CLINICAL STUDY REPORT SYNOPSIS: RA0010

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: CDP6038	**Volume:** Not applicable	
Name of active ingredient: olokizumab (CDP6038)	**Page:** Not applicable	

Title of study: A multicenter, randomized, double-blind, placebo-controlled, single dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of intravenous and subcutaneous CDP6038 in male and female subjects with rheumatoid arthritis on a stable dose of methotrexate

Investigator(s): Six Investigators enrolled subjects in the study.

Study site(s): Subjects were enrolled at 6 sites, 3 in USA and 3 in Germany

Publication(s) (reference[s]): None at the time of reporting.

Studied period: 4Q2009 to 3Q2010 **First subject enrolled:** 14 Oct 2009 **Last subject completed:** 20 Sep 2010	**Phase of development:** Phase 1/2a

Objective(s): The primary objectives of the study were to characterize the pharmacokinetic (PK)/pharmacodynamic (PD) relationship between systemic olokizumab (CDP6038) exposure and C-reactive protein (CRP) suppression, following single-dose CDP6038 administration via intravenous (iv) infusion and subcutaneous (sc) injection to subjects with rheumatoid arthritis (RA) and to evaluate the safety and tolerability of single doses of CDP6038 in RA subjects over a therapeutic dose range (as defined by CRP suppression). The secondary objectives of the study were to determine the absolute bioavailability of CDP6038 given via sc administration in comparison with iv infusion in subjects with RA, to assess the immunogenicity of single-dose CDP6038 in subjects with RA, and to assess, on an exploratory basis, changes in clinical response and other systemic biomarkers with CDP6038 dosing.

Methodology: The study was a randomized, double-blind, placebo-controlled, single-dose study in male and female subjects with RA and relatively low disease activity on stable doses of methotrexate (MTX). As a core design, the study consisted of 2 cohorts of subjects. The study was originally designed to recruit 36 subjects in both cohorts with a maximum of 72 subjects in total with a 3:1 randomization of active to placebo. Cohort 1 comprised 2 dose groups. Group 1 received iv CDP6038 at a dose of either 0.1mg/kg, 1mg/kg, or iv placebo, and Group 2 of Cohort 1 received sc CDP6038 at a dose of 1mg/kg or sc placebo. Based on 4-week PK/PD data from subjects in Cohort 1, an optimization step was performed to propose the doses and routes of administration to be evaluated in

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Cohort 2. In addition to safety and tolerability considerations, the optimized doses for Cohort 2 were derived by the UCB pharmacometrics team, utilizing CRP and CDP6038 plasma concentration-time data, for optimal exploration of the CRP response surface. The optimized dose and route of administration of CDP6038 selected for Cohort 2 was 3mg/kg sc. Protocol Amendment 5 introduced adaptability into the design of the study such that new literature or information could be incorporated into the PK/PD model and simulations and allow a re-estimation of sample size. As a result of this re-estimation the planned sample size of Cohort 1 was reduced to 24 subjects and the sample size for Cohort 2 was reduced to 12 subjects.

Subjects were randomized centrally either to CDP6038 or to placebo dosing (within each cohort) after successful screening in such a way as to ensure a reasonable spread of CRP values over the study as compared to the expected distribution of CRP values in the targeted population. This was achieved by means of a probability-based randomization method that aimed at maintaining, as closely as possible, the same proportion of subjects with low CRP values (<3.5mg/L) as subjects with high CRP values (≥3.5mg/L), while reducing, as much as possible, the number of subjects to be excluded at Screening as a result of low CRP values. Allocation to dose route (iv or sc) was open, but allocation to active or placebo medication was blinded. All subjects participated in 1 group only within the study and, thus, were dosed only once, either with CDP6038 or placebo.

Number of subjects (planned and analyzed): 72 subjects were originally planned (36 subjects in each of 2 cohorts). Following Protocol Amendment 5, a re-evaluation of sample size was performed which determined that the study objectives could be met with a reduced sample size of 36 subjects, ie, 24 subjects in Cohort 1 and 12 subjects in Cohort 2. However, Cohort 1 recruitment had already exceeded 24 subjects at the time of the re-evaluation (27 subjects) and Cohort 2 exceeded recruitment by 1 subject (13 subjects) giving a total of 40 subjects who were analyzed for the study.

Diagnosis and main criteria for inclusion: Subjects with a diagnosis of RA (according to the 1987 American College of Rheumatology criteria) of more than 6 months' duration, on a stable methotrexate (MTX) dose of 5 to 25mg/week for at least 3 months prior to Screening. Subjects with ≤9 swollen and ≤9 tender/painful joints (28-joint count) or a disease activity score 28-joint count based on C-reactive protein (DAS28[CRP]) of ≤5.10, and a minimum Screening CRP of 0.5mg/L.

