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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: CP-690,550

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: NCT00413660

PROTOCOL NO.: A3921025

PROTOCOL TITLE: A Phase 2b, Randomized, Double Blind, Placebo Controlled, Multicenter Study to Compare 6 Dose Regimens of CP-690,550 Versus Placebo, Each Combined with Methotrexate, Administered for 6 Months in the Treatment of Subjects with Active Rheumatoid Arthritis Who Have Had An Inadequate Response to Methotrexate Alone

Study Centers: There were a total of 72 centers. There were 4 centers in Argentina, 4 centers in Brazil, 3 centers in Bulgaria, 4 centers in Chile, 6 centers in Czech Republic, 4 centers in Hungary, 2 centers in Mexico, 6 centers in Poland, 3 centers in Slovakia, 4 centers in Spain, 2 centers in Sweden, 4 centers in Turkey, 25 centers in the United States.

Study Initiation and Completion Dates: 30 January 2007 to 12 August 2008

Phase of Development: Phase 2

Study Objectives: The primary objective was to compare the efficacy of 6 dose levels of oral CP-690,550 (20 mg once daily [QD]; and 15 mg, 10 mg, 5 mg, 3 mg and 1 mg twice daily [BID]), versus placebo, for the treatment of signs and symptoms, administered over 12 weeks, in subjects with active rheumatoid arthritis (RA) on a stable background of methotrexate (MTX) who had had an inadequate response to MTX alone.

The secondary objectives of this study were:

- To examine the durability of the response of 6 dose levels/regimes of oral CP-690,550 (20 mg QD; 15 mg, 10 mg, 5 mg, 3 mg and 1 mg BID) versus placebo, in combination with MTX, administered over 6 months for the treatment of the signs and symptoms in subjects with active RA.

- To evaluate the safety and tolerability of all dose levels of oral CP-690,550 (20 mg QD; 15 mg, 10 mg, 5 mg, 3 mg and 1 mg BID) versus placebo administered over 6 months to subjects with active RA.

- To characterize the relationship between doses, plasma concentrations of CP-690,550 and efficacy and safety outcome measures in subjects with active RA.

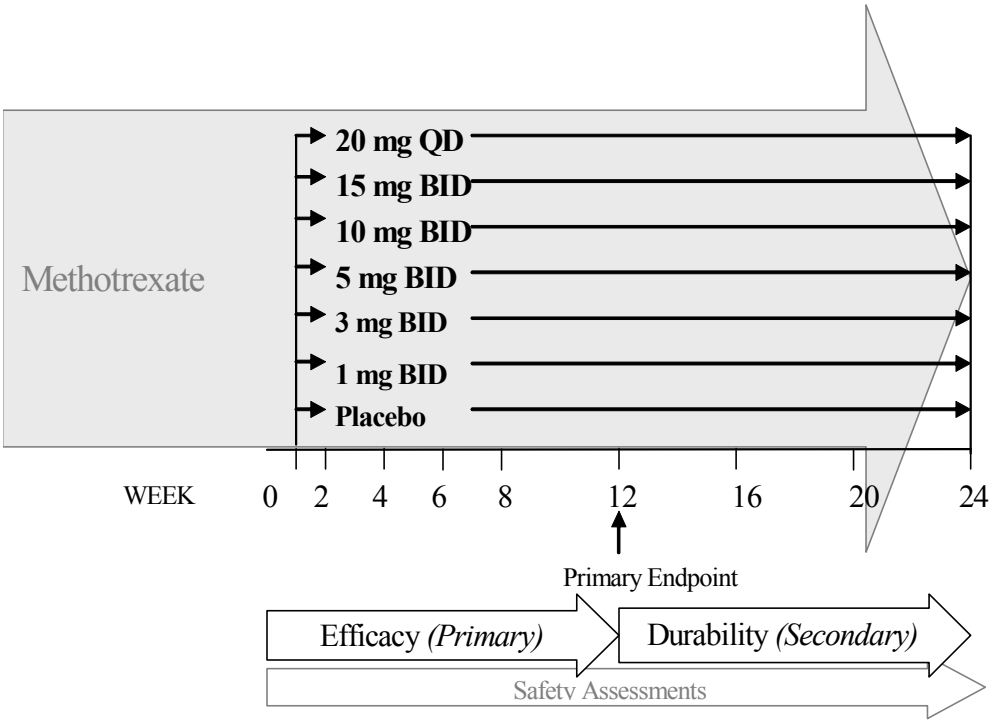
- To evaluate health status and functional status in these subjects.

METHODS

Study Design Study Design: This was a Phase 2b, randomized, double-blind, placebo-controlled, parallel group study. It was planned to randomize 483 subjects with RA, who had had an inadequate response to MTX alone, in a 1:1:1:1:1:1:1 ratio to receive 1 of 6 dose regimens of CP-690,550 (20 mg QD; 15 mg, 10 mg, 5 mg, 3 mg and 1 mg BID) or placebo tablets.

For each subject, the study comprised 10 visits: screening (28 days prior to first study drug administration), baseline (Day 0; randomization to treatment), and 8 on-treatment visits at Weeks 2, 4, 6, 8, 12, 16, 20, and 24 (or early termination). There was a ±3 day window for all post randomization visits. The study design is presented in Figure S1.

Figure S1. Study Design



Subjects randomized to the CP-690,550 3 mg BID, 1 mg BID, 20 mg QD and placebo groups, who failed to achieve a minimum improvement of at least 20% reduction in both swollen and painful / tender joint counts over baseline at the Week 12 visit, were labeled "non-responders" and automatically reassigned, for the remaining 12 weeks of their study participation, to the dose of 5 mg BID. Subjects randomized to the 15, 10 and 5 mg BID groups who failed to achieve a minimum improvement remained on their originally assigned dose. No other dose adjustments of CP-690,550 were allowed. Subjects, investigators and Pfizer study personnel were blinded to reassignment.

Subjects with more than 10 consecutive days or a total of more than 14 days of interrupted study drug were to be withdrawn from the study.

During the study subjects remained on stable background arthritis therapy, which had to include MTX (supplemented with folic acid), and may have included non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxyenase-2 (COX-2) inhibitors, allowed opioids, acetaminophen and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day). A single dose reduction of no more than 5 mg MTX weekly was allowed for confirmed elevation of transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2 x upper limit of normal (ULN). In order for the subject to remain in the study, the transaminase levels had to be documented as being improved within 2 weeks of the dose reduction.

Dosing of CP-690,550 could be temporarily discontinued for up to 10 consecutive days, for confirmed cytopenias, for infections which did not meet criteria for serious (those requiring parenteral antimicrobial therapy or hospitalization), for surgical procedures or for other moderate to severe AEs.

Number of Subjects (Planned and Analyzed): The planned number of subjects in each of the 7 treatment groups was 69. There were 71, 68, 71, 75, 75, 80 and 69 subjects in the 1, 3, 5, 10, and 15 mg BID, 20 mg QD and Placebo treatment groups.

Diagnosis and Main Criteria for Inclusion: The subjects were at least 18 years old and had active RA at both screening and baseline visits, defined as ≥6 joints tender or painful on motion and ≥6 joints swollen. Each subject also had to have either erythrocyte sedimentation rate (ESR) (Westergren method) >ULN in the local laboratory or C-reactive protein (CRP) >7 mg/L in the central laboratory at Screening.

Subjects had been taking oral or parenteral MTX continuously for at least 4 months and on a stable dosage of 7.5 to 25 mg weekly for at least 6 weeks prior to first dose of study drug. Stable weekly doses less than 15 mg were allowed only in the presence of documented intolerance to or toxicity from higher doses. Subjects must have an inadequate clinical response to MTX, defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from MTX plus the presence of sufficient residual disease activity to meet the entry criteria.

Study Treatment: Study drug was self-administered by the subject except for the doses taken at the study center. The 2 daily doses were to be taken at approximate 12-hour intervals with or

without food. Subjects randomized to CP-690,550 20 mg QD received a matching placebo for the evening dose to maintain the blind.

Subjects were automatically reassigned in a blinded manner to a different dose of CP-690,550 on the basis of pre-defined non-responses; other dose adjustments of CP-690,550 were not allowed.

CP-690,550 was provided as 5 and 1 mg tablets by the sponsor. Placebo was also supplied by the sponsor.

