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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the US

NATIONAL CLINICAL TRIAL NO.: NCT00550446

PROTOCOL NO.: A3921035

PROTOCOL TITLE: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Active Comparator, Multicenter Study to Compare 5 Dose Regimens of CP-690,550 and Adalimumab versus Placebo, Administered for 6 Months in the Treatment of Subjects with Active Rheumatoid Arthritis.

Study Centers: There were a total of 59 study centers. There were 2 centers in Brazil, 4 centers in Bulgaria, 3 centers in Chile, 3 centers in Croatia, 5 centers in the Czech Republic, 3 centers in Germany, 2 centers in Greece, 1 center in Hungary, 2 centers in Italy, 4 centers in Mexico, 2 centers in Republic of Korea, 3 centers in Romania, 1 center in Slovakia, 5 centers in Ukraine, and 19 centers in the United States.

Study Initiation and Completion Dates: 05 September 2007 to 14 January 2009

Phase of Development: Phase 2

Study Objectives: The primary objective was to characterize the dose-response of CP-690,550 over the range of 1-15 mg twice daily (BID) on American College of Rheumatology 20 (ACR20) response criteria at 12 weeks.

Secondary:

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

2. To compare the efficacy of adalimumab 40 mg subcutaneous (sc) every other week (QOW), administered over 12 weeks, versus placebo for the treatment of signs and symptoms in subjects with active RA.

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

4. To evaluate the safety of switching from adalimumab to CP-690,550.

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

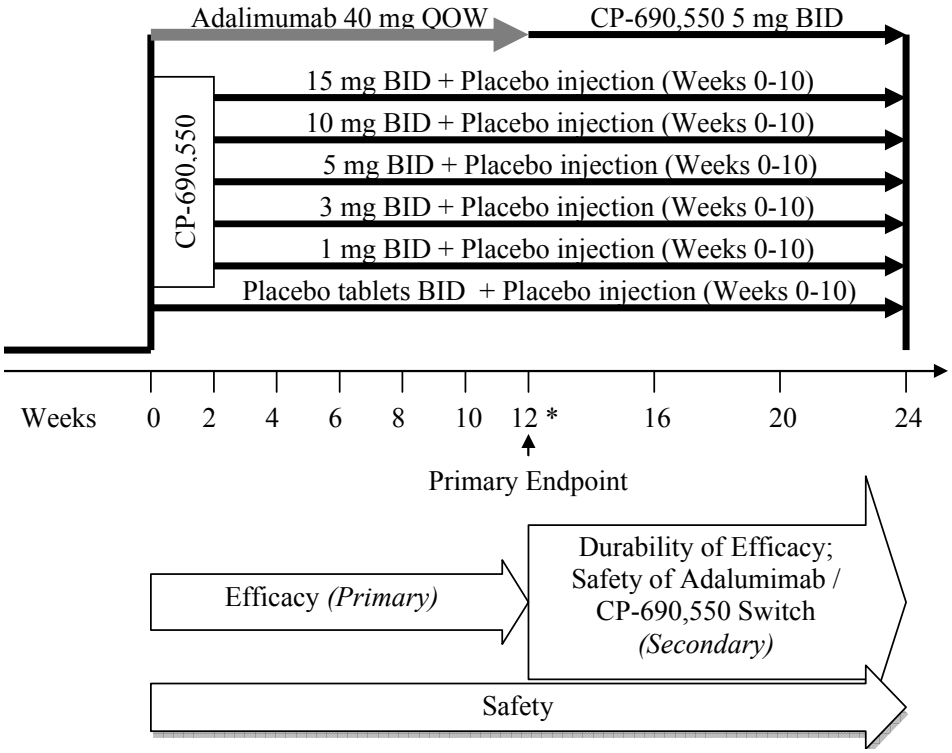
6. To characterize the relationship among doses, plasma concentrations of CP-690,550 and efficacy and safety outcome measures in subjects with active RA.

METHODS

Study Design: This was a Phase 2B, randomized, double-blind, placebo-controlled, active comparator, parallel group study. Subjects were randomized to 1 of: oral CP-690,550 (1, 3, 5, 10 or 15 mg BID), adalimumab 40 mg sc QOW, or placebo. A total of 350 subjects were required; 50 subjects for each study group.

For each subject, the study comprised 11 visits: screening (28 days prior to first study drug administration), baseline (Day 0; randomization to treatment), and 9 on-treatment visits at Weeks 2, 4, 6, 8, 10, 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 received study drug as outpatients, returning to the study site for evaluations at Baseline (Day 0-the day of randomization/the first dose of study medication [maximum period from laboratory assessments to dosing was approximately 28 days]), and at the ends of Weeks 2, 4, 6, 8, 10,12, 16, 20, and 24/early termination.

Number of Subjects (Planned and Analyzed): Approximately 50 subjects/arm, or 350 subjects total, were to be enrolled from approximately 50 sites globally. Assigned study

treatment was to continue for 24 weeks. A total of 54, 52, 50, 61, 57 53 and 59 subjects were randomized to the 1, 3, 5, 10, 15 mg BID, adalimumab QOW and placebo treatment groups, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects had to be at least 18 years old, with a diagnosis of RA, based upon the ACR Criteria, with at least 4 of the 7 criteria, for at least 6 months prior to randomization, to have met the ACR 1991 Revised Criteria for Global Functional Status in RA, Class I, II or III, to have active disease, and to have failed an adequate study of therapy with at least 1 disease modifying antirheumatic drugs (DMARD) due to lack of efficacy or toxicity to be eligible for entry into the study.

