.5)	4 (3.0)
Sinusitis	1 (0.8)	1 (0.7)	4 (3.0)
Upper respiratory tract infection	5 (3.8)	2 (1.5)	4 (3.0)
Urinary tract infection	5 (3.8)	3 (2.2)	3 (2.3)
Injury, poisoning, and procedural complications			
Muscle strain	0	3 (2.2)	0
Investigations			
Blood creatine phosphokinase increased	0	3 (2.2)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.8)	1 (0.7)	5 (3.8)
Back pain	3 (2.3)	3 (2.2)	2 (1.5)
Muscle spasms	0	1 (0.7)	3 (2.3)
Rheumatoid arthritis	3 (2.3)	1 (0.7)	4 (3.0)
Nervous system disorders			
Headache	3 (2.3)	8 (6.0)	1 (0.8)
Psychiatric disorders			
Depression	2 (1.5)	4 (3.0)	1 (0.8)
Respiratory, thoracic, and mediastinal disorders			
Cough	3 (2.3)	0	5 (3.8)
Skin and subcutaneous tissue disorders			
Skin lesion	1 (0.8)	3 (2.2)	0
Vascular disorders			
Hypertension	1 (0.8)	3 (2.2)	1 (0.8)

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities, v = version, N = number of patients, n = number of patients meeting prespecified criteria, No. = number
[a]MedDRA (v13.1) coding dictionary applied.

From Months 3 to 6, the most frequently experienced TEAEs by MedDRA SOC (v13.1) overall were infections and infestations (CP-690,550 5 mg: 20.3%; CP-690,550 10 mg: 22.4%; placebo → CP-690,550 5 mg: 16.7%; placebo → CP-690,550 10 mg: 15.2%), gastrointestinal disorders (CP-690,550 5 mg: 7.5%; CP-690,550 10 mg: 9.0%; placebo → CP-690,550 5 mg: 13.6%; placebo → CP-690,550 10 mg: 10.6%), and musculoskeletal and connective tissue disorders (CP-690,550 5 mg: 9.8%; CP-690,550 10 mg: 6.7%; placebo → CP-690,550 5 mg: 4.5%; placebo → CP-690,550 10 mg: 6.1%).

The most commonly experienced TEAEs by MedDRA preferred term for the CP-690,550 5 mg sequence were nasopharyngitis and rheumatoid arthritis (each in 5/133 patients, 3.8%).

The most commonly experienced TEAEs by preferred term for the CP-690,550 10 mg sequence were upper respiratory tract infection (7/134 patients, 5.2%) and nasopharyngitis (5/134 patients, 3.7%). The most commonly experienced TEAE by preferred term for the placebo → CP-690,550 5 mg treatment sequence were nausea and hypertension (3/66 patients, 4.5%). The most commonly experienced TEAEs by preferred term for the placebo → CP-690,550 10 mg treatment sequence were anemia, diarrhea, gastritis, folliculitis, vitamin D deficiency, arthralgia, and headache (each with 2/66 patients, 3.0%) (Table 7).

The proportions of patients experiencing AEs and SAEs from Months 3 to 6 were similar across the 4 treatment sequences. The highest rate of SAEs and discontinuations due to AEs was for the CP-690,550 10 mg treatment sequence. The CP-690,550 5 mg and the placebo → CP-690,550 5 mg treatment sequences had the highest proportion of patients with severe AEs. The placebo → CP-690,550 5 mg treatment sequence had the highest proportion of patients who had their dose reduced or temporarily discontinued due to AEs during Months 3 to 6.

Table 7. Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥2% of Patients in Any Treatment Sequence, Months 3 to 6); All Causalities