Efficacy Evaluations:

The primary measure of efficacy was the ACR20 responder rate at Week 12. The secondary measures of efficacy included:

- The number of subjects who had an ACR20 response at all visits except Week 12.
- The number of subjects who had an ACR50 response at all available visits.
- The number of subjects who had an ACR70 response at all available visits.
- Disease Activity Score (DAS) was assessed using the DAS 28-3 (CRP or ESR).
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- SF-36 Health Survey
- EuroQol EQ-5D
- Medical Outcomes Study (MOS)-Sleep Scale
- FACIT-Fatigue Scale

ESR was collected at Baseline and Week 12 and analyzed by a local laboratory. This data is not summarized in this report as it was only collected as the baseline for the long-term roll-over safety study.

Safety Evaluations: Safety was assessed by the spontaneous reporting of AEs, physical examinations (Screening, Baseline, and Weeks 2, 4, 6, 8, 12, 16, 20 and 24) electrocardiograms (ECGs) (Screening, Baseline, and Weeks 6 and 12), temperature, blood pressure and heart rate measurement (Screening, Baseline, and Weeks 2, 4, 6, 8, 12, 16, 20 and 24), and clinical laboratory results (Screening, Baseline, and Weeks 2, 4, 6, 8, 12, 16, 20 and 24) in all subjects who received at least 1 dose of study drug. Investigators and sponsor clinicians reviewed individual subject data throughout the conduct of the study to ensure subject well-being.

Statistical Methods: Two sets of analyses were planned. The first set involved the efficacy data up to Week 12, the interpretation of which was that of a randomized dose-response study. The second set incorporated post Week 12 efficacy data, as post Week 12 some of the subjects may have been reassigned to other doses. The post reassignment analyses were exploratory in nature.

The null hypothesis stated that there was no difference from placebo in ACR20 response at Week 12. The alternative stated that there was an increasing dose-response relationship.

The full analysis set (FAS) included all subjects randomized to the study who received at least 1 dose of the randomized investigational drug (CP-690,550 or placebo). The primary analysis population for this study was defined by the full analysis set of subjects. Subjects who had a protocol deviation thought to affect the efficacy analysis were excluded from the analysis from the point in time on or after the deviation occurred. The W12 analysis set is the dataset of all subjects who reached Week 12 without dropping from the study. The safety analysis set was defined as those subjects who received at least 1 dose of the randomized investigational drug (CP-690,550 or placebo) and was equivalent to the FAS.

Analysis of Primary Endpoint: The primary analysis was that of ACR20 at Week 12. The ACR20 response to the BID doses, including placebo, was analyzed using logistic regression.

An Emax model was fitted. The Emax model employed was a nonlinear model in dose with an intercept term and a slope term known as Emax, which is the coefficient of the expression "dose/ED50+ dose" and represents the maximal effect due to drug; ED50 represents a dose that achieves 50% of the maximum drug effect. The overall maximum effect is the sum of the intercept and the Emax parameter. For a fixed ED50, the Emax model reduces to a linear equation (linear in the term dose/ED50+ dose). A pre-specified ED50 value was chosen based upon analyses of a previous study (A3921019). The estimation of the Emax parameter provided a test of statistical significance that served as a trend test. The chosen value of 5 for ED50 was specified before any blind break. The analysis of the primary endpoint is detailed in Table S1.

Table S1. Summary of Primary Endpoint Analysis

Endpoint	Statistical Method	Model, Covariates, Strata	Missing Data	Interpretation
ACR20 at Week 12	Logistic regression (fixing ED50)	None; omit QD arm	BOCF	Primary Analysis

BOCF = Baseline observation carried forward, QD = Once daily
The full analysis set was used except where noted

Analysis of Secondary Endpoints: Secondary analyses included 4-parameter Emax models for the ACR variables in separate analyses, as well as descriptive statistics. These were based on the FAS. No covariates were employed.

The components of the ACR criteria were each analyzed using the longitudinal linear model. These were based on the FAS. Each endpoint's baseline value was used as a covariate.

Binomial variables such as whether a subject was in remission were analyzed using a normal approximation to the binomial. Any descriptive statistics were generally based on the full analysis set and missing values were ignored.

The ACR50 and ACR70 variables were analyzed in a similar manner as described for ACR20.

Safety Parameters: All subjects who received at least 1 dose of study drug were included in the analysis of safety. The safety data were summarized descriptively by randomized dose group through appropriate data tabulations and descriptive statistics. Note that whenever appropriate, displays of descriptive statistics incorporated the fact that subjects had been reassigned as per the protocol.

Interim Analysis: An interim analysis at 100% accrual at the completion of Week 12 was performed. Because Week 12 was the primary analysis, there were no issues of type I error spending.

Changes in the Planned Analyses: Listed as secondary analyses were Bayesian analyses for ACR20, ACR50 and ACR70. These were separate analyses for each endpoint, performed "by week". These were to be performed only on the BID doses including placebo.

Instead, a single longitudinal Emax model with Bayesian priors was implemented for each endpoint. Missing data were handled by the longitudinal model itself, that is, the missing data were assumed to be missing at random.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S2. Of 685 subjects screened, 509 were randomized to treatment, and 507 took study drug. Two subjects were randomized in error, and no drug was given.

A similar number of subjects discontinued the study from each dose group, ranging from 9 to 15 subjects. The primary reason for discontinuation was AEs in most of the CP-690,550 groups (Table S2) and lack of efficacy in the placebo group.

Table S2. Subject Disposition

	CP-690,550						
	1 mg BID	**3 mg BID**	**5 mg BID**	**10 mg BID**	**15 mg BID**	**20 mg QD**	**Placebo**
Number (%) of Subjects							
Screened: N=685							
Randomized to Study Treatment	71	68	71	75	75	80	69
Treated	70	68	71	74	75	80	69
Completed	61 (85.9)	57 (83.8)	56 (78.9)	66 (88.0)	60 (80.0)	66 (82.5)	54 (78.3)
Discontinued	9 (12.7)	11 (16.2)	15 (21.1)	8 (10.7)	15 (20.0)	14 (17.5)	15 (21.7)
Reason for discontinuation							
Related to study drug	4 (8.2)	3 (5.5)	2 (2.8)	4 (5.4)	7 (9.3)	5 (7.5)	8 (15.7)
Adverse event	2 (4.1)	3 (5.5)	1 (1.4)	4 (5.4)	7 (9.3)	5 (7.5)	3 (5.9)
Lack of efficacy	2 (4.1)	0	1 (1.4)	0	0	0	5 (9.8)
Not related to study drug	5 (10.2)	8 (14.5)	13 (18.3)	4 (5.4)	8 (10.7)	8 (11.9)	6 (11.8)
Adverse event	1 (2.0)	0	2 (2.8)	1 (1.4)	3 (4.0)	1 (1.5)	0
Lost to follow-up	0	2 (3.6)	1 (1.4)	0	1 (1.3)	0	0
Other	4 (8.2)	3 (5.5)	9 (12.7)	1 (1.4)	3 (4.0)	5 (7.5)	4 (7.8)
No longer willing	0	3 (5.5)	1 (1.4)	2 (2.7)	1 (1.3)	2 (3.0)	2 (3.9)

Table S3 summarizes the number of subjects that were included in the efficacy and safety analyses. The following analysis populations were defined for this study - the full analysis set (FAS), per protocol set and Week 12 set. The FAS included all subjects who were randomized to the study and received at least one dose of the randomized study drug (CP-690,550 or placebo). The primary analysis population for this study was based on the FAS population. The Week 12 set was all subjects who reached Week 12 without discontinuing from the study. The per protocol set excluded subjects who had a protocol deviation thought to affect the efficacy analysis. The safety analysis set was defined as those subjects who received at least 1 dose of the randomized study drug (CP-690,550 or placebo) and was equivalent to the FAS.