Study Treatment: CP-690,550 tablets and matching placebo for oral administration were dispensed in bottles. Subjects were dispensed 3 bottles. Subjects were instructed to take 1 tablet from each bottle in the morning and one tablet from each bottle in the evening. On study visit days, subjects took their morning oral dose at the clinic It was suggested that doses of oral drug should be administered approximately 12 hours apart. CP-690,550 could be administered with or without food.

Study drug for sc injection (ie, adalimumab and matching placebo) was administered every other week according to the subject's treatment assignment on Day 0, and Weeks 2, 4, 6, 8, and 10.

Subjects were automatically reassigned to a different dose of CP-690,500 at Week 12 on the basis of pre-defined non-responses, and all subjects receiving adalimumab were reassinged to CP-690,500 at the end of Week 12. CP-690,550 was provided as 1, 3 and 5 mg tablets by the sponsor. Placebo and adalimumab were also supplied by the sponsor.

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

- 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.
- The number of subjects who had an ACR90 response at all available visits.
- Disease Activity Score (DAS) using DAS28-3 (CRP) and DAS28-4 (ESR).
- Health Assessment Questionnaire-Disability Index (HAQ-DI).
- SF-36 health Survey.
- EuroQol EQ-5D.
- Medical Outcomes Study (MOS)-Sleep Scale.
- Function Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale.

Pharmacokinetic Evaluations: Blood samples (4 mL) were collected at Week 4 and Week 16 predose, and 1, 2 and 4 hours postdose to analyze the plasma for future metabolite identification/further evaluations.

Pharmacodynamic Evaluations: Reticulocyte counts were assessed in order to detect potential potential janus kinase 2 (JAK)-mediated effects on erythropoeisis. Reticulocyte counts were measured in the central laboratory using standard methodology.

Safety Evaluations: Safety was assessed by the reporting of adverse events (AEs), physical examinations (Screening, Baseline, and Weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24/early termination) electrocardiograms (ECGs) (Screening, Baseline, and Weeks 6, 12 and 24/early termination), temperature, blood pressure and heart rate measurements (Screening, Baseline, and Weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24/early termination) and clinical laboratory evaluations(Screening, Baseline, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24/early termination) or as specified.

Statistical Methods: Two sets of analyses were performed. The first set involved those of 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 forced-reassigned to other doses. The post reassignment analyses were exploratory in nature.

Primary Endpoint Analysis: An E_{max} model was fit. An E_{max} model is a nonlinear model in dose; it has an intercept term and a slope term known as E_{max}, which is the coefficient on the expression "dose/(ED50 + dose)," where ED50 represents a dose that achieves 50% of the maximum effect. The maximum effect is the sum of the intercept and the E_{max} parameter. For a fixed ED50, the E_{max} model is reduced to a linear equation, that is, linear in the term dose/(ED50 + dose). By using a pre-specified ED50 value that was chosen based upon analyses of a previous study (A3921019), that is, not estimated from the data in this study, the estimation of the E_{max} parameter yielded a test of statistical significance that served as a trend test, linear in dose/(ED50 + dose). Also, the adalimumab dose and the placebo dose were compared using a normal approximation to the difference in binomial random variables, however no formal comparisons between adalimumab and CP-690,550 were performed.

Secondary Endpoints Analysis: For the component variables of the ACR criteria, a longitudinal linear model was employed using PROC MIXED in the statistical analysis software for change from baseline values. The variables were treated as continuous. The fixed effects of treatment (active doses and placebo), week, and treatment-by-week interaction were included as fixed effects, along with subject as a random effect. Compound symmetry was assumed for the random subject effect. The effect of week started with Week 1, and the actual baseline value was included as a covariate. Estimates of mean values and the mean differences from placebo at each week were derived from the model. Contrasts versus placebo were formed, along with 95% confidence intervals (CI). Descriptive statistics of the actual and change from baseline values were calculated.

Endpoints that were not time dependent (eg, area under the ACR-n curve) were analyzed with a linear model (PROC MIXED). The effects of treatment (each of the active doses and

placebo) and center were included as fixed effects. Contrasts versus placebo were formed, along with 95% CI. Descriptive statistics were calculated.

The DAS of each subject was categorized at each visit from the calculation of the DAS 28-3 (CRP) and the DAS 28-4 (ESR). Descriptive statistics for each treatment group at each visit were displayed.

Note that for the ACR endpoints (ACR20, ACR50, etc.), missing data could be handled using the method of Last Observation Carried Forward (LOCF). Missing values in the individual components of the ACR were handled using the longitudinal linear model as described above.

Pharmacokinetic Analysis: PK parameter values were derived from the analysis of plasma concentration-time data if CP-690,550 using nonlinear mixed effects modeling approaches. The results are presented in a separate report.

Safety Parameters: AEs were summarized according to the sponsor standards. AEs were displayed for the entire treatment period, from Baseline to Week 12 and from Week 12 to end of treatment (that is, AEs that occurred after Week 12, to better understand the effect of the switch from adalimumab). Serious adverse event (SAE) presentations were derived from a separate, centralized, AE monitoring database.

Interim Analyses: An interim analysis was performed at Week 12 to assess the viability of doses being studied. This involved estimating the probability of detecting statistical significance if the trends continued. It may have led to internal decision making for the development of CP-690,550; for example, this information could be used to plan additional studies. It was *not* meant to stop any treatment arm early to declare efficacy. The non viability analysis focused on the ACR20 endpoint.

RESULTS

Subject Disposition and Demography: A total of 555 subjects were screened and 386 were randomized to treatment (Table S1). Of these subjects, 384 took study drug and were evaluated for safety and efficacy. Between 70% and 91% of subjects completed the study. The highest proportion of subjects discontinuing during the double blind treatment period was 30% from the adalimumab treatment group, and across all treatment groups, the majority of discontinuations were not attributed to study drug, except in the adalimumab treatment group, where there were more treatment-related discontinuations than non-treatment-related discontinuations.