System Organ Class[a] Preferred Term[a]	CP-690,550 5 mg BID (N=133) n (%)	CP-690,550 10 mg BID (N=134) n (%)	Placebo → CP-690,550 5 mg BID (N=66) n (%)	Placebo → CP-690,550 10 mg BID (N=66) n (%)
No. patients with an AE	57 (42.9)	58 (43.3)	24 (36.4)	28 (42.4)
Blood and lymphatic system disorders				
Anemia	0	2 (1.5)	0	2 (3.0)
Gastrointestinal disorders				
Diarrhea	0	2 (1.5)	2 (3.0)	0
Gastritis	2 (1.5)	0	1 (1.5)	2 (3.0)
Mouth ulceration	3 (2.3)	0	1 (1.5)	0
Nausea	1 (0.8)	2 (1.5)	3 (4.5)	0
Vomiting	0	2 (1.5)	2 (3.0)	1 (1.5)
Infections and infestations				
Bronchitis	4 (3.0)	2 (1.5)	2 (3.0)	1 (1.5)
Folliculitis	0	0	0	2 (3.0)
Gastroenteritis	1 (0.8)	1 (0.7)	2 (3.0)	0
Nasopharyngitis	5 (3.8)	5 (3.7)	1 (1.5)	0
Sinusitis	0	4 (3.0)	1 (1.5)	0
Upper respiratory tract infection	3 (2.3)	7 (5.2)	2 (3.0)	1 (1.5)
Urinary tract infection	3 (2.3)	1 (0.7)	1 (1.5)	1 (1.5)
Metabolism and nutrition disorders				
Vitamin D deficiency	0	0	0	2 (3.0)
Musculoskeletal and connective tissue disorders				
Arthralgia	0	0	0	2 (3.0)
Back pain	2 (1.5)	3 (2.2)	0	1 (1.5)
Rheumatoid arthritis	5 (3.8)	0	2 (3.0)	0
Nervous system disorders				
Headache	1 (0.8)	2 (1.5)	0	2 (3.0)
Skin and subcutaneous tissue disorders				
Skin lesion	1 (0.8)	3 (2.2)	0	0
Vascular disorders				
Hypertension	2 (1.5)	1 (0.7)	3 (4.5)	1 (1.5)

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, n = number of patients meeting prespecified criteria, v = version, No. = number

[a] MedDRA (v13.1) coding dictionary applied

Discontinuations due to Adverse Events: Of the 32 patients who discontinued the study due to AEs (26 during treatment with CP-690,550 and 6 during treatment with placebo), 17 discontinued due to AEs considered related to study drug (Table 8).

Table 8. Discontinuations Due to Treatment-Emergent Adverse Events

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Patient	**System Organ Class**	**MedDRA Preferred Term**	**Treatment Phase**	**Study Start Day[a]/ Study Stop Day[a]**	**Severity/ Outcome**	**Causality**
CP-690,550 5 mg BID						
Patient	Gastrointestinal disorders	Pancreatitis[b]	Active	158/ 167	Severe/ resolved	Study drug
Patient	Mental disorder	Mental breakdown[b]	Active	129/ [>131]	Severe/ still present	Other: abrupt discontinuation of steroid treatment
Patient	General disorders and administration site conditions	Edema peripheral	Active	30/ [>63]	Severe/ still present	Study drug
Patient	Injury, poisoning, and procedural complications	Overdose	Active	35/ 81	Mild/ resolved	Other; patient forgot dosing instructions
Patient	Gastrointestinal disorders	Tongue edema	Active	30/ 39	Mild/ resolved	Study drug
Patient	Immune system disorders	Drug hypersensitivity	Active	18/ 22	Moderate/ resolved	Study drug
Patient	Investigations	Hepatic enzyme increased	Active	85/ [>155]	Moderate/ still present	Disease under study
Patient	Musculoskeletal and connective tissue disorders	Myalgia	Active	91/ [>126]	Moderate/ still present	Disease under study
Patient	Gastrointestinal disorders	Abdominal pain upper	Active	8/ 33	Mild/ resolved	Study drug
Patient	Musculoskeletal and connective tissue disorders	Back pain	Active	3/ 27	Mild/ resolved	Study drug
	Reproductive system and breast disorders	Breast engorgement	Active	3/ 27	Mild/ resolved	Study drug
		Vaginal discharge	Active	3/ 27	Mild/ resolved	Study drug
Patient	Skin and subcutaneous tissue disorders	Panniculitis[b]	Active	153/ [>182]	Severe/ still present	Study drug
Patient	Infections and infestations	Hematoma infection	Active	98/ [>129]	Moderate/ still present	Study drug
CP-690,550 10 mg BID						
Patient	Investigations	Blood creatinine increased	Active	121/ [>165]	Mild/ still present	Study drug
Patient	Investigations	Liver function test abnormal	Active	99/ 196	Moderate/ resolved	Concomitant treatment: investigator believed INH therapy was the most like cause, but binge ETOH was confounding factor
Patient	Eye disorders	Ulcerative keratitis	Active	67/ 85	Severe/ resolved	Study drug
		Ulcerative keratitis	Active	86/ 229	Severe/ resolved	Study drug

Abbreviations: BID = twice daily, ETOH = ethyl alcohol, INH = isonicotinic acid hydrazide, MedDRA = Medical Dictionary for Regulatory Activities, v = version
MedDRA (v13.1) coding dictionary applied. All events were treatment-emergent. Values in brackets were imputed from incomplete dates and time.

[a] Duration of adverse event; day relative to start of study treatment. First day of treatment = Day 1.

[b] Serious adverse event, according to investigator assessment.