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Test product, dose(s) and mode of administration, batch number(s):
CDP6038 0.1mg/kg and CDP6038 1mg/kg administered by iv infusion over 120 minutes, and CDP6038 1mg/kg and CDP6038 3mg/kg administered by sc injection. Batch numbers: BX1003315, BX1003888, BX1003316, BX1003889, BX1004059.

Duration of treatment: Single dose. The duration of the study for each subject was approximately 15 weeks, including a 3-week Screening Period and a 12-week postdose Follow-up Period.

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo (commercially available 0.9% sodium chloride for injection, administered by iv infusion or sc injection. Batch numbers: BX1003317, BX1003318, BX1003887.

Criteria for evaluation:

Pharmacokinetics:

- Concentration-time profiles of CDP6038 in plasma
- Standard non-compartmental PK parameters of CDP6038: maximum plasma concentration (C_{max}), clearance (CL), volume of distribution (V_d), area under the plasma concentration time curve from time 0 to infinity (AUC), time of maximum plasma concentration (t_{max}), and the terminal elimination half-life ($t_{1/2}$) of CDP6038 in plasma. An assessment of bioavailability, F, comparing the sc to iv exposure was also made.
- Anti-CDP6038 antibodies in plasma

Pharmacodynamics:

- Plasma concentrations of CRP.

Pharmacokinetics/pharmacodynamics:

- Clearance, V2 (volume of the central compartment), V3(volume of the peripheral compartment), V_{max} (maximal rate of non-linear clearance), K_m (Michaelis-Menten constant of non-linear clearance), EC50 (concentration leading to 50% of maximal CRP suppression), Gamma (slope of concentration effect on CRP suppression), and K_{eo} (the rate constant characterizing the lag-time between concentration and effect)

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Exploratory systemic biomarkers:

- Serum carboxy-terminal crosslinked telopeptide of type I collagen (CTX-I) and amino-terminal propeptide of type I procollagen (PINP); serum amino-terminal propeptide of type IIA procollagen (PIIANP) and urinary carboxy-terminal crosslinked telopeptide of type II collagen (CTX-II); matrix metalloproteinase 3 (MMP3) and vascular endothelial growth factor (VEGF)
- Serum amyloid A (SAA), fibrinogen, interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), soluble signal transducing receptor (sgp130), rheumatoid factor, anti-cyclic citrinullated peptide antibodies, anti-IL-6 autoantibodies, and antinuclear antibodies.

Clinical variables:

- DAS28(CRP)

Safety:

- Adverse event (AE) recording (nature, frequency, severity, and relationship to study drug)
- Vital signs (pulse rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], body temperature [oral])
- Physical examination
- Safety laboratory tests (hematology, clinical chemistry, and urinalysis)
- Standard 12-lead electrocardiogram (ECG)

Statistical methods:

Pharmacokinetics: Pharmacokinetic analyses were performed on the per-protocol PK population. CDP6038 plasma concentration-time data were listed and summarized by dose/route of administration and scheduled sampling time. Individual and geometric mean CDP6038 plasma concentration-time profiles were presented on a linear and semi-logarithmic scale. Anti-CDP6038 antibody data were listed and presented descriptively by dose/route wherever relevant.

The CDP6038 plasma concentration-time data were analyzed via noncompartmental analysis within WinNonlin (Version 5.2, Pharsight Corp.). The C_{max} and t_{max}, following iv and sc administration was derived directly from the observed data. The area under the plasma concentration-time curve, AUC(0-t), was calculated via the trapezoidal rule (linear up and log-linear down) within WinNonlin. An extrapolation of the area under the curve to

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infinity (AUC) was made according to the equation $AUC=AUC_{0-t}+Clast/\lambda_z$, where λ_z is the elimination rate constant, determined by linear regression of the log-transformed concentration-time data.

An estimate of the $t_{1/2}$, was also assessed according to the equation $t_{1/2}=\ln(2)/\lambda_z$.

The absolute bioavailability, F, of CDP6038 following sc administration, in comparison to that observed following iv administration was determined according to the following formula:

$$F = \frac{AUC_{sc} Dose_{iv}}{AUC_{iv} Dose_{sc}}$$

where AUC = mean area under the concentration time curve from time 0 to infinity for the dose group following iv or sc administration of CDP6038.

Pharmacodynamics: Pharmacodynamic analyses were performed on the per-protocol PD population (PPPD). Levels of CRP were listed by subject and dose/route and descriptive statistics tabulated per dose/route and for each time point as applicable. Descriptive statistics were also calculated for the percentage inhibition and for the intraindividual differences from predose for CRP within each dose/route group at each time point of determination as applicable. Individual graphs tracking a given subject were supplied, and the time course of mean (±standard deviation [SD]) percentage decrease in CRP values were presented graphically.