Table S1. Subject Disposition

	CP-690,550 BID										
	1 mg		**3 mg**		**5 mg**	**10 mg**	**15 mg**	**Adalimumab[a]**		**Placebo**	
Number of Subjects (%)											
Screened 555											
Randomized to study treatment	54		52		50	61	57	53		59	
Treated	54		51		49	61	57	53		59	
Completed	40 (74.1)		43 (82.7)		43 (86.0)	55 (90.2)	52 (91.2)	37 (69.8)		43 (72.9)	
Discontinued	14 (25.9)		8 (15.4)		6 (12.0)	6 (9.8)	5 (8.8)	16 (30.2)		16 (27.1)	
Discontinuation from double-blind treatment period											
	N = 37	**r = 17**	**N = 34**	**r = 17**	**N = 49**	**N = 61**	**N = 57**	**N = 9**	**r = 44**	**N = 34**	**r = 25**
Related to study drug	5 (13.5)	1 (5.9)	1 (2.9)	1 (5.9)	2 (4.1)	2 (3.3)	2 (3.5)	6 (66.7)	2 (4.5)	3 (8.8)	1 (4.0)
Adverse event	2 (5.4)	0	0	0	1 (2.0)	1 (1.6)	2 (3.5)	3 (33.3)	0	0	0
Lack of efficacy	3 (8.1)	1 (5.9)	1 (2.9)	1 (5.9)	1 (2.0)	1 (1.6)	0	3 (33.3)	2 (4.5)	3 (8.8)	1 (4.0)
Not related to study drug	8 (21.6)	0	5 (14.7)	1 (5.9)	4 (8.2)	4 (6.6)	3 (5.3)	3 (33.3)	5 (11.4)	12 (35.3)	0
Adverse Event	2 (5.4)	0	3 (8.8)	0	0	0	1 (1.8)	0	4 (9.1)	1 (2.9)	0
Lost to follow-up	0	0	1 (2.9)	0	1 (2.0)	1 (1.6)	1 (1.8)	1 (11.1)	0	3 (8.8)	0
Other	4 (10.8)	0	1 (2.9)	1 (5.9)	0	1 (1.6)	0	1 (11.1)	1 (2.3)	5 (14.7)	0
No longer willing to participate	2 (5.4)	0	0	0	3 (6.1)	2 (3.3)	1 (1.8)	1 (11.1)	0	3 (8.8)	0

N = total number of evaluable subjects, r = reassigned after Week 12 to CP-690.550 5 mg BID
Discontinuations ocurring outside the lag period were attributed to the last study treatment receieved.
[a] Adalimumab 40 mg every other week from baseline to Week 10, CP-690,550 5 mg BID from Week 12 to 24.

The efficacy anaylsis populations defined for this study were the full analysis set (FAS), the per-protocol (PP) set and the Week 12 set. The FAS included all subjects 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 for the study was defined by the FAS of subjects. The PP analysis population excluded subjects who had a protocol deviation thought to affect the efficacy analysis. The Week 12 analysis set included all subjects who reached Week 12 without discontinuing from the study. The safety analysis set was equivalent to the FAS. Table S2 summarizes the number of subjects included in the efficacy and safety analyses populations.

Table S2. Subject Evaluation Groups

	CP-690,550 BID					Adalimumab[a]	Placebo
	1 mg	3 mg	5 mg	10 mg	15 mg		
Number of Subjects (%)							
Screened: 555							
Assigned to study treatment	54	52	50	61	57	53	59
Treated	54	51	49	61	57	53	59
Completed	40 (74.1)	43 (82.7)	43 (86.0)	55 (90.2)	52 (91.2)	37 (69.8)	43 (72.9)
Discontinued	14 (25.9)	8 (15.4)	6 (12.0)	6 (9.8)	5 (8.8)	16 (30.2)	16 (27.1)
Analyzed for efficacy							
Full analysis set	54 (100.0)	51 (98.1)	49 (98.0)	61 (100.0)	57 (100.0)	53 (100.0)	59 (100.0)
Per protocol set	52 (96.3)	48 (92.3)	49 (98.0)	59 (96.7)	55 (96.5)	53 (100.0)	56 (94.9)
Week 12 set	44 (81.5)	46 (88.5)	46 (92.0)	57 (93.4)	54 (94.7)	46 (86.8)	46 (78.0)
Analyzed for safety							
Adverse events	54 (100.0)	51 (98.1)	49 (98.0)	61 (100.0)	57 (100.0)	53 (100.0)	59 (100)
Laboratory data	53 (98.1)	51 (98.1)	48 (96.0)	61 (100.0)	57 (100.0)	53 (100.0)	57 (96.6)

Discontinuations ocurring outside the lag period were attributed to the last study treatment received.
[a] Adalimumab 40 mg every other week from baseline to Week 10, CP-690,550 5 mg from Week 12 to 24.

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 clinically insignificant magnitude of efficacy with the 1 mg BID dose. Efficacy was also demonstrated by improvement in the HAQ-DI and each of the other 6 individual components of the ACR response, 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 with the slope parameter being statistically significant at Week 12 ($p<0.0001$).

Secondary Evaluations:

ACR20 Response at Weeks 2, 4, 6, 8, and 12: The slope parameter of the linear-trend test on the ACR20 response, using BOCF for handling missing values, was also significant at Weeks 2, 4, 6, 8, 10 and 12, demonstrating that there was a dose-response in the data beginning at Week 2.

At Week 2, the 10 and 15 mg BID dose groups achieved a placebo-corrected ACR20 response rate with responses of 35.6% and 23.3% respectively. These responses were statistically significant with p-values of <0.0001 and 0.0034 for the 10 and 15 mg BID dose groups respectively. At Week 6 and Week 12, all dose groups, with the exception of the 1 mg BID dose group, achieved placebo-corrected ACR20 response rates that were at least 20 percentage points greater than and statistically significantly superior to placebo.