Table 8. Discontinuations Due to Treatment-Emergent Adverse Events (continued)

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Patient	**System Organ Class**	**MedDRA Preferred Term**	**Treatment Phase**	**Study Start Day[a]/ Study Stop Day[a]**	**Severity/ Outcome**	**Causality**
CP-690,550 10 mg BID (continued)						
Patient	Infections and infestations	Pyelonephritis[b]	Active	117/ 127	Moderate/ resolved	Study drug
Patient	Cardiac disorders	Pericarditis[b]	Active	149/ 163	Moderate/ resolved	Disease under study
Patient	Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism[b]	Active	131/ 138	Severe/ resolved	Other: patient's comorbidities
Patient	Infections and infestations	Urinary tract infection	Active	54/ 69	Mild/ resolved	Study drug
Patient	Musculoskeletal and connective tissue disorders	Myalgia	Active	95/ 99	Mild/ resolved	Study drug
Patient	Blood and lymphatic system disorders	Anemia	Active	97/ 103	Moderate/ resolved	Study drug
	Gastrointestinal disorders	Nausea[b]	Active	97/ 103	Moderate/ resolved	Study drug
		Vomiting[b]	Active	91/ 97	Moderate/ resolved	Study drug
Patient	Infections and infestations	Diverticulitis[b]	Active	171/ 177	Severe/ resolved	Study drug
	Renal and urinary disorders	Renal failure acute	Active	171/ 177	Severe/ resolved	Study drug
Patient	Vascular disorders	Aortic aneurysm[b]	Active	7/ 48	Severe/ resolved	Other illness: pre-existing abdominal aortic aneurysm; condition not known at screening
Patient	Investigations	Blood creatine phosphokinase increased	Active	44/ 59	Moderate/ resolved	Other: without specific myopathologic disease; biopsy 2004
Placebo → CP-690,550 5 mg BID						
Patient	Nervous system disorders	Dizziness	Active[c]	35/ [>57]	Moderate/ still present	Study drug
Patient	Gastrointestinal disorders	Diarrhea	Active[c]	25/ 29	Moderate/ resolved	Study drug

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities, v = version
MedDRA (v13.1) coding dictionary applied. All events were treatment-emergent. Values in brackets were imputed from incomplete dates and time.

[a] Duration of adverse event; day relative to start of study treatment. First day of treatment = Day 1.
[b] Serious adverse event, according to investigator assessment.
[c] Patient had not advanced from treatment with placebo to treatment with CP-690,550 at the time of the onset of the event.

Table 8. Discontinuations Due to Treatment-Emergent Adverse Events (continued)

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Patient	**System Organ Class**	**MedDRA Preferred Term**	**Treatment Phase**	**Study Start Day[a]/ Study Stop Day[a]**	**Severity/ Outcome**	**Causality**
Placebo → CP-690,550 5 mg BID (continued)						
Patient	Metabolism and nutrition disorders	Diabetes mellitus	Active[c]	29/ [>85]	Mild/ still present	Other illness: adult onset diabetes mellitus
Patient	Respiratory, thoracic, and mediastinal disorders	Pneumonia aspiration[b]	Active	142/ 159	Severe/ resolved	Study drug
Placebo → CP-690,550 10 mg BID						
Patient	Investigations	Blood creatinine increased	Active[c]	81/ [>85]	Severe/ still present	Other illness: diagnosis pending investigations
		Hemoglobin decreased	Active[c]	81/ [>85]	Moderate/ still present	Other: acute nephritis
	Renal and urinary disorders	Goodpasture's syndrome[b]	Active[c]	81/ [>85]	Moderate/ still present	Other illness: autoimmune disorder
Patient	Investigations	Hemoglobin decreased	Active	121/ [>173]	Moderate/ still present	Other: unknown etiology
Patient	Metabolism and nutrition disorders	Dehydration[b]	Active[c]	6/ 18	Severe/ resolved	Other illness: unknown
Patient	General disorders and administration site conditions	Drug ineffective[b]	Active[c]	15/ 124	Moderate/ resolved	Background study drug: methotrexate and prednisolone
	Pregnancy, puerperium, and perinatal conditions	Pregnancy[b]	Active[c]	15/ 17	Severe/ resolved	Concomitant treatment: insufficient capacity of mercilon to control conception

Abbreviations: BID = twice daily, ETOH = ethyl alcohol, INH = isonicotinic acid hydrazide, MedDRA = Medical Dictionary for Regulatory Activities, v = version
MedDRA (v13.1) coding dictionary applied. All events were treatment-emergent. Values in brackets were imputed from incomplete dates and time.

[a] Duration of adverse event; day relative to start of study treatment. First day of treatment = Day 1.

[b] Serious adverse event, according to investigator assessment.