Table S3. Subject Evaluation Groups

	CP-690,550						Placebo
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	
Randomized	71	68	71	75	75	80	69
Treated	70	68	71	74	75	80	69
Analyzed for Efficacy							
Week 12 Set	64 (90.1)	59 (86.8)	64 (90.1)	66 (88.0)	66 (88.0)	70 (87.5)	61 (88.4)
Per Protocol Set	64 (90.1)	66 (97.1)	66 (93.0)	73 (97.3)	72 (96.0)	78 (97.5)	68 (98.6)
Full Analysis Set	70 (98.6)	68 (100.0)	71 (100.0)	74 (98.7)	75 (100.0)	80 (100.0)	69 (100.0)
Analyzed for Safety							
Adverse Events	70 (98.6)	68 (100.0)	71 (100.0)	74 (98.7)	75 (100.0)	80 (100.0)	69 (100.0)
Laboratory Data	70 (98.6)	68 (100.0)	71 (100.0)	73[a] (97.3)	75 (100.0)	80 (100.0)	69 (100.0)

[a] one subject was randomized in error: no drug was given and no laboratory samples were taken during double-blind study period.

Treatment groups were comparable with regard to demography and baseline characteristics. Subjects ranged in age from 18 to 81 years with mean ages ranging from 50.8 to 56.0 years between treatment groups. The majority of the subjects were white women.

Efficacy Results: A dose response for ACR20, ACR50 and ACR70 was observed across the CP-690,550 groups, with the lowest response rates (difference from placebo at Week 12) in the 1 mg BID group and the highest response rates in the 10 mg BID group for ACR20 and 15 mg BID group for ACR50 and ACR70. There was a lack of separation from placebo and the clinically insignificant magnitude of efficacy with the 1 mg BID dose. Efficacy was also demonstrated by improvement in the ACR response criteria, including the HAQ-DI and each of the other 6 individual components, and by changes from baseline in the DAS28-3(CRP).

Primary Evaluations: The linear-trend test based on the ACR20 response, using BOCF for handling missing values, established a dose-response (Table S4) with the slope parameter being statistically significant at Week 12 ($p = 0.0053$).

Table S4. Linear Trend Test of ACR20 Response at Week 12

Parameter	Estimate	DF	Chi-Square	Pr> Chi-Square	Intercept Only	Full Model
Intercept	-0.36	1	3.9	0.0484	593.4	587.5
Slope	1.03	1	7.8	0.0053	597.5	595.6
					591.4	583.5
Odds Ratio	2.81					
90% Lower	1.53					
90% Upper	5.18					

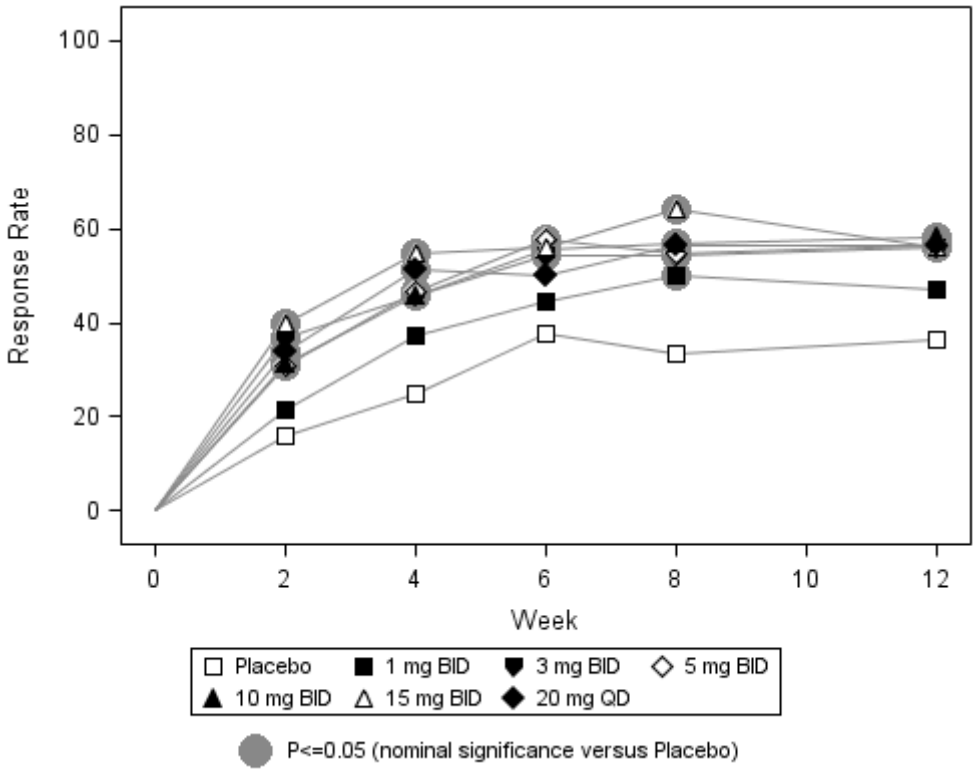
Missing data were imputed by baseline observation carried forward and the full analysis dataset was used.
Doses 0, 1, 3, 5, 10 and 15 were transformed using [Dose/(Dose + ED50)] where ED50 was chosen to be 5. The 20 mg QD dose was omitted from this analysis.

Secondary Evaluations

ACR20 Response at Weeks 2, 4, 6, 8 and 12: The linear-trend test based on the ACR20 response, using BOCF for handling missing values, established a dose-response from as early as Week 2. The slope parameter was statistically significant at Weeks 2, 4, 6 and 8, demonstrating that there was a basic dose-response in the data.

The ACR20 response rates are displayed in Figure S2 (in a longitudinal fashion within each treatment group). The nominal significance of the comparison to placebo at a given week is indicated with a gray circle around the plotting symbol. By nominal significance, it is meant that the p-value is being used as a descriptive statistic to indicate the strength of the separation from placebo, with no correction for multiple comparisons, multiple endpoints, etc.

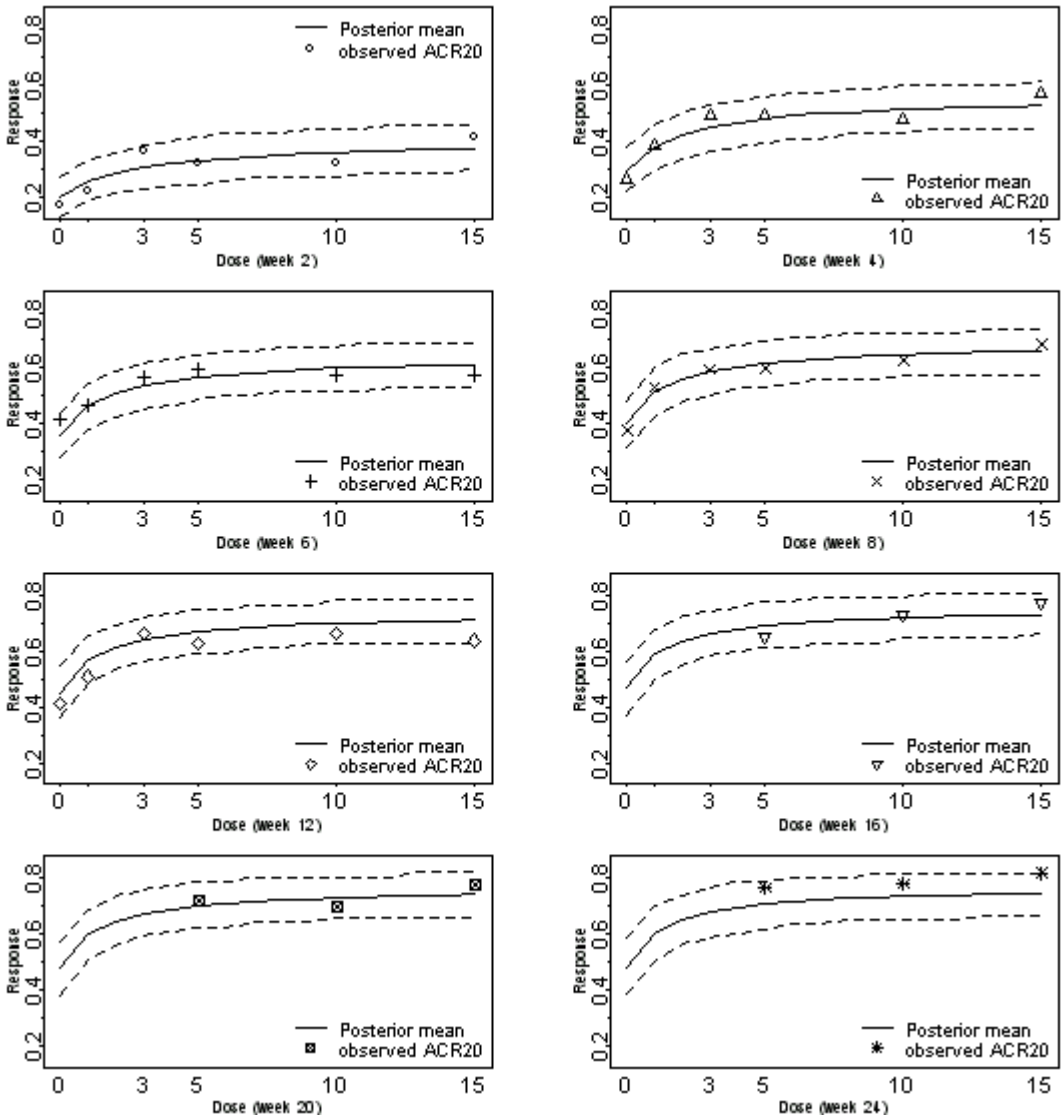
Figure S2. ACR20 Response at Weeks 2, 4, 6, 8 and 12 of CP-690,550