As a test of the robustness of the results, the analyses were repeated using LOCF as the method of imputation. The outcome of the analysis using the LOCF method was very similar to that using the BOCF method. The adalimumab dose group achieved a placebo corrected ACR20 response rate of 18.4% at Week 12 compared to placebo, which was statistically significantly superior to placebo.

ACR50 Response at Weeks 2, 4, 6, 8, and 12: All dose groups showed an improvement in response versus placebo from Week 2. The 10 and 15 mg BID dose groups showed a statistically significant improvement from Week 2 and the 3 and 5 mg BID dose group at Week 12. The 1 mg BID dose group and adalimumab dose group did not show statistically significant improvement versus placebo.

ACR70 Response at Weeks 2, 4, 6, 8, and 12: All dose groups showed an improvement in response versus placebo from Week 2. The 10 and 15 mg BID dose groups showed a statistically significant improvement from Week 2 and the 5 mg BID dose group at Week 12. The 1 and 3 mg BID dose groups and adalimumab dose group did not show statistically significant improvement versus placebo.

ACR90 Response at Weeks 2, 4, 6, 8, and 12: None of the dose groups showed a statistically significant difference from placebo at Week 2, and only the 10 mg BID dose groups showed a statistically significant difference from placebo at Week 6. At Week 12, the 10 and 15 mg BID dose groups both showed statistically significant difference from placebo. Adalimumab did not show a statistically significant ifference from placebo at Weeks 2, 6 or 12.

ACR20, 50 and 70 Results From Longitudinal E_{max} Model: Overall, the observed data are well within the prediction intervals with no evidence of bias as a function of dose or time.

ACR Assessments:

Tender/Painful Joint Count (68): All treatment groups, including placebo and adalimumab, showed decreases from Baseline at all Weeks 6 and 12, and all treatment groups, apart from placebo and adalimumab showed a decrease from Baseline at Week 2. At Week 2, only the 10 mg BID dose group showed a statistically significant decrease from Baseline ($p = 0.0431$) compared to placebo. At Weeks 6 and 12, the 5, 10 and 15 mg BID dose groups all showed significant decreases from Baseline. Adalimumab did not show a statistically significant decrease.

Swollen Joint Count (66): All treatment groups, including placebo and adalimumab, showed decreases from Baseline at all time points: Weeks 2, 6 and 12, apart from 3 mg BID dose group at Week 2 which showed in increase from Baseline. At Weeks 6, all CP-690,550 dose groups apart from the 3 mg BID dose group showed a statistically significant decrease from

Baseline compared to placebo. At Week 12, the 5, 10 and 15 mg BID dose groups showed statistically significant decreases from Baseline. Adalimumab showed a statistically significant decrease at Week 12 only ($p = 0.0254$).

Patient's Assessment of Arthritis Pain: The 1 mg BID dose group was not significantly different from placebo at Weeks 2, 6 or 12. The 3 mg BID dose group was significantly different from placebo at Week 2 but not at Weeks 6 or 12. The 5, 10 and 15 mg BID dose groups were all significantly different from placebo at Weeks 2, 6 and 12. Adalimumab was statistically significantly different from placebo at Week 2 but not at Weeks 6 and 12.

Patient's Global Assessment of Arthritis Pain: The 5, 10 and 15 mg BID dose groups showed statistically significant differences from placebo at Weeks 2, 6 and 12. The 3 mg BID dose group showed statistically significant differences from placebo at Week 2 only. The 1 mg BID dose group did not show statistically significant differences from placebo and adalimumab showed a statistically significant difference from placebo at Week 2 only.

Physician's Global Assessment of Arthritis: At Weeks 2, 6, and 12 all dose groups, with the exception of the 1 mg BID dose group at all time points, the 3 mg and 5 mg BID dose groups at Week 2, and the 3 mg BID dose group at Week 12, showed statistically significant difference from placebo. At Week 12, only the 5, 10 and 15 mg BID dose groups showed statistically significant differences from placebo. Adalimumab showed decreases from Baseline in the mean change, but the decreases were not statistically significant.

Health Assessment Questionnaire-Disability Index: At Week 2, the 10 and 15 mg BID dose groups showed statistically significant differences from placebo. At Week 6, the 10 and 15 mg BID dose groups showed statistically significant differences and at Week 12, all dose groups with the exception of the 1 and 3 mg BID dose groups showed statistically significant differences from placebo. Adalimumab showed a decrease from Baseline in the mean change, but the decrease was not statistically significant.

C-Reactive Protein (CRP): All dose groups, including adalimumab, showed statistically significant decreases from Baseline compared to placebo at Weeks 2, 6 and 12.

Disease Activity Score Assessment:

DAS28-3(CRP): At Weeks 2, 6 and 12, all dose groups, with the exception of the 1 mg BID dose group, were statistically significantly different in mean changes from Baseline compared to placebo. Adalimumab showed statistically significant separation from placebo at Week 2 and Week 6 but not at Week 12.

DAS28-4(ESR): At Weeks 6 and 12, mean changes from Baseline for all dose groups, with the exception of the 1 mg BID dose group, and the 3 mg BID dose group at Week 12, were statistically significantly different compared to placebo. At Week 2, the 10 and 15 mg BID dose groups were statistically significantly different in the mean change from Baseline compared to placebo. Adalimumab did not show statistically significant separation from placebo up to Week 12.

SF-36 Domain Scores: The largest change in scores occurred in the Bodily Pain, Vitality, Physical Functioning and Role Physical domains. At least 1 treatment arm surpassed the common 5-point change approximating a minimally important difference in each domain.