[c] Patient had not advanced from treatment with placebo to treatment with CP-690,550 at the time of the onset of the event.

Deaths: A 51-year-old female (placebo → CP-690,550 10 mg treatment sequence), experienced an AE of pulmonary embolism on Day 131 (ie, after advancing to CP-690,550 10 mg on Day 85); the investigator considered the event as not related to study drug, but related to concomitant treatment (ie, Necon 1/35). Study drug was stopped on Day 131 due to this event. This patient died on Day 132 of the study due to the pulmonary embolism.

Serious Adverse Events: Table 9 presents SAEs by treatment; these data are cumulative through 08 April 2011 as reported in the safety database. Overall, 6 patients in the CP-690,550 5 mg treatment sequence experienced 6 SAEs (3 SAEs [pancreatitis, panniculitis, and bronchopneumonia] were considered related to treatment with CP-690,550), and 8 patients in the CP-690,550 10 mg treatment sequence experienced 11 SAEs (7 SAEs [ulcerative keratitis, pyelonephritis, vomiting, nausea, anemia, diverticulitis, and renal failure acute] were considered related to treatment with CP-690,550). Four patients in the placebo → CP-690,550 5 mg treatment sequence experienced 7 SAEs (1 SAE [pneumonia aspiration] was considered related to treatment with CP-690,550; 3 SAEs occurred before the patients advanced to treatment with CP-690,550). Five patients in the placebo → CP-690,550 10 mg treatment sequence experienced 9 SAEs (3 SAEs [interstitial lung disease, anemia, and hyponatremia] were considered related to treatment with CP-690,550; 6 SAEs occurred before the patients advanced to treatment with CP-690,550) (Table 9).

Table 9. Patients with Treatment-Emergent Serious Adverse Events

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Age/Sex	**Suspect Drug**	**MedDRA Preferred Term (Day of Onset)**	**Outcome**	**Causality**	**Action Taken with Respect to Study Drug**
CP-690,550 5 mg BID					
48/F	CP-690,550	Pancreatitis (156)	Recovered	Related	Permanently withdrawn
46/F	CP-690,550	Mental disorder (129)	Recovering	Unrelated	Permanently withdrawn
	Prednisone	Mental disorder (129)	Recovering	Related	Posttherapy
61/F	CP-690,550	Back pain (33)	Recovering	Unrelated	Posttherapy
70/F	CP-690,550	Cerebrovascular accident (78)	Recovered	Unrelated	Temporarily withdrawn
	CP-690,550	Cerebrovascular accident (137)	Recovering	Unrelated	Temporarily withdrawn
49/F	CP-690,550	Panniculitis (153)	Recovering	Related	Permanently withdrawn
	Methotrexate sodium	Panniculitis (153)	Recovering	No data	Dose not changed
66/F	CP-690,550	Bronchopneumonia (174)	Recovered	Related	Dose not changed
	Methotrexate sodium	Bronchopneumonia (174)	Recovered	Related	Unknown
	Prednisone	Bronchopneumonia (174)	Recovered	No data	Unknown
CP-690,550 10 mg BID					
60/F	CP-690,550	Ulcerative keratitis (86)	Recovered	Related	Not applicable
	Methotrexate sodium	Ulcerative keratitis (86)	Recovered	Related	Dose increased
53/F	CP-690,550	Pyelonephritis (117)	Recovered	Related	Permanently withdrawn
	Methotrexate	Pyelonephritis (117)	Recovered	Related	Temporarily withdrawn
	Prednisone	Pyelonephritis (117)	Recovered	Related	Temporarily withdrawn
52/F	CP-690,550	Pericarditis (149)	Recovered	Unrelated	Permanently withdrawn
54/F	CP-690,550	Pulmonary embolism (131)	Recovered	Unrelated	Permanently withdrawn
76/F	CP-690,550	Vomiting (97)	Recovered	Related	Permanently withdrawn
		Nausea (97)	Recovered	Related	
		Anemia (97)	Recovered	Related	
44/F	CP-690,550	Cholelithiasis (106)	Recovered	Unrelated	Temporarily withdrawn
64/M	CP-690,550	Diverticulitis (171)	Recovered	Related	Permanently withdrawn
		Renal failure acute (171)	Recovered	Related	Permanently withdrawn
78/F	CP-690,550	Aortic aneurysm (7)	Recovered	Unrelated	Permanently withdrawn

The events in this table are cumulative through 08 April 2011. Age was age (in years) at screening. MedDRA (v13.1) coding dictionary applied.
Abbreviations: BID = twice daily, F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, v = version

Table 9. Patients with Treatment-Emergent Serious Adverse Events (continued)