The 1 mg BID dose failed to achieve both clinically and statistically significant separation from placebo. The remaining BID doses did separate from placebo both statistically and in clinically meaningful increases, especially on the order of 20 percentage points at Week 12. The CP-690,550 20 mg QD group was significantly different from placebo at all visits except Week 6.

ACR20 Results from Longitudinal Emax model: The model-predicted posterior mean (80% prediction interval) for the proportions of ACR20 response rates by week are presented in Figure S3 along with the observed ACR20 response rates. The observed and predicted response rates are well within the prediction intervals with no evidence of bias as a function of dose or time. The model-estimated placebo-adjusted ACR20 response rates at Week 12 are 12, 19, 22, 25, and 26% for the 1, 3, 5, 10 and 15 mg BID doses, respectively.

Figure S3. Posterior Mean (80% Prediction Interval) Model-Predicted ACR20 Responses at Weeks 2 Through 24 for BID Doses



Note: Observed ACR20 values are intentionally omitted for placebo, 1 mg BID, and 3 mg BID after Week 12 because some subjects in those groups were advanced to 5 mg BID due to lack of efficacy.

ACR50 Response at Weeks 2, 4, 6, 8 and 12: The 1 mg BID dose failed to achieve significant separation from placebo and at some weeks was similar to placebo. The remaining BID doses did separate from placebo from Week 4, both statistically and in clinically meaningful increases, with the exception of 10 mg BID at Weeks 8 and 12. The CP-690,550 20 mg QD group was significantly improved relative to placebo at all time points.

ACR50 Results from Longitudinal Emax model: Overall, the observed data were well within the prediction intervals with no evidence of bias as a function of dose or time. The model-estimated

placebo-adjusted ACR50 response rates at Week 12 were 8, 16, 21, 27, and 30% for 1, 3, 5, 10 and 15 mg BID doses, respectively.

ACR70 Response at Weeks 2, 4, 6, 8 and 12: Consistent with the results for ACR20 and ACR50, the 1 mg BID dose was indistinguishable from placebo. The 5 and 15 mg BID doses and the 20 mg QD dose separated from placebo, with statistically significant increases from Week 4. Somewhat anomalous were the 3 mg BID dose, which at times outperformed 5 mg BID, and the 10 mg BID dose, which generally underperformed both 5 and 15 mg BID doses.

ACR70 Results from Longitudinal Emax model: Overall, the observed data were well within the prediction intervals with no evidence of bias as a function of dose or time. The model-estimated placebo-adjusted ACR70 response rates at Week 12 were 4, 10, 13, 18, and 20% for 1, 3, 5, 10 and 15 mg BID doses, respectively.

ACR90 Response at Weeks 2, 4, 6, 8 and 12: None of the differences for active treatment compared to placebo were statistically significant.

ACR Assessments

Tender/Painful Joint count (68): The 1 mg BID dose was not statistically different from placebo. The 5, 10 and 15 mg BID doses and the 20 mg QD dose separated from placebo, with statistically significant decreases from Week 2. Somewhat anomalous were the 3 mg BID dose, which at times outperformed 5 mg BID, and the 10 mg BID dose, which generally underperformed both 5 and 15 mg BID doses.

Swollen Joint Count (66): The 1 mg BID dose was not statistically different from placebo. The 5, 10 and 15 mg BID doses and the 20 mg QD dose separated from placebo, with statistically significant decreases from Week 2. Somewhat anomalous were the 3 mg BID dose, which at times outperformed 5 mg BID, and the 10 mg BID dose, which generally underperformed both 5 and 15 mg BID doses. At Week 8, only the 5 and 15 mg BID doses were statistically significantly different from placebo.

Patient's Assessment of Arthritis Pain: The 1 mg BID dose was not statistically different from placebo until Week 12. The 10 and 15 mg BID doses and the 20 mg QD dose separated from placebo; with statistically significant decreases from Week 2 (the decrease with the 10 mg BID dose was not statistically significant at Week 4). The 3 and 5 mg BID doses separated from placebo, with statistically significant decreases from Week 6.

Patient's Global Assessment of Arthritis: The 1 mg BID dose was not statistically different from placebo. The 10 and 15 mg BID doses and the 20 mg QD dose separated from placebo, with statistically significant decreases from Week 2. At Week 6 the 20 mg QD dose was not statistically significantly different from placebo. The 5 mg BID dose was statistically different from placebo after Week 6 and the 3 mg BID dose was statistically different from placebo after Week 8.

Physician's Global Assessment of Arthritis: The 1 mg BID dose was not statistically different from placebo. The 10 and 15 mg BID dose separated from placebo with statistically significant

decreases from Week 2 that continued until Week 12. At Week 12 the 3, 5, 10 and 15 mg BID doses and the 20 mg QD dose were statistically significantly decreased from placebo.

Health Assessment Questionnaire-Disability Index: The HAQ-DI values decreased over time and with increased dose of CP-690,550, which is indicative of improved functional status. CP-690,550 1 mg BID did not separate from placebo until Week 12. Decreases from baseline were statistically significant compared to placebo from Week 4 in the other BID doses, with the exception of 10 mg BID. The CP-690,550 20 mg QD was statistically significant compared to placebo from Week 4.

C-Reactive Protein (CRP): The 1, 3, 5, 10 and 15 mg BID doses and the 20 mg QD dose separated from placebo, with statistically significant decreases from Week 2. The 1 mg BID dose outperformed 3 mg BID at Weeks 4 and 12. The 10 mg BID dose outperformed 5 mg BID at Weeks 8 and 12.

Disease Activity Score Assessment: The 1 mg BID dose was not statistically different from placebo for the majority of the assessment weeks (Weeks 2, 6 and 8). The 3, 5, 10 and 15 mg BID doses as well as 20 mg QD dose separated from placebo, with statistically significant decreases from Week 2. The 3 mg BID dose outperformed 5 mg BID at times.

SF-36 Domain Scores: At Week 12 the 20 mg QD dose group had the highest (best) score for each of the SF-36 domains, with the exception of vitality, for which the 15 mg BID dose group performed best. For all domains the CP-690,550 dose groups had higher scores than the placebo group.

Statistically significant differences from placebo in change from baseline at Week 12 were seen in 15 mg BID for vitality; 20 mg QD for social function; 20 mg QD and 15, 5, 3 and 1 mg BID for mental health; 20 mg QD and 15 mg BID for physical function; and 20 mg QD and 15, 10, 5, 3 and 1 mg BID for bodily pain. Role-emotion, role-physical and general health showed no statistically significant differences from placebo in change from baseline at Week 12.

SF-36 Component Scores: Placebo had lower scores than the active treatment group for both components.

Physical Component: A dose-related trend was observed for the physical component of the SF-36 survey and the 20 mg QD group had a higher score than the 15 mg BID dose group. Statistically significant differences from placebo in change from baseline at Week 12 were seen in 20 mg QD and 15 mg BID group.

Mental Component: No dose-related trend was observed for the mental component of the SF-36 survey. The 20 mg QD dose had the highest score of 4.35. The 1, 3, 5 and 15 mg BID dose scores were similar to the 20 mg QD dose score. Placebo and the 10 mg BID dose groups had similarly low scores. Statistically significant differences from placebo in change from baseline at Week 12 were seen in 20 mg QD and 15, 5, 3 and 1 mg BID.