Statistically significant differences from placebo in change from Baseline at Week 12 were seen in the 10 and 15 mg BID dose groups for vitality and bodily pain, in the 15 mg BID dose group for role-physical, and in the 5, 10 and 15 mg BID dose groups for physical function.

SF-36 Component Scores: For the physical component, an increase in the score was observed with an increase in the dose group compared to placebo. Statistically significant differences from placebo were observed for the 5, 10 and 15 mg BID dose groups, and a dose related trend was noted. For the mental component, the 3 mg BID dose group had the lowest score, and placebo had a higher score than the remainder of the dose groups except for adalimumab which was similar to placebo. No statistically significant differences from placebo were observed for any of the dose groups, and no dose related trend was evident.

EuroQol EQ-5D: Statistically significant differences from placebo were observed for the 10 and 15 mg BID dose groups and a dose related trend was noted. Adalimumab was not significantly different from placebo.

Medical Outcomes Study (MOS)-Sleep Scale: Significant differences were observed between the 5 mg treatment arm and placebo at Week 2 for the awakenings domain of the MOS-Sleep scale ($P<0.05$) that failed to persist through Week 12 ($P=0.8$). No other significant differences were observed.

FACIT-Fatigue Scale: A statistically significant improvement in the FACIT-fatigue scale was observed for the 10 and 15 mg BID dose groups at Week 12. Adalimumab was not significantly different from placebo.

Pharmacodynamic Results: There was 1 statistically significant difference at Week 2 between the CP-690,550 15 mg treatment group and placebo, however for the remainder of the time points, this difference was not statistically significant, and there were no statistical or clinically significant differences in reticulocyte counts between any of the remaining treatment groups and placebo or from Baseline.

Safety Results:

Adverse Events: All causality AEs and treatment related AEs are summarized in Table S3 and Table S4, for the complete double-blind treatment period. Some subjects that were in the placebo group as well as those in the 1 and 3 mg BID and adalimumab QOW groups were 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 reassignment, 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 dose 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 adalimumab dose group had the highest percentage of subjects who discontinued due to an AE (4 subjects, 7.5%). All treatment groups, had at least 1 subject discontinue due to an AE, with the exception of the 5 mg BID dose group, which had no discontinuations due to an AE.

Post Week 12 the percentage of subjects who had an AE was similar across all dose groups, with the highest proportion of subjects reporting an AE in the 5 mg BID dose group (16 subjects, 33%). There were generally fewer discontinuations post Week 12, with no discontinuations reported in the 10 mg BID and placebo dose groups.

Subjects reported SAEs at almost all treatment groups including adalimumab and placebo, with the highest number in the 15 mg BID CP-690,550 treatment group, but none in the 5 mg BID CP-690,550 treatment group.

Treatment emergent AEs occurring in ≥3 subjects in any treatment group for all causality AEs are presented in Table S5. The highest number of all causality AEs were reported in the Infections and Infestations System Organ Class (SOC), and the highest number of treatment-related AEs were reported in in the Gastrointestinal Disorders SOC. Adalimumab had no reported all causality AEs in ≥3 subjects for the first 12 weeks of the study.

The most frequently reported AEs (all causality) from post baseline to Week 12 were diarrhea, nausea, bronchitis, urinary tract infection, dizziness, headache and rash. Of these AEs, urinary tract infection (5 subjects, 10.2%) in the 5 mg BID dose group, had the highest reported incidence followed by headache (5 subjects, 8.2%) in the 10 mg BID dose group.

Table S3. Summary of Treatment-Emergent Adverse Events, All Causality (Double-Blind Treatment Period)

	CP-690,550 BID							Adalimumab[a]		Placebo	
	1 mg		3 mg		5 mg	10 mg	15 mg				
	n (%)	r (%)	n (%)	r (%)	n (%)	n (%)	n (%)	n (%)	r (%)	n (%)	r (%)
Number of Subjects (%):											
Evaluable for adverse events	37	17	34	17	49	61	57	9	44	34	25
Number of adverse events	42	9	39	12	68	93	103	5	59	28	31
With adverse events	19 (51.4)	5 (29.4)	18 (52.9)	6 (35.3)	27 (55.1)	36 (59.0)	35 (61.4)	5 (55.6)	28 (63.6)	16 (47.1)	13 (52.0)
With serious adverse events	2 (5.4)	0	1 (2.9)	0	0	1 (1.6)	4 (7.0)	0	4 (9.1)	2 (5.9)	0
With severe adverse events	1 (2.7)	0	2 (5.9)	0	1 (2.0)	0	5 (8.8)	0	0	2 (5.9)	0
Discontinued due to adverse events	4 (10.8)	0	3 (8.8)	0	1 (2.0)	1 (1.6)	3 (5.3)	3 (33.3)	4 (9.1)	1 (2.9)	0
Dose reduced or temporary discontinuation due to adverse event	1 (2.7)	0	2 (5.9)	0	3 (6.1)	2 (3.3)	5 (8.8)	0	1 (2.3)	1 (2.9)	0

n = number of subjects, r = reassigned after Week 12 to CP-690.550 5 mg BID, BID = twice daily
[a] Adalimumab 40 mg every other week from baseline to Week 10, CP-690,550 5 mg from Week 12 to 24.