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Age/Sex	**Suspect Drug**	**MedDRA Preferred Term (Day of Onset)**	**Outcome**	**Causality**	**Action Taken with Respect to Study Drug**
Placebo → CP-690,550 5 mg BID					
62/F	CP-690,550	Cerebrovascular accident (101)	Recovered	Unrelated	Temporarily withdrawn
	Placebo	Cerebrovascular accident (101)	Recovered	Unrelated	Temporarily withdrawn
36/F	Placebo	Joint sprain (18)	Recovered	Unrelated	Dose not changed
		Contusion (18)	Recovered	Unrelated	
		Foot fracture (18)	Recovered	Unrelated	
81/F	Celecoxib	Transient ischemic attack (113)	Recovered	Unrelated	Permanently withdrawn
		Hypertensive crisis (113)	Recovered	Related	
	CP-690,550	Transient ischemic attack (113)	Recovered	Unrelated	Temporarily withdrawn
		Hypertensive crisis (113)	Recovered	Unrelated	
	Placebo	Transient ischemic attack (113)	Recovered	Unrelated	Temporarily withdrawn
		Hypertensive crisis (113)	Recovered	Unrelated	
81/F	CP-690,550	Pneumonia aspiration (142)	Recovered	Related	Permanently withdrawn
	Methotrexate	Pneumonia aspiration (142)	Recovered	Related	Unknown
	Placebo	Pneumonia aspiration (142)	Recovered	Related	Posttherapy
	Prednisone	Pneumonia aspiration (142)	Recovered	Related	Unknown
Placebo → CP-690,550 10 mg BID					
52/M	Placebo	Glomerular vascular disorder (85)	Recovering	Unrelated	Permanently withdrawn
80/F	Placebo	Dehydration (6)	Recovered	Unrelated	Permanently withdrawn
79/F	CP-690,550	Interstitial lung disease (198)	Recovered	Related	Dose not changed
		Anemia (198)	Recovered	Related	
		Hyponatremia (85)	Recovered	Related	
	Placebo	Interstitial lung disease (198)	Recovered	Related	Posttherapy
		Anemia (198)	Recovered	Related	
		Hyponatremia (85)	Recovered	Related	
51/F	CP-690,550	Pulmonary embolism (131)	Fatal	Unrelated	Permanently withdrawn
	Ethinylestradiol, norelgestromin	Pulmonary embolism (131)	Fatal	Related	No data
	Placebo	Pulmonary embolism (131)	Fatal	Unrelated	Permanently withdrawn

The events in this table are cumulative through 08 April 2011. Age was age (in years) at screening. MedDRA (v13.1) coding dictionary applied.
Abbreviations: BID = twice daily, F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, v = version

Table 9. Patients with Treatment-Emergent Serious Adverse Events (continued)

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Age/Sex	**Suspect Drug**	**MedDRA Preferred Term (Day of Onset)**	**Outcome**	**Causality**	**Action Taken with Respect to Study Drug**
Placebo → CP-690,550 10 mg BID (continued)					
35/F	Desogestrel, ethinylestradiol	Drug ineffective (15)	Recovered	No data	Permanently withdrawn
		Unintended pregnancy (15)	Recovered	No data	
		Abortion spontaneous (17)	Recovered	No data	
	Methotrexate sodium	Drug ineffective (15)	Recovered	Related	Permanently withdrawn
		Unintended pregnancy (15)	Recovered	Unrelated	
		Abortion spontaneous (17)	Recovered	Related	
	Methylprednisolone	Drug ineffective (15)	Recovered	Related	Permanently withdrawn
		Unintended pregnancy (15)	Recovered	Related	
		Abortion spontaneous (17)	Recovered	Unrelated	
	Placebo	Drug ineffective (15)	Recovered	Unrelated	Permanently withdrawn
		Unintended pregnancy (15)	Recovered	Unrelated	
		Abortion spontaneous (17)	Recovered	Unrelated	

The events in this table are cumulative through 08 April 2011. Age was age (in years) at screening. MedDRA (v13.1) coding dictionary applied.
Abbreviations: BID = twice daily, F = female, MedDRA = Medical Dictionary for Regulatory Activities, v = version

Infections: A serious infection was any infection that required hospitalization for treatment, required parenteral antimicrobial therapy, or met other criteria that required it to be classified as an SAE. A patient who experienced a serious infection was to be discontinued from the study. Three patients and 2 patients were reported to have a serious infection at the Month 4.5 and the Month 6 visits, respectively. No patient in the placebo → CP-690,550 10 mg treatment sequence experienced a serious infection. The following 5 serious infections were reported during this study: panniculitis, bronchopneumonia, pyelonephritis, diverticulitis, and pneumonia aspiration.