EuroQol EQ-5D: Statistically significant increases from placebo in change from baseline at Week 12 were seen in 20 mg QD, 15, 10 and 1 mg BID treatment groups.

Medical Outcomes Study (MOS)-Sleep Scale: Statistically significant differences from placebo in change from baseline at Week 12 were seen in 3 mg BID treatment group for sleep problems summary, overall sleep problems and sleep disturbance. Statistically significant differences from placebo in change from baseline at Week 12 were also seen in 5 and 10 mg BID treatment groups for quantity.

FACIT-Fatigue Scale: There was no improvement or dose response in the FACIT-Fatigue Scale. None of the differences from placebo in change from baseline were statistically significant

Safety Results:

All causality AEs for the entire double-blind treatment period are summarized in Table S5. It should be noted that some subjects that were in the placebo group as well as those in the 1 and 3 mg BID and 20 mg QD groups may have been reassigned to the 5 mg BID treatment group after Week 12; these are summarized under their original dose but in a separate group, labeled "(r)", than those who remained on their original dose throughout the study. Because of the re-assignment discussion of AE frequency is primarily confined to the post-baseline to Week 12 period and to the un-reassigned subjects for the double-blind treatment period.

During the post-baseline to Week 12 period the 10 and 15 mg BID treatment groups had the highest proportion of subjects reporting an AE and the other dose groups had proportions of subjects reporting an AE that were similar to placebo. The 15 mg BID group reported the highest percentage of subjects who discontinued due to an AE. All treatment groups had at least 1 subject discontinue due to an AE.

Post Week 12 the percentage of subjects who had an AE was similar across all treatment groups. There were generally fewer discontinuations post Week 12 and the percentages who discontinued were similar across the treatment groups.

Subjects reported SAEs at all doses of CP-690,550, with the highest number in the 15 mg BID treatment group.

Table S5. Summary of Treatment-Emergent Adverse Events, All Causalities (Double-Blind Treatment Period)

	CP-690,550										
	1 mg BID n (%)	1 mg BID (r) n (%)	3 mg BID n (%)	3 mg BID (r) n (%)	5 mg BID n (%)	10 mg BID n (%)	15 mg BID n (%)	20 mg QD n (%)	20 mg QD (r) n (%)	Placebo n (%)	Placebo (r) n (%)
Subjects evaluable for AEs	49	21	55	13	71	74	75	67	13	51	18
Total number of AEs	65	55	78	30	135	157	138	118	25	69	26
Subjects with at least 1 AE	29 (59.2)	14 (66.7)	38 (69.1)	10 (76.9)	47 (66.2)	50 (67.6)	57 (76.0)	41 (61.2)	6 (46.2)	29 (56.9)	12 (66.7)
Subjects with at least 1 SAE	1 (2.0)	1 (4.8)	4 (7.3)	0	4 (5.6)	1 (1.4)	6 (8.0)	4 (6.0)	0	0	0
Subjects with at least 1 severe AE	1 (2.0)	2 (9.5)	2 (3.6)	0	4 (5.6)	7 (9.5)	6 (8.0)	2 (3.0)	0	0	0
Number of deaths	0	0	1 (1.8)	0	0	0	0	0	0	0	0
Number discontinued due to AE	3 (6.1)	0	2 (3.6)	0	3 (4.2)	5 (6.8)	10 (13.3)	6 (9.0)	0	3 (5.9)	0
Subjects with dose reduction or temporary discontinuation due to AE	4 (8.2)	4 (19.0)	5 (9.1)	0	10 (14.1)	10 (13.5)	6 (8.0)	7 (10.4)	1 (7.7)	7 (13.7)	0

Except for the number of AEs, subjects were counted only once per treatment in each row.
(r) = re-assigned, AE = adverse event, BID = twice daily, QD = once daily , SAE = serious adverse event.

Treatment emergent all causality AEs occurring in ≥5% of subjects in any treatment group for the double-blind treatment period are presented in Table S6. Most of the AEs were mild in severity. For CP-690,550 treatment groups, all causality AEs occurred most frequently in the MedDRA Infections and Infestations System Organ Class (SOC), followed by AEs in the Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders and Investigations SOCs. For the placebo treatment group, AEs were also most common in the Infections and Infestations and Gastrointestinal Disorders SOCs, followed by AEs in the Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue Disorders SOCs.

The incidence of ECG and vital sign events was low and similar across treatment groups. The laboratory events are discussed in the next section.

From baseline to Week 12, the most frequently reported AEs (all causality) are presented in Table S.

The incidence of AEs was similar in the re-assigned groups compared to the baseline to Week 12 5 mg BID group. The number of AEs in the re-assigned groups was similar to that before the re-assignment.

Table S6. Treatment-Emergent All Causality AEs Occurring at an Incidence of 5% or Greater

Page 1 of 4

System Organ Class/Preferred Term (MedDRA)	CP-690,550									Placebo	Placebo
	1 mg BID n (%)	1 mg BID (r) n (%)	3 mg BID n (%)	3 mg BID (r) n (%)	5 mg BID n (%)	10 mg BID n (%)	15 mg BID n (%)	20 mg QD n (%)	20 mg QD (r) n (%)	n (%)	(r) n (%)
Cardiac disorders	**0**	**4 (19)**	**2 (3.6)**	**0**	**2 (2.8)**	**2 (2.7)**	**0**	**4 (6.0)**	**0**	**0**	**1 (5.6)**
Supraventricular extrasystoles	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Gastrointestinal disorders	**10 (20.4)**	**7 (33.3)**	**11 (20.0)**	**1 (7.7)**	**17 (23.9)**	**18 (24.3)**	**17 (22.7)**	**13 (19.4)**	**3 (23.1)**	**12 (23.5)**	**4 (22.2)**
Toothache	1 (2.0)	0	0	0	0	0	0	0	1 (7.7)	0	0
Gastritis	0	2 (9.5)	2 (3.6)	0	1 (1.4)	3 (4.1)	0	0	0	0	1 (5.6)
Constipation	0	1 (4.8)	1 (1.8)	0	1 (1.4)	2 (2.7)	1 (1.3)	0	1 (7.7)	1 (2.0)	0
Diarrhoea	7 (14.3)	1 (4.8)	1 (1.8)	1 (7.7)	9 (12.7)	1 (1.4)	3 (4.0)	1 (1.5)	1 (7.7)	2 (3.9)	0
Abdominal pain upper	2 (4.1)	1 (4.8)	2 (3.6)	0	1 (1.4)	2 (2.7)	1 (1.3)	0	1 (7.7)	3 (5.9)	1 (5.6)
Breath odour	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Dyspepsia	1 (2.0)	1 (4.8)	0	0	0	3 (4.1)	2 (2.7)	1 (1.5)	0	1 (2.0)	2 (11.1)
Flatulence	0	1 (4.8)	0	0	0	2 (2.7)	0	0	1 (7.7)	1 (2.0)	0
Nausea	2 (4.1)	1 (4.8)	3 (5.5)	1 (7.7)	3 (4.2)	5 (6.8)	4 (5.3)	2 (3.0)	0	1 (2.0)	0
Vomitting	0	1 (4.8)	2 (3.6)	1 (7.7)	3 (4.2)	1 (1.4)	2 (2.7)	4 (6.0)	0	2 (3.9)	0
Dry mouth	0	1 (4.8)	0	0	0	0	0	0	0	1 (2.0)	1 (5.6)
General disorders and administration site disorders	**2 (4.1)**	**1 (4.8)**	**2 (3.6)**	**2 (15.4)**	**6 (8.5)**	**6 (8.1)**	**6 (8.0)**	**7 (10.4)**	**1 (7.7)**	**3 (5.9)**	**1 (5.6)**
Pyrexia	1 (2.0)	0	0	0	3 (4.2)	1 (1.4)	0	3 (4.5)	0	1 (2.0)	1 (5.6)
Chest pain	1 (2.0)	0	2 (3.6)	1 (7.7)	0	1 (1.4)	2 (2.7)	1 (1.5)	1 (7.7)	0	0
Fatigue	0	1 (4.8)	0	1 (7.7)	1 (1.4)	2 (2.7)	0	2 (3.0)	0	0	0
Immune system disorders	**0**	**0**	**0**	**0**	**0**	**1 (1.4)**	**1 (1.3)**	**0**	**0**	**0**	**1 (5.6)**
Allergy to arthropod bite	0	0	0	0	0	0	1 (1.3)	0	0	0	1 (5.6)