Table S4. Summary of Treatment-Emergent Adverse Events, Treatment Related (Double-Blind Treatment Period)

	CP-690,550 BID							Adalimumab[a]		Placebo	
	1 mg		3 mg		5 mg	10 mg	15 mg				
	n (%)	r (%)	n (%)	r (%)	n (%)	n (%)	n (%)	n (%)	r (%)	n (%)	r (%)
Number of Subjects (%):											
Evaluable for adverse events	37	17	34	17	49	61	57	9	44	34	25
Number of adverse events	15	4	14	9	32	40	48	3	33	14	12
With adverse events	10 (27.0)	3 (17.6)	7 (20.6)	4 (23.5)	12 (24.5)	24 (39.3)	21 (36.8)	3 (33.3)	17 (38.6)	7 (20.6)	4 (16.0)
With serious adverse events	1 (2.7)	0	0	0	0	0	1 (1.8)	0	0	0	0
With severe adverse events	0	0	0	0	0	0	2 (3.5)	0	0	0	0
Discontinued due to adverse events	2 (5.4)	0	0	0	1 (2.0)	1 (1.6)	2 (3.5)	3 (33.3)	0	0	0
Dose reduced or temporary discontinuation due to adverse event	0	0	0	0	1 (2.0)	0	3 (5.3)	0	0	0	0

n = number of subjects, r = reassigned after Week 12 to CP-690.550 5 mg BID, BID = twice daily
[a] Adalimumab 40 mg every other week from baseline to Week 10, CP-690,550 5 mg from Week 12 to 24.

Table S5. Treatment-Emergent All Causality Adverse Events Occurring at an Incidence of ≥3 Subjects by Preferred Term

System Organ Class/Preferred Term (MedDRA v11.1)	CP-690,550 BID							Adalimumab[a]		Placebo	
	1 mg		3 mg		5 mg	10 mg	15 mg				
	n (%)	r (%)	n (%)	r (%)	n (%)	n (%)	n (%)	n (%)	r (%)	n (%)	r (%)
Gastrointestinal disorders											
Diarrhea	2 (5.4)	0	3 (8.8)	0	3 (6.1)	4 (6.6)	1 (1.8)	0	1 (2.3)[b]	0	1 (4.0)
Abdominal pain upper	1 (2.7)	0	1 (2.9)	1 (5.9)	0	0	2 (3.5)	0	1 (2.3)	0	3 (12.0)
Nausea	2 (5.4)	1 (5.9)	1 (2.9)	0	2 (4.1)	3 (4.9)	2 (3.5)	0	2 (4.5)	0	0
General disorders and administration site conditions											
Chest discomfort	0	0	0	0	0	0	3 (5.3)	0	0	0	0
Infections and infestations											
Bronchitis	1 (2.7)	0	2 (5.9)	1 (5.9)	2 (4.1)	2 (3.3)	4 (7.0)	0	3 (6.8)	0	1 (4.0)
Nasopharyngitis	0	1 (5.9)	0	0	2 (4.1)	3 (4.9)	2 (3.5)	0	1 (2.3)	1 (2.9)	1 (4.0)
Upper respiratory tract infection	2 (5.4)	0	0	0	2 (4.1)	3 (4.9)	3 (5.3)	0	0	1 (2.9)	1 (4.0)
Urinary tract infection	3 (8.1)	0	2 (5.9)	1 (5.9)	5 (10.2)	3 (4.9)	6 (10.5)	0	2 (4.5)	2 (5.9)	1 (4.0)
Influenza	0	0	0	0	0	1 (1.6)	0	0	3 (6.8)	0	2 (8.0)
Metabolism and Nutrition Disorders											
Hypertriglyceridemia	0	1 (5.9)	0	0	0	1 (1.6)	3 (5.3)	0	0	0	0
Muscoskeletal and connective tissue disorders											
Back pain	0	0	2 (5.9)	0	0	1 (1.6)	3 (5.3)	0	1 (2.3)	0	1 (4.0)
Nervous system disorders											
Headache	0	0	2 (5.9)	0	2 (4.1)	6 (9.8)	3 (5.3)	0	3 (6.8)	1 (2.9)	0
Dizziness	2 (5.4)	0	0	1 (5.9)	0	2 (3.3)	3 (5.3)	0	2 (4.5)	1 (2.9)	0
Skin and subcutaneous tissue disorders											
Pruritus	0	0	0	0	0	1 (1.6)	0	0	3 (6.8)	0	0
Rash	1 (2.7)	0	0	0	1 (2.0)	0	3 (5.3)	0	4 (9.1)	0	1 (4.0)
Vascular disorders											
Hypertension	0	0	0	0	1 (2.0)	3 (4.9)	2 (3.5)	0	0	1 (2.9)	0

MedDRA = medical dictionary for regulatory activities, BID = twice daily, r = reassigned after Week 12 to CP-690.550 5 mg BID, BID = twice daily, n = total number of subjects

[a] Adalimumab 40 mg every other week from Baseline to Week 10, CP-690,550 5 mg from Week 12 to 24, [b] AE occurred prior to dose reassignement and was reassigned to CP-690,550 at Week 12.

Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, were observed in 5 patients: 3 subjects had pneumonia, 1 had acute pyelonephritis and 1 had infection of ankle joint.

Standardized MedDRA Queries (SMQs) of dyslipidemia, erythropenia, leukopenia, acute renal failure, ischemic cerebrovascular disease, and possible drug related hepatic disorders AEs were examined. Few subjects discontinued due to these AEs. No AEs indicative of ischemic heart disease or myocardial infarction were reported.

Twenty subjects permanently discontinued due to a treatment emergent AE and 9 of these subjects had AEs recorded as related to study treatment. The majority of these AEs were mild or moderate, with only 3 AEs reported as severe and 6 AEs recorded as SAEs. Six subjects discontinued due to abnormal laboratory test results, 1 in the 1 mg BID dose group, 2 in the 3 mg BID dose group, 2 in the adalimumab dose group, and 1 in the adalimumab dose group after reassignment.