From baseline up to Month 3, all treated infections were mild or moderate in severity, with the exception of 2 severe infections (CP-690,550 10 mg treatment [eye infection and tooth abscess]). The only treated infections occurring in ≥2 patients in either CP-690,550 group were upper respiratory tract infection, urinary tract infection, bronchitis, and tonsillitis. Rates of treated-infection AEs were higher in the CP-690,550 5 mg group (26 treated infections) and the placebo group (24 treated infections) compared with the CP-690,550 10 mg group (17 treated infections).

From Months 3 to 6, all treated infections were mild or moderate in severity, with the exception of 1 severe infection each in the CP-690,550 10 mg treatment sequence (diverticulitis) and the placebo → CP-690,550 5 mg treatment sequence (pneumonia aspiration). The only treated infection AEs occurring in ≥2 patients in any CP-690,550 sequence were upper respiratory tract infection, bronchitis, nasopharyngitis, sinusitis, and urinary tract infection.

Laboratory Values: Only patients who received CP-690,550 10 mg had creatine kinase (CK) elevations (>3.0 × upper limit of normal [ULN]) through Month 3 (with normal baseline) (2 [1.6%] patients). One patient (0.8%) who received CP-690,550 5 mg and 3 (2.3%) patients who received CP-690,550 10 mg had a CK elevation (>3.0 × ULN) (without regard to baseline abnormality) through Month 3.

There were no patients in the CP-690,550 5 mg treatment sequence, the placebo → CP-690,550 5 mg sequence, or placebo → CP-690,550 10 mg sequence with normal baseline CK values who developed CK elevations (>3.0 × ULN) at Month 6; the number of patients with normal baseline CK values who developed CK elevations in the CP-690,550 10 mg treatment sequence remained constant from Months 3 to 6 (2 patients at Month 3 and 2 patients at Month 6).

A trend of increasing mean hemoglobin concentrations compared with placebo was observed for patients who received CP-690,550 5 mg, whereas there appeared to be no change for patients who received CP-690,550 10 mg and a modest decline for placebo compared to baseline over the first 3 months of treatment.

By Month 6, mean hemoglobin concentrations were slightly higher than baseline concentrations in the CP-690,550 5 mg BID and placebo → CP-690,550 5 mg BID treatment sequences, whereas mean hemoglobin concentrations were similar to baseline in the CP-690,550 10 mg BID and placebo → CP-690,550 10 mg BID treatment sequences. These changes in mean hemoglobin concentration were modest and clinically insignificant.

Most instances of decreased hemoglobin were mild to moderate in severity; 2 instances of decreased hemoglobin were in the potentially life-threatening category (placebo → CP-690,550 10 mg treatment sequence), 1 at Month 3 and the other at Month 4.5.

Both CP-690,550 treatments (5 mg or 10 mg) had mean decreases from baseline in neutrophil counts at Month 3 (the decreases were from baseline to Month 1 and then they stabilized to Month 3). The mean neutrophil counts for patients who received placebo were stable from baseline through Month 3. No patients had an absolute neutrophil count $<0.5 \times 10^3/mm^3$. Both CP-690,550 treatment sequences had mean decreases from baseline in neutrophil counts that began after baseline to Month 1, but stabilized through Month 6; these were not considered clinically meaningful. The mean neutrophil counts for the placebo → CP-690,550 treatment sequences decreased after initiation of CP-690,550 treatment at Month 3.

The proportions of patients with mild neutropenia (defined as absolute neutrophil count [ANC] ≥ 1.5 to $<2 \times 10^3/\mu L$) were higher in the CP-690,550 10 mg treatment sequence at Week 2 and Month 4.5 compared with the other treatment sequences; at Months 1 and 6, the placebo → CP-690,550 10 mg treatment sequence had the highest proportions of patients with mild neutropenia. The proportions of patients with moderate to severe neutropenia were ≤1.9% at all visits for all treatment sequences. No patients had life-threatening neutropenia (defined as ANC $<0.5 \times 10^3/\mu L$).

Treatment with CP-690,550 5 or 10 mg was associated with a mean decrease from baseline in neutrophil counts at Month 3 (-0.86 and $-0.67 \times 10^3/mm^3$, respectively) and Month 6 (-0.71 and $-0.70 \times 10^3/mm^3$, respectively). Similarly, for patients in the placebo → CP-690,550 5 mg treatment sequence, a mean decrease in neutrophil counts from baseline was noted at Month 3 ($-0.01 \times 10^3/mm^3$) and Month 6 ($-0.90 \times 10^3/mm^3$). For patients in the placebo → CP-690,550 10 mg treatment sequence, a mean increase from baseline in neutrophil counts was noted at Month 3 ($0.15 \times 10^3/mm^3$) compared with a mean decrease at Month 6 ($-0.88 \times 10^3/mm^3$).