(r) = re-assigned, AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 11.0)

Table S6. Treatment-Emergent All Causality AEs Occurring at an Incidence of 5% or Greater

System Organ Class/Preferred Term (MedDRA)	CP-690,550									Placebo	Placebo
	1 mg BID n (%)	1 mg BID (r) n (%)	3 mg BID n (%)	3 mg BID (r) n (%)	5 mg BID n (%)	10 mg BID n (%)	15 mg BID n (%)	20 mg QD n (%)	20 mg QD (r) n (%)	n (%)	(r) n (%)
Infections and infestations	**10 (20.4)**	**9 (42.9)**	**17 (30.9)**	**8 (61.5)**	**27 (38.0)**	**26 (35.1)**	**28 (37.3)**	**24 (35.8)**	**6 (46.2)**	**12 (23.5)**	**5 (27.8)**
Sinusitis bacterial	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Onychomycosis	0	0	0	0	0	0	0	0	1 (7.7)	0	0
Tinea cruris	0	0	0	1 (7.7)	0	0	0	0	0	0	0
Tinea pedis	1 (2.0)	0	0	0	0	1 (1.4)	0	1 (1.5)	1 (7.7)	0	0
Bronchitis	1 (2.0)	1 (4.8)	2 (3.6)	0	1 (1.4)	1 (1.4)	2 (2.7)	1 (1.5)	0	1 (2.0)	1 (5.6)
Ear infection	0	1 (4.8)	0	0	0	0	0	0	1 (7.7)	0	0
Gastroenteritis	0	0	0	0	2 (2.8)	4 (5.4)	2 (2.7)	1 (1.5)	0	1 (2.0)	0
Nasopharyngitis	1 (2.0)	2 (9.5)	2 (3.6)	1 (7.7)	5 (7.0)	2 (2.7)	6 (8.0)	4 (6.0)	1 (7.7)	3 (5.9)	0
Pharyngitis	1 (2.0)	0	3 (5.5)	1 (7.7)	2 (2.8)	0	1 (1.3)	2 (3.0)	1 (7.7)	2 (3.9)	0
Pharyngotonsillitis	1 (2.0)	0	1 (1.8)	0	2 (2.8)	0	1 (1.3)	0	0	0	1 (5.6)
Sinusitis	2 (4.1)	0	1 (1.8)	0	0	3 (4.1)	1 (1.3)	0	1 (7.7)	0	0
Upper respiratory tract infection	1 (2.0)	0	0	3 (23.1)	5 (7.0)	5 (6.8)	2 (2.7)	4 (6.0)	2 (15.4)	1 (2.0)	2 (11.1)
Urinary tract infection	1 (2.0)	1 (4.8)	3 (5.5)	2 (15.4)	5 (7.0)	4 (5.4)	5 (6.7)	6 (9.0)	0	0	0
Herpes simplex	0	0	1 (1.8)	1 (7.7)	0	0	1 (1.3)	0	0	0	0
Influenza	1 (2.0)	1 (4.8)	0	1 (7.7)	2 (2.8)	5 (6.8)	3 (4.0)	1 (1.5)	1 (7.7)	1 (2.0)	0
Oral herpes	0	2 (9.5)	1 (1.8)	1 (7.7)	1 (1.4)	2 (2.7)	1 (1.3)	1 (1.5)	0	0	1 (5.6)
Injury, poisoning and procedural complications	**2 (4.1)**	**1 (4.8)**	**4 (7.3)**	**0**	**2 (2.8)**	**4 (5.4)**	**2 (2.7)**	**1 (1.5)**	**0**	**4 (7.8)**	**1 (5.6)**
Excoriation	0	0	0	0	0	2 (2.7)	0	0	0	0	1 (5.6)
Investigations	**1 (2.0)**	**6 (28.6)**	**5 (9.1)**	**1 (7.7)**	**1 (1.4)**	**7 (9.5)**	**11 (14.7)**	**8 (11.9)**	**1 (7.7)**	**1 (2.0)**	**1 (5.6)**
Electrocardiogram abnormal	0	0	0	0	0	0	0	0	1 (7.7)	0	0
Haematocrit decreased	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Haemoglobin decreased	0	1 (4.8)	0	0	0	1 (1.4)	1 (1.3)	0	0	0	1 (5.6)
Alanine aminotranferase increased	0	1 (4.8)	1 (1.8)	0	0	0	5 (6.7)	1 (1.5)	1 (7.7)	1 (2.0)	0
Aspartate aminotransferase increased	0	0	1 (1.8)	0	0	0	5 (6.7)	2 (3.0)	0	0	0
Weight increased	0	0	1 (1.8)	1 (7.7)	0	0	0	0	0	0	0

(r) = re-assigned, AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 11.0)

Table S6. Treatment-Emergent All Causality AEs Occurring at an Incidence of 5% or Greater

System Organ Class/Preferred Term (MedDRA)	CP-690,550									Placebo	Placebo
	1 mg BID n (%)	1 mg BID (r) n (%)	3 mg BID n (%)	3 mg BID (r) n (%)	5 mg BID n (%)	10 mg BID n (%)	15 mg BID n (%)	20 mg QD n (%)	20 mg QD (r) n (%)	n (%)	(r) n (%)
Metabolism and nutritional disorders	**3 (6.1)**	**1 (4.8)**	**2 (3.6)**	**0**	**2 (2.8)**	**4 (5.4)**	**7 (9.3)**	**5 (7.5)**	**0**	**0**	**2 (11.1)**
Glucose tolerance impaired	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Hypercholesterolaemia	1 (2.0)	1 (4.8)	1 (1.8)	0	0	0	4 (5.3)	2 (3.0)	0	0	0
Hyperuricaemia	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Musculoskeletal and connective tissue disorders	**6 (12.2)**	**1 (4.8)**	**4 (7.3)**	**4 (30.8)**	**11 (15.5)**	**8 (10.8)**	**6 (8.0)**	**8 (11.9)**	**0**	**3 (5.9)**	**2 (11.1)**
Osteopenia	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Arthralgia	0	0	2 (3.6)	2 (15.4)	1 (1.4)	2 (2.7)	2 (2.7)	0	0	0	0
Rheumatoid arthritis	2 (4.1)	1 (4.8)	0	1 (7.7)	2 (2.8)	1 (1.4)	0	0	0	1 (2.0)	1 (5.6)
Muscle spasms	0	0	0	1 (7.7)	0	1 (1.4)	0	1 (1.5)	0	0	0
Pain in extremity	0	0	0	1 (7.7)	1 (1.4)	0	1 (1.3)	0	0	1 (2.0)	0
Synovial cyst	0	0	0	1 (7.7)	1 (1.4)	0	0	0	0	0	0
Tendonitis	0	0	0	0	1 (1.4)	0	1 (1.3)	0	0	0	1 (5.6)
Nervous system disorders	**4 (8.2)**	**3 (14.3)**	**1 (1.8)**	**3 (23.1)**	**6 (8.5)**	**9 (12.2)**	**5 (6.7)**	**9 (13.4)**	**4 (30.8)**	**3 (5.9)**	**1 (5.6)**
Headache	2 (4.1)	1 (4.8)	0	2 (15.4)	2 (2.8)	3 (4.1)	4 (5.3)	9 (13.4)	3 (23.1)	1 (2.0)	0
Burning sensation	0	0	0	0	0	0	0	0	0	0	1 (5.6)
Dizziness	0	0	1 (1.8)	1 (7.7)	1 (1.4)	3 (4.1)	0	1 (1.5)	0	0	0
Hypoasthesia	1 (2.0)	0	0	0	0	0	0	1 (1.5)	1 (7.7)	0	0
Paraesthesia	0	0	0	0	0	1 (1.4)	0	0	1 (7.7)	0	0
Somnolence	0	1 (4.8)	0	0	2 (2.8)	0	0	0	1 (7.7)	0	0
Psychiatric disorders	**1 (2.0)**	**3 (14.3)**	**1 (1.8)**	**1 (7.7)**	**2 (2.8)**	**3 (4.1)**	**4 (5.3)**	**0**	**0**	**2 (3.9)**	**0**
Insomnia	1 (2.0)	1 (4.8)	1 (1.8)	1 (7.7)	2 (2.8)	2 (2.7)	1 (1.3)	0	0	0	0
Reproductive system and breast disorders	**1 (2.0)**	**1 (4.8)**	**0**	**1 (7.7)**	**1 (1.4)**	**1 (1.4)**	**2 (2.7)**	**0**	**0**	**0**	**0**
Genital discharge	0	0	0	1 (7.7)	0	0	0	0	0	0	0