Fifteen subjects temporarily discontinued due to a treatment emergent AE, 4 had AEs which were recorded as related to study treatment and 2 subjects had AEs that were attributed to laboratory error. All of these related AEs were mild or moderate, with only 2 unrelated AEs reported as severe: 1 attributed to concomitant medication, and 1 attributed to the disease under study. Two of these AEs were classified as an SAE.

Fourteen subjects reported SAEs during the study which are summarized in Table S6.

Table S6. Serious AEs Including Deaths and Discontinuations

Sex/ Age	MedDRA Preferred Term	Event Start Day/Stop Day[a]	Severity	Outcome	Relationship to Treatment
Pre-Randomization					
F/61	Headache	NA	Not known	Resolved	NA
	Nausea	NA	Not known	Resolved	NA
	Vomiting	NA	Not known	Resolved	NA
	Asthenia	NA	Not known	Resolved	NA
F/51	Influenza like illness	NA	Not known	Unknown	Unrelated
CP-690,550 1 mg BID					
M/73	Pneumonia	167/180	Severe	Resolved	Other - unknown
F/40	Pneumonia	164/183	Moderate	Resolved	Study drug
CP-690,550 3 mg BID					
F/65	Anemia	30/34	Severe	Resolved	Concomitant treatment
	Gastric ulcer	36/38	Mild	Resolved	Other - unknown
CP-690,550 10 mg BID					
F/68	Meniscus lesion	152/152	Moderate	Resolved	Disease under study
	Osteoarthritis	152/152	Moderate	Resolved	Disease under study
CP-690,550 15 mg BID					
F/36	Gastritis	106/107	Severe	Resolved	Other - stress
F/68	Cerebrovascular accident	140/>140	Severe	Fatal	Other illness
	Depressed level of consciousness	178/>178	Not known	Not Resolved	Unrelated
M/55	Intervertebral disc protrusion	122/139	Severe	Resolved	Other illness
F/71	Meningitis bacterial	39/56	Severe	Resolved	Study drug
	Pneumonia pneumcoccal	39/41	Severe	Resolved	Study drug
	Pneumcoccal sepsis	35/42	Severe	Resolved	Study drug
	Sinusitis	41/41	Severe	Resolved	Study drug
Adalimumab					
F/58[b]	Pyelonephritis acute	150/155	Mild	Resolved	Other illness
F/72[b]	Knee arthroplasty	86/114	Moderate	Resolved	Disease under study
F/58[b]	Postmenopausal hemorrhage	102/149	Mild	Resolved	Other - unknown
F/53	Renal cell carcinoma	79/141	Mild	Resolved	Other illness
Placebo					
F/39	Panic attack	28/34	Severe	Resolved	Other - stress
F/36	Wound infection	143/168	Severe	Resolved	Disease under study

NA = not applicable, AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities (Version 11.1).

[a] Day relative to first day of study treatment (Day 1), [b] Occurred post Week 12 switch to CP-690,550 5 mg BID treatment

Two subjects reported 5 SAEs considered by the investigator to be related to study drug.

One death was reported during treatment and following review by the study sponsor it was concluded that cerebrovascular accident and depressed level of consciousness were not related to blinded CP-690,550 or clinical trial procedure.

Laboratory Data:

Epstein-Barr Virus: At Week 12, all dose groups had an increase in mean blood EBV DBA levels greater than placebo, with the 1, 10, and 15 mg BID dose groups having a statistically significant difference. The 1 and 10 mg BID dose groups had a statistically significant mean change from Baseline at Week 12.

Anemia: Mean changes from Baseline in hemoglobin were small across all treatment groups. Hemoglobin declined in the placebo group at Week 2, 6, and 12 with mean values of -0.09, -0.21, and -0.22 g/dL, respectively. Most dose groups behaved similarly and were not significantly different from placebo. The exception was the 5 mg BID and the adalimumab groups. Mean Hemoglobin was significantly higher in these groups relative to placebo at the Week 12 and Week 6 time points, respectively. A confirmed hemoglobin value <8.0 g/dL or a decrease from baseline of ≥30% was a protocol mandated criterion for discontinuation from the study. No subject met these criteria.

Neutrophils: Neutrophils increased in the placebo group at Week 2, 6, and 12. In contrast, mean neutrophils declined in most dose groups and adalimumab at Week 2, 6, and 12. At Week 2, the decline in the 10 and 15 mg BID dose groups were significant relative to placebo. At Week 6, the decline in the 5, 10 and 15 mg BID dose groups were significant relative to placebo. At Week 12, the decline in the 3, 5, 10 and 15 mg BID dose groups were significant relative to placebo. In the adalimumab group, the decline in mean neutrophils was significant at Week 2 and Week 12 but not at Week 6.

Severe neutropenia (absolute neutrophil counts between 500 and 1000/microliter, inclusive) was observed at Week 2 in 1 subject in the 1 mg BID dose group, and at Week 4 for 1 subject in the adalimumab dose group. All other reported instances were mild.

Lipid Elevations: Dose-dependent increases in serum lipids (total cholesterol, HDL cholesterol [HDL-C], and LDL cholesterol [LDL-C]) were observed in CP-690-550 treatment groups. All treatment groups demonstrated increases from baseline in HDL and LDL over the 24 week period. The increases in both HDL-C and LDL-C were statistically significantly different from placebo in all CP-690,550 dose groups at all time points apart from the 1 mg BID dose group. Total cholesterol/HDL-C ratio was essentially unchanged over the 12 weeks, and no difference from placebo in this ratio was observed. The LDL/HDL ratio remained similar throughout the study.

Apolipoprotein: Apolipoprotein A-I showed an increase from Baseline in all treatment groups, including placebo, however these increases did not appear to be dose related. Apolipoprotein B showed an increase from Baseline in all treatment groups, including placebo, which appeared to be dose related, with a greater percentage increase observed at higher doses.