Overall, 8 patients had at least 1 instance of moderate to severe neutropenia. Of these, 3 patients had 5 total AEs related to infection. Each of the infections was considered as not serious, and all but 1 infection was treated. Each infection was mild or moderate in severity.

The CP-690,550 treatments (5 and 10 mg) had mean decreases from baseline in platelet levels at Month 1 that stabilized through Month 3; at Month 3, the mean platelet values for patients who received placebo remained near baseline levels.

The CP-690,550 treatment sequences (5 mg and 10 mg) had mean decreases from baseline in platelet levels at Month 1 that stabilized through Month 6. A slight decrease in platelet values was noted for patients in the placebo → CP-690,550 treatment sequences approximately 1 month after advancing to CP-690,550 following Month 3 (ie, Month 4.5); by Month 6, the levels remained below baseline levels.

A greater proportion of patients who received CP-690,550 10 mg (32/133 patients, 24.06%) had alanine aminotransferase (ALT) values ≥ULN through Month 3 than those who received

CP-690,550 5 mg (20/132 patients, 15.15%) or placebo (17/131 patients, 12.98%). A greater proportion of patients who received CP-690,550 5 mg (19/132 patients, 14.39%) had aspartate aminotransferase (AST) values ≥ULN through Month 3 than those who received CP-690,550 10 mg (16/133 patients, 12.03%) or placebo (13/131 patients, 9.92%). Note that each of these patients had normal baseline values

Similar proportions of patients (with normal baseline values) in the CP-690,550 5 mg and 10 mg treatment sequences had AST, ALT, and total bilirubin values ≥ULN at Months 3 to 6. A slightly higher proportion of patients in the placebo → CP-690,550 5 mg treatment sequence (with normal baseline values) compared with the placebo → CP-690,550 10 mg treatment sequence (with normal baseline values) had AST and total bilirubin values ≥ULN at Months 3 to 6.

There were no patients with laboratory abnormalities that satisfied the laboratory criteria for Hy's Law.

The mean changes from baseline in bilirubin through Month 6 were minimal in all treatment sequences.

There was a modest increase from baseline through Month 3 in mean serum creatinine values for the CP-690,550 treatments (5 mg or 10 mg). Changes from baseline through Month 6 were similar among treatments, with the exception of a numerically higher mean change at Month 3 for patients in the placebo → CP-690,550 10 mg treatment sequence; the large change at Month 3 was due to a single patient in this treatment group diagnosed with antiglomerular basement membrane disease (Goodpasture's syndrome). The mean changes from baseline in serum creatinine values through Month 6 were minimal in all treatments; the median creatinine values (change from baseline) for each sequence at each time point were 0.0 to 0.1 mg/dL.

Increases from baseline in mean high-density lipoprotein (HDL) occurred at Month 1 for patients who received CP-690,550 5 mg and 10 mg and were sustained at Month 3. Mean HDL levels for placebo patients remained stable through Month 3. Increases in mean HDL occurred at Month 1 for patients in the CP-690,550 5 mg and 10 mg sequences and were sustained at Month 6. After patients in the placebo → CP-690,550 treatment sequences advanced to CP-690.550, increases in mean HDL levels were seen at Month 6.

Increases in mean low-density lipoprotein (LDL) occurred at Month 1 for the CP-690,550 5 mg and 10 mg sequences and were sustained at Month 3. Mean LDL levels for placebo remained stable through Month 3. Increases in mean LDL occurred at Month 1 for CP-690,550 5 mg and 10 mg and were sustained at Month 6. When patients in the placebo → CP-690,550 treatment sequences advanced to CP-690.550, increases in mean LDL levels were seen at Month 6.

There was a modest increase in mean triglyceride concentrations from baseline through Month 1 and then remained stable to Month 3 in the CP-690,550 5 mg group. There were minimal and clinically insignificant changes in triglycerides noted in each of the treatment sequences from baseline through Month 6.

Increases in mean total cholesterol occurred at Month 1 for CP-690,550 5 mg and 10 mg and were sustained at Month 3. Mean total cholesterol levels for the placebo group remained stable through Month 3. Increases in mean total cholesterol occurred at Month 1 for the CP-690,550 5 mg and 10 mg sequences and were sustained at Month 6. When patients in the placebo → CP-690,550 treatment sequences advanced to CP-690.550, increases in mean total cholesterol levels were seen at Month 6.