(r) = re-assigned, AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 11.0)

Table S6. Treatment-Emergent All Causality AEs Occurring at an Incidence of 5% or Greater

System Organ Class/Preferred Term (MedDRA)	CP-690,550									Placebo	Placebo
	1 mg BID n (%)	1 mg BID (r) n (%)	3 mg BID n (%)	3 mg BID (r) n (%)	5 mg BID n (%)	10 mg BID n (%)	15 mg BID n (%)	20 mg QD n (%)	20 mg QD (r) n (%)	n (%)	(r) n (%)
Respiratory, thoracic and mediastinal	**3 (6.1)**	**3 (14.3)**	**4 (7.3)**	**1 (7.7)**	**5 (7.0)**	**9 (12.2)**	**6 (8.0)**	**6 (9.0)**	**1 (7.7)**	**6 (11.8)**	**1 (5.6)**
Wheezing	0	0	0	0	0	1 (1.4)	1 (1.3)	0	0	0	1 (5.6)
Cough	1 (2.0)	0	2 (3.6)	0	3 (4.2)	6 (8.1)	2 (2.7)	2 (3.0)	1 (7.7)	0	0
Sinus congestion	0	0	1 (1.8)	1 (7.7)	0	1 (1.4)	1 (1.3)	0	0	1 (2.0)	0
Skin and subcutaneous tissue disorders	**5 (10.2)**	**1 (4.8)**	**6 (10.9)**	**1 (7.7)**	**6 (8.5)**	**9 (12.2)**	**7 (9.3)**	**4 (6.0)**	**1 (7.7)**	**6 (11.8)**	**0**
Erythema	0	0	0	0	0	0	0	0	1 (7.7)	0	0
Rash	1 (2.0)	0	2 (3.6)	0	2 (2.8)	4 (5.4)	2 (2.7)	1 (1.5)	0	1 (2.0)	0
Acne	0	0	0	1 (7.7)	0	1 (1.4)	0	0	0	0	0
Vascular disorders	**3 (6.1)**	**1 (4.8)**	**3 (5.5)**	**0**	**2 (2.8)**	**3 (4.1)**	**3 (4.0)**	**2 (3.0)**	**0**	**1 (2.0)**	**1 (5.6)**
Hypertension	2 (4.1)	1 (4.8)	2 (3.6)	0	1 (1.4)	2 (2.7)	2 (2.7)	2 (3.0)	0	0	1 (5.6)

(r) = re-assigned, AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 11.0)

Table S7. Treatment-Emergent All Causality AEs Occurring at an Incidence of 5% or Greater (Post Baseline to Week 12)

System Organ Class/Preferred Term (MedDRA)	CP-690,550						Placebo n (%)
	1 mg BID n (%)	3 mg BID n (%)	5 mg BID n (%)	10 mg BID n (%)	15 mg BID n (%)	20 mg QD n (%)	
Gastrointestinal disorders	**14 (20.0)**	**9 (13.2)**	**14 (19.7)**	**15 (20.3)**	**10 (13.3)**	**15 (18.8)**	**14 (20.3)**
Diarrhea	5 (7.1)	2 (2.9)	7 (9.9)	1 (1.4)	1 (1.3)	1 (1.3)	2 (2.9)
Nausea	3 (4.3)	4 (5.9)	3 (4.2)	5 (6.8)	4 (5.3)	2 (2.5)	1 (1.4)
Infections and infestations	**12 (17.1)**	**21 (30.9)**	**22 (31.0)**	**19 (25.7)**	**20 (26.7)**	**23 (28.8)**	**15 (21.7)**
Nasopharyngitis	1 (1.4)	1 (1.5)	4 (5.6)	2 (2.7)	3 (4.0)	2 (2.5)	3 (4.3)
Upper respiratory tract infection	0	3 (4.4)	5 (7.0)	1 (1.4)	2 (2.7)	4 (5.0)	2 (2.9)
Urinary tract infection	1 (1.4)	4 (5.9)	4 (5.6)	1 (1.4)	4 (5.3)	5 (6.3)	0
Influenza	1 (1.4)	1 (1.5)	1 (1.4)	4 (5.4)	3 (4.0)	1 (1.3)	0
Investigations	**7 (10.0)**	**3 (4.4)**	**1 (1.4)**	**4 (5.4)**	**11 (14.7)**	**8 (10.0)**	**2 (2.9)**
Alanine aminotranferase increased	1 (1.4)	1 (1.5)	0	0	5 (6.7)	1 (1.3)	1 (1.4)
Aspartate aminotranferase increased	0	1 (1.5)	0	0	5 (6.7)	2 (2.5)	0
Nervous system disorders	**7 (10.0)**	**4 (5.9)**	**6 (8.5)**	**6 (8.1)**	**2 (2.7)**	**11 (13.8)**	**3 (4.3)**
Headache	3 (4.3)	2 (2.9)	2 (2.8)	2 (2.7)	2 (2.7)	10 (12.5)	1 (1.4)
Respiratory, thoracic and mediastinal disorders	**6 (8.6)**	**5 (7.4)**	**4 (5.6)**	**7 (9.5)**	**3 (4.0)**	**5 (6.3)**	**4 (5.8)**
Cough	1 (1.4)	2 (2.9)	3 (4.2)	5 (6.8)	1 (1.3)	3 (3.8)	0

(r) = re-assigned, AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 11.0)

There were 5 subjects with 5 serious infections during the study. Three subjects had pneumonia, 1 had a urinary tract infection and 1 had a respiratory tract infection.

A total of 33 subjects discontinued due to AEs according to the subject summary information. The AE data collected in the study has 30 subjects recorded as discontinuing the study due to an AE. The 3 subjects causing the differences between these 2 totals are described. One subject discontinued due to a urinary tract infection but this information was not on the AE page of the CRF. A second subject died due to pneumonia, the subject summary should have recorded the discontinuation reason as death but it was recorded as AE. A third subject suffered from severe vomiting and withdrew her consent to continue the study. The AE page did not capture that the subject discontinued due to the AE. Twenty-five subjects had at least 1 AE considered related to treatment. The treatment-related discontinuations were generally evenly distributed in the treatment groups except for the 15 mg treatment group where the number of treatment related discontinuations was higher. There were no discontinuations due to AEs in the reassigned treatment groups after Week 12. Eight subjects discontinued the study due to AEs not considered related to treatment. Five subjects discontinued due to abnormal laboratory test results: 4 subjects in the 15 mg BID treatment group and 1 subject in the placebo treatment group. These were recorded as discontinuations due to AEs and not as discontinuations due to laboratory abnormalities.

Treatment emergent AEs leading to discontinuation are presented in Table S8.