Pharmacokinetics/pharmacodynamics: The relationship between CDP6038 plasma concentration-time data and CRP suppression was explored via an inhibitory maximum effect (Emax) model with a lag-time between concentration and effect. The analysis was performed via nonlinear mixed effects modeling within the population modeling software NONMEM, Version VI, level 2.0. The data were analyzed during the study to support re-evaluation of the sample size and dose optimization, and a final analysis at the end of the study.

Exploratory biomarkers: Exploratory biomarker analysis was performed on the PPPD. All parameters were listed by subject and dose/route and summarized using descriptive statistics. Individual graphs tracking a given subject were supplied and the time course of the mean (±SD) percentage inhibition/stimulation was presented graphically, where applicable.

Clinical variables: The clinical variables analyses were performed on the per-protocol population for clinical efficacy (PPPC) and the intention-to-treat (ITT) population. The DAS28(CRP) was calculated according to the following formula:

$$DAS28(CRP)=0.56*\sqrt{TJC}+0.28*\sqrt{SJC}+0.36*\ln(CRP[mg/L]+1)+0.014*PtGADA(mm)+0.96$$

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Individual subject data on DAS28(CRP) were listed and descriptive statistics calculated by visit, dose/route, and overall. Changes from Baseline were also reported by visit, by dose/route, and overall. As CDP6038 is planned to be developed for patients with moderate to severe RA, ie, those with a DAS28(CRP) of >3.2, a posthoc descriptive analysis on DAS28(CRP) score was added to the planned analysis using a subgroup population, ie, subjects with a Baseline DAS28(CRP) >3.2.

Safety: Adverse events were classified according to the Medical Dictionary for Regulatory Activities. Incidence tables were used to summarize AEs by maximum event intensity, causal relationship with CDP6038, and by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grading. Laboratory values, vital signs, ECG, and changes from Baseline at Day 1 predose or Day -1 respectively were summarized by descriptive statistics per dose, route, and time point. Frequency tables of values outside the normal ranges were produced by treatment and time point for all safety parameters. Changes between Screening and Discharge laboratory parameters were presented in shift tables. Shift tables using the CTCAE Version 4.0 were also made by time point and by parameter for laboratory parameters having CTCAE grades. For lipids, the National Cholesterol Education Program (NCEP) classifications were used.

Summary and conclusions:

Subject disposition: A total of 40 subjects were randomized in 2 cohorts. Cohort 1 consisted of 5 treatment groups (CDP6038 0.1mg/kg iv+MTX [n=6], CDP6038 1mg/kg iv+MTX [n=7], placebo iv+MTX [n=5], CDP6038 1mg/kg sc+MTX [n=8], and placebo sc+MTX [n=1]) and a subsequent Cohort 2 consisted of 2 treatment groups (CDP6038 3mg/kg sc+MTX [n=9] and placebo sc+MTX [n=4]). In total, 30 subjects were randomized to treatment with CDP6038+MTX and 10 subjects to placebo+MTX. Thirty-eight subjects completed the study and 2 subjects, 1 in the placebo iv+MTX and 1 in the CDP6038 1mg/kg sc+MTX group, discontinued the study early due to an AE (exacerbation of RA symptoms) and a protocol deviation (taking prohibited concomitant medication predisolone), respectively.

Pharmacokinetic results: The maximum concentration following sc administration was achieved within a median of 7 days following CDP6038 3mg/kg and 13 days following CDP6038 of 1mg/kg. The estimate of $t_{1/2}$ was consistent regardless of route of administration or dose, ranging on a median basis from 21 to 36 days across the dose/route of administration groups. Overall, the median $t_{1/2}$ was 31 days (range 12 to 63 days). Bioavailability determined from the nonlinear mixed effects PK/PD modeling, pooling data from RA0001 and RA0010, was 75.6%. Noncompartmental analysis, based solely on