Both CP-690,550 treatment sequences had increases from baseline in mean apolipoprotein A-I and B-100 concentrations at Month 3, and the increases were sustained at Month 6. For both placebo → CP-690,550 treatment sequences, mean levels remained constant from baseline at Month 3 (ie, prior to advancement to CP-690,550); by Month 6, both placebo → CP-690,550 treatment sequences also had increases from baseline in mean apolipoprotein A-I and B-100 levels. Minimal changes were noted from baseline in the ratios of apolipoprotein A-I and B-100.

Vital Signs Measurements: Greater decreases from baseline were noted in systolic BP for patients on placebo compared with CP-690,550 (5 mg or 10 mg) at Week 2 and Month 1. Changes in systolic BP over the 6-month study period were variable across treatment groups, with no observable dose-response relationship.

Overall, changes from baseline in diastolic BP were small and variable, and without any observable dose-response relationship.

The proportion of patients meeting Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) criteria for Stage 1 or 2 hypertension remained relatively stable throughout the 6 months of therapy, with no consistent changes over time in the CP-690,550 5 or 10 mg dose groups. The highest rate of patients with Stage 1 or 2 hypertension was noted in the placebo → CP-690,550 10 mg sequence at Week 2 (16/62 patients [25.8%]), Month 4.5 (17/53 patients [32.1%]), and Month 6 (18/49 patients [36.7%]). The proportion of patients in the placebo → CP-690,550 treatment sequences meeting JNC7 criteria was variable after advancing to CP-690,550 at Month 3.

Mean weight increased from baseline through Month 3 for CP-690,550 5 mg and CP-690,550 10 mg; mean weight remained stable through Month 3 for the placebo group. The CP-690,550 treatment sequences had an increase in mean weight from baseline through Month 6. Mean weight for the placebo → CP-690,550 treatment sequences remained stable until Month 3 (when CP-690,550 treatment began); an increase in mean weight was noted for the placebo → CP-690,550 10 mg treatment sequence at Month 6.

Conclusions:

- Treatment with CP-690,550 (5 and 10 mg BID) was efficacious compared with placebo in reducing the signs and symptoms of RA in patients with RA as measured by the co-primary endpoint, ACR20 response rate at Month 3; this difference from placebo was observed as early as Week 2.

- Treatment with CP-690,550 (5 and 10 mg BID) was efficacious compared with placebo in improving the physical function status of patients with RA as measured by the co-primary endpoint, HAQ-DI response rate at Month 3, with CP-690,550 10 mg demonstrating a statistically significant difference from placebo as early as 2 weeks.

- Treatment with CP-690,550 5 mg and 10 mg BID was efficacious compared with placebo with respect to the third primary efficacy variable, with an increase over placebo for the proportion of patients achieving DAS28-4(ESR) scores <2.6 at Month 3.

- Treatment with CP-690,550 (5 mg and 10 mg BID) was efficacious compared with placebo in improving secondary endpoints of signs and symptoms of RA in patients with RA, including ACR20, ACR50, ACR70, HAQ-DI, DAS28-3(CRP), and DAS28-4(ESR).

- Patients who received placebo for 3 months and then advanced to CP-690,550 treatment (5 mg or 10 mg BID) for 3 months showed improvement in all efficacy measures (ACR20, ACR50, ACR70, HAQ-DI, DAS28-3[CRP], and DAS28-4[ESR]).

- Treatment with CP-690,550 resulted in improvements in a variety of patient-reported measures when compared with placebo. Improvements at CP-690,550 doses of 5 and 10 mg BID were observed at 3 months and continued through Month 6 in SF-36 domain and component scores, FACIT fatigue scores, EQ-5D health state profile and the WLQ. In addition, improvements at both CP-690,550 5 and 10 mg BID doses were observed in a subset of measures of sleep (MOS-SS).

- Patients treated with CP-690,550 10 mg BID generally showed numerically greater ACR20/50/70 response rates, and improvements from baseline in DAS28 and HAQ-DI, compared with those treated with CP-690,550 5 mg BID.

- Efficacy responses were sustained in the CP-690,550 5 mg and 10 mg BID sequences through Month 6.

- The most frequently reported AEs by MedDRA SOC were infections and infestations, and the frequencies were similar among treatments.

- The proportion of patients with SAEs was comparable between the CP-690,550 treatment groups.

- Three patients and 2 patients, respectively, were reported to have a serious infection at the Month 4.5 visit (1 each in CP-690,550 5 mg, CP-690,550 10 mg, and placebo → CP-690,550 5 mg) and the Month 6 visit (1 each in CP-690,550 5 mg and CP-690,550 10 mg). There were no opportunistic infections reported during this study.

- There were no reported malignancy events during this study.

- Changes in laboratory parameters were observed for CP-690,550 5 mg and 10 mg relative to placebo, including decreases in neutrophil counts, increases in HDL and LDL levels, and changes in hemoglobin levels.