Table S8. Treatment-Emergent AEs Leading to Permanent Discontinuation

MedDRA Preferred Term	Start Day/ Stop Day	Severity	Outcome	Relationship to Treatment
CP-690,550 1 mg BID				
Urticaria	90/98	Moderate	Resolved	Related
Dyspepsia	115/136	Moderate	Resolved	Related
Myalgia	116/136	Moderate	Resolved	Related
Pruritus	116/136	Moderate	Resolved	Related
Pharyngolaryngeal pain	12/>45	Moderate	Still present	Concomitant treatment
CP-690,550 3 mg BID				
Urinary tract infection	29/40	Mild	Resolved	Other
Chest pain	55/>59	Moderate	Still present	Related
CP-690,550 5 mg BID				
Pneumonia	51/56	Severe	Resolved	Related
Migraine	42/56	Mild	Resolved	Related
Furuncle	134/162	Moderate	Resolved	Other illness
Staphylococcal infection	134/162	Moderate	Resolved	Other illness
Gastritis	78/>87	Moderate	Still present	Other illness
CP-690,550 10 mg BID				
Herpes zoster	51/72	Severe	Resolved	Related
Nausea	1/9	Moderate	Resolved	Related
Alopecia	49/119	Mild	Resolved	Related
Lower respiratory tract infection	78/96	Moderate	Resolved	Related
Wheezing	72/91	Moderate	Resolved	Other illness
CP-690,550 15 mg BID				
Alanine aminotransferase increased	51/63	Moderate	Resolved	Related
Aspartate aminotransferase increased	51/63	Moderate	Resolved	Related
Hypercholesterolaemia	44/>52	Mild	Still present	Related
Gastric ulcer	106/109	Severe	Resolved	Concomitant treatment
Oral candidiasis	90/120	Moderate	Resolved	Related
Chest discomfort	25/32	Moderate	Resolved	Other illness
Urinary tract infection	67/81	Moderate	Resolved	Other illness
Alanine aminotransferase increased	29/92	Moderate	Resolved	Related
Aspartate aminotransferase increased	29/78	Moderate	Resolved	Related
Alanine aminotransferase increased	29/127	Mild	Resolved	Related
Diarrhoea	2/12	Moderate	Resolved	Related
Vomiting	2/12	Moderate	Resolved	Related

AEs=adverse events, BID=twice daily, MedDRA=Medical Dictionary for Regulatory Activities (Version 11.0). One subject who died is not included in this table as they temporarily discontinued prior to death. One subject who discontinued due to a SAE (Urinary tract infection) is included in this table but this detail was not captured in the project database however was recorded in the safety database

Table S8. Treatment-Emergent AEs Leading to Permanent Discontinuation

Page 2 of 2

MedDRA Preferred Term	Start Day/ Stop Day	Severity	Outcome	Relationship to Treatment
CP-690,550 20 mg QD				
Vomiting	60/70	Moderate	Resolved	Related
Abdominal pain	62/82	Moderate	Resolved	Other illness
Pyrexia	62/82	Moderate	Resolved	Related
Anorexia	62/82	Moderate	Resolved	Other illness
Angina pectoris	25/28	Moderate	Resolved	Related
Headache	25/28	Mild	Resolved	Related
Atrial fibrillation	85/95	Moderate	Resolved	Other illness
Abdominal pain	9/57	Moderate	Resolved	Related
Pneumonia	96/117	Moderate	Resolved	Related
Placebo				
Transaminases increased	29/36	Mild	Resolved	Related
Diarrhoea	65/>85	Mild	Still present	Related
Herpes zoster	83/104	Moderate	Resolved	Related

AEs=adverse events, BID=twice daily, MedDRA=Medical Dictionary for Regulatory Activities (Version 11.0). One subject who died is not included in this table as they temporarily discontinued prior to death. One subject who discontinued due to a SAE (Urinary tract infection) is included in this table but this detail was not captured in the project database however was recorded in the safety database.

There were 6 subjects that met the criteria specified in the protocol for discontinuation due elevated creatinine, however these subjects did not discontinue.

Four subjects had temporary discontinuations due to abnormal laboratory test results recorded as AEs; 3 subjects in the 15 mg treatment group (alanine aminotransferase increased, aspartate aminotransferase increased and blood bilirubin increased) and 1 subject in the placebo treatment group (alanine aminotransferase).

Twenty-one subjects reported SAEs during the study. Five subjects reported 5 SAEs considered by the investigator to be related to the study drug (Table S5).

Table S9. Treatment-Related Serious Adverse Events

SAE Preferred Term[a]	Suspect drug (Dose)	Event Onset Days[b]	Relationship to CP-690,550	Outcome
Urinary tract infection	CP-690,550 (3 mg BID) MTX (15 mg weekly)	31	Related	Recovered
Pneumonia	CP-690,550 (5 mg BID) MTX (15 mg weekly)	51	Related	Recovered
Pneumonia	CP-690,550 (3 mg BID)	43	Related	Death
Respiratory tract infection	CP-690,550 (10 mg BID) MTX (20 mg weekly)	78 415	Related	Recovered
Pneumonia	CP-690,550 (20 mg QD) MTX (17.5 mg)	96 484	Related	Not recovered

MTX = Methotrexate
[a] MedDRA v11.0
[b] Days are relative to the day of starting therapy (Day 1)

Serious infections were few, not dose responsive and not associated with neutropenia.

Two deaths were reported in this study. One was before randomization, the other was attributed to the events of respiratory failure and cardiac failure secondary to bilateral pneumonia and occurred in the 3 mg BID treatment group. The investigator and sponsor could not exclude a contributory role of CP-690,550 to the event of pneumonia.

Laboratory Data: At Week 12 all CP-690,550 treatment groups had increases in mean blood Epstein-Barr virus deoxyribonuleic acid (EBV DNA) levels greater than placebo, although only statistically significant in the 5 mg BID group and median blood EBV DNA levels were less than 10 copies/500 ng DNA (the reference laboratories ULN). This continued out to Week 24 with the median blood EBV DNA levels remaining less than 10 copies/500 ng DNA for all treatment groups.

During the study EBV DNA levels reached or exceeded the level of potential concern (>500 copies/500 ng DNA) in 4 subjects. There were 2 subjects in the 5 mg BID treatment group. One subject had an EBV DNA level of 817 copies/500 ng DNA on Day 169 and reported no AEs during the study. One subject had an EBV DNA level of 1900 copies/500 ng DNA on Day 85 and reported no AEs at the time of the abnormal value. One subject (10721006) in the 15 mg BID had an EBV DNA level of 722 copies/500 ng DNA on Day 86 and reported no associated AEs. One subject in the 20 mg QD treatment group had an EBV DNA level of 665 copies/500 ng DNA on Day 111. Pneumonia (SAE) was reported on Day 96 and the subject discontinued from the study on Day 117 and reported no AEs during the study.

Dose related changes in hemoglobin (and associated incidences of anemia) and neutrophils were observed. Incidences of neutropenia were low. Small mean increases in serum

creatinine from baseline were observed across all treatment groups, including placebo. At Week 12, the differences were statistically significant in the 3, 10 and 15 mg BID groups compared to placebo. Dose dependent increases in LDL, HDL, and total cholesterol were observed. The increases appeared to plateau by approximately Week 6 out to Week 24 for HDL. LDL appeared to plateau from Week 6 out to Week 24 for the 10 and 15 mg BID and 20 mg QD treatment groups but continued to increase for the 1, 3 and 5 mg BID treatment groups. Increased incidences of potentially significant ALT increases were observed in the CP-690,550 15 mg BID treatment group.

Mean changes from baseline in diastolic or systolic blood pressure were generally small, and no notable trends were observed.

The ECG data showed no clinically significant changes. The changes were generally small and no notable trends were observed.

No IgG level was <300 mg/dL at Week 24 and only 1 subject in the CP-690,550 10 mg BID treatment group experienced a drop to <50% of baseline value.

CONCLUSIONS: CP-690,550 was efficacious in all doses greater than 1 mg BID at Week 12 as measured by ACR20 response rates. A dose response for ACR20, ACR50 and ACR70 was observed across the CP-690,550 groups, with the lowest dose, 1 mg BID CP-690,550 not separating significantly from placebo.

All doses of CP-690,550 greater than 1 mg BID demonstrated sustained efficacy after Week 12 for ACR20, ACR50 ACR70 and DAS28 CRP.

CP-690,550 at doses of 1 mg BID, 3 mg BID, 5 mg BID, 10 mg BID, 15 mg BID and 20 mg QD is safe and well tolerated when compared to placebo over a treatment period of 24 weeks. CP-690,550 is associated with decreases in hemoglobin and neutrophils, increases in serum lipids and a small increase in serum creatinine. CP-690,550 is also associated with an increased incidence of infection compared to placebo. These effects can be monitored and are manageable.

Significant improvements in a wide spectrum of health outcomes were observed in subjects treated with CP-690,550, including bodily pain, physical functioning, health status, health utility, and sleep.

Nonlinear, longitudinal, dose-response models provided adequate descriptions of selected measures of efficacy (ACR20, ACR50 and ACR70) and safety (hemoglobin) data to inform dose selection for future studies

A range of doses appears suitable to evaluate further in Phase 3 studies.