Serum Creatinine Assays: Small increases from Baseline were generally observed in mean serum creatinine levels at Weeks 2, 6, and 12, for all treatment groups, but the differences from placebo reached statistical significance at isolated time points only. The percentage of subjects with an increase of 50% over baseline at least once during the study, ranged from 1.8% to 8.2% across all CP-690,550 treatment groups, compared to 5.4% and 4.0% for the placebo and placebo (r) groups, respectively. These increases did not appear to be dose related.

A total of 23 subjects reported >50% increase in serum creatinine levels from baseline, 5 each in the 3 and 10 mg BID dose groups, 4 in the 15 mg BID dose group, 3 each in the adalimumab and placebo treatment groups, 2 in the 5 mg BID dose group and 1 in the 1 mg BID treatment group.

The CP-690,550 15 mg BID dose group was statistically significantly different from Baseline compared to placebo in creatinine clearance at Week 2 and 12. All other dose groups were not statistically significant at any of the remaining time points.

Transaminase Elevations: AST levels at >3 x ULN were observed in 1, 1, and 2 subjects in the 3, 5, and 15 mg BID, dose groups, respectively, and in no subject in the placebo or adalimumab treatment groups. ALT levels >3 x ULN were observed in 2 subjects each in the 15 mg BID and adalimumab dose groups, respectively, and in no subjects in the placebo treatment group.

AST levels at >2 x ULN were observed in 1, 1, 1, 2, 3 subjects in the 3, 5, 10, 15 mg BID and adalimumab dose groups, respectively. ALT levels >2 x ULN were observed in 2, 1, 1, 2 and 3 subjects in the 3, 5, 10, 15 mg BID and adalimumab dose groups, respectively. No subjects in the placebo group for AST or ALT levels <2 x ULN were observed.

No subject who experienced AST or ALT >3 x ULN also experienced an increase in total bilirubin >2 x ULN or 2 mg/dL.

An elevation in AST or ALT >3 X ULN, confirmed by 2 consecutive tests that did not resolve promptly with adjustment of concomitant medication, was a protocol mandated criterion for discontinuation from study. The percentage of subjects with ALT elevations >3 x ULN at least once during the study, ranged from 0% to 3.6% across all CP-690,550 treatment groups, compared to 0% for the placebo treatment group and 0% to 3.8% for adalimumab, respectively.

Platelets: In the placebo group, mean platelets increased at Week 2, 6, and 12 relative to baseline by 20.27, 15.08, and 27.26 x $10^3/mm^3$), respectively. In contrast, platelet levels decreased in all dose groups and adalimumab at Week 6 and 12 and these differences from placebo were all significant with the exception of the 1 mg BID group at Week 6. At Week 2, changes in mean platelets relative to baseline were mixed across the dose groups. At Week 2, mean platelets were significantly decreased relative to placebo in the adalimumab group.

In general, mean platelets decreased relative to placebo through Week 24. One subject in the 10 mg BID dose group experienced thrombocytopenia (platelets <0.5 x LLN, normal

baseline) laboratory test abnormalities when normal at baseline for platelets <0.5 x LLN during the double-blind treatment period, and 1 subject in the placebo group experienced elevated platelets >1.75 x ULN.

Other Safety Results: Small changes from Baseline in mean diastolic (range +2.49 to -1.77) and systolic (range +6.55 to -2.55) blood pressures were observed, but no dose–related trend was apparent and none of the changes were thought to be clinically significant. Statistically significant changes were observed for diastolic blood pressure at Week 10 for the 1, 3 and 5 mg and 15 mg BID dose groups and Week 12 for the 10 and 15 mg BID dose groups and adalimumab.

No IgG level was below 300 mg/dL at Week 24 (Table 13.5.18.1) and only 1 subject experienced a drop to <50% of baseline value. This subject was in the 1 mg BID dose group that was reassigned to the 5 mg bid dose group after Week 12.

Conclusions: CP-690,550 dosed 3–15 mg BID as monotherapy was superior to placebo in ACR20 response rates at Week 12:

- CP-690,550 5 mg BID was 34% age points above placebo (BOCF);
- CP-690,550 10 mg BID was 47% age points above placebo (BOCF).

All doses greater than 1 mg BID demonstrated efficacy at Week 2 as measured by ACR20 response rates (BOCF). A dose response for ACR20, ACR50 and ACR70 was observed across the CP-690,550 dose groups, apart from the 3 mg BID group, which did not show a dose repsonse for ACR50 at Weeks 2, 6 or 12:

- No dose response was observed for CP-690,550 1 mg BID
- CP-690,550 3 mg BID was less efficacious than 5 mg BID
- CP-690,550 5 mg BID was less efficacious than 10 mg BID
- CP-690,550 10 mg BID was generally less efficacous than 15 mg BID
- Adalimumab was efficacious at Week 12 as measured by ACR20 response rates.

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

HAQ: There was a dose and time dependent decrease in HAQ observed for all treatment groups, with 5, 10 and 15 mg BID showing a statistically significant separation from placebo at Week 12.

CRP: There were prompt reductions in all active doses, and prompt increases on placebo. Adalimumab appeared to lose some of its effect after Week 2.

CP-690,550 at doses of 1 mg BID, 3 mg BID, 5 mg BID, 10 mg BID, and 15 mg BID 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 small increases in serum creatinine.

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.

CP-690,550 was associated with an increased incidence of infection compared to placebo. There was no dose response for significant infections. No opportunistic infections were seen.

Longitudinal, dose-response models provided adequate descriptions of selected measures of efficacy (ACR20, ACR50 and ACR70) and safety (hemoglobin, neutrophils, serum creatinine, lipids) data to inform dose selection for future studies.

The data support the inclusion of both 5 and 10 mg BID in all Phase 3 studies.