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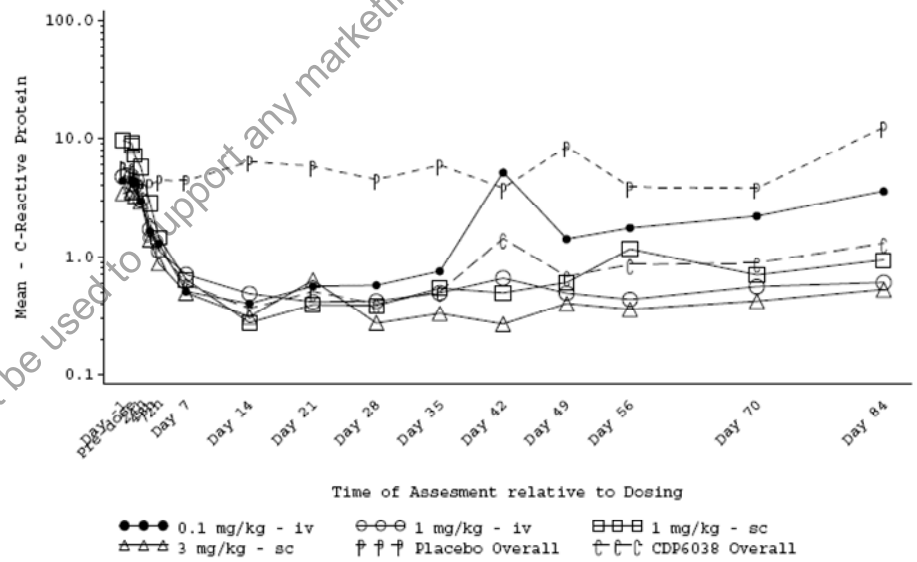
RA0010 data, yielded a bioavailability of 66.2%.

Antibodies to CDP6038 were detected in the plasma of 1 subject in the CDP6038 1mg/kg iv+MTX group only. The subject had anti-CDP6038 antibodies detectable (just above the LOQ, 0.15µg/mL) on Day 21, Day 28, and Day 35. There was no evidence of lower CDP6038 plasma concentrations in this subject at these time points compared to the other subjects in the same dose group. Apart from an upper respiratory tract infection on Day 21 the subject had no other AEs which were temporally related to the occurrence of anti-CDP6038 antibodies.

Pharmacodynamic results: Dose-dependent and sustained suppression of CRP levels was seen following CDP6038+MTX compared to placebo+MTX (see figure below). In the CDP6038 0.1mg/kg iv+MTX group CRP levels were seen to show signs of recovery within a few weeks while in the CDP6038 3mg/kg sc group the reductions in CRP were sustained to Day 84.

Mean CRP values (µg/mL) over time for each CDP6038 dose and route per time-point (semi-logarithmic scale) - PPPD



CRP=C-reactive protein; iv=intravenous; PPPD=per-protocol pharmacodynamic population; sc=subcutaneous

Pharmacokinetic/pharmacodynamic results: A pooled analysis of the final CDP6038 plasma concentration-time data from the first-in-human study, RA0001, and RA0010 was performed, via nonlinear mixed effects modeling within the population PK software

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(NONMEM). The data were adequately described by a 2-compartment, first-order absorption (sc administration) and first-order elimination model. Minimal nonlinear clearance or evidence of target mediated clearance was observed and could not be estimated within the model.

The relationship between CRP plasma concentration-time data and individual predicted CDP6038 plasma concentrations was graphically explored, and highlighted a lag-time between concentration and effect. The relationship between CRP plasma concentration-time data and individual predicted CDP6038 plasma concentrations was modeled using an inhibitory Emax model with a lag-time between CDP6038 plasma concentrations and CRP suppression within NONMEM. A summary of the population PK/PD parameters is EC50=0.415µg/mL(CV%=23.4%) and Gamma (γ) 0.86 (CV%=17.4%). The value of Emax was fixed to 0.99. It was possible to estimate between subject variability (IIV) on Baseline effect, EC50, γ and K_{eo}. Residual error was reasonably characterized by a proportional error model.

The final estimates of the population PK parameters of CDP6038 as well as the EC50 (µg/mL) against CRP suppression, were incorporated into a PK-PD simulation model for DAS28 (adaptation of the model described in Frey et al, 2007). An efficacy translation factor was also incorporated in the model, to translate a biomarker potency estimate to an efficacy estimate. The final simulations to inform the design of the subsequent Phase 2b study, were performed in R, and the predicted outcome for a 2 and 4 weekly sc regimen on a mg basis simulated, summarizing the % of patients with a DAS28 <2.6 at Week 24.

Exploratory biomarker results: For the markers of bone (CTX-I, PINP) and cartilage (CTX-II, PIIANP) turnover the data were very variable and there were no observable changes postdose. This was also true of the synovial abnormality marker MMP3. For the other synovial marker, VEGF, however, postdose reductions were seen by Day 14 in each of the CDP6038+MTX treatment groups (mean change from predose ±SD: -34.96±19.72pg/mL, -20.70±23.76pg/mL, -36.44±37.96pg/mL, and -31.77±41.86pg/mL in the CDP6038 0.1mg/kg iv, CDP6038 1mg/kg iv, CDP6038 1mg/kg sc, and CDP6038 3mg/kg sc+MTX groups, respectively) compared to placebo (+10.98±47.51pg/mL). For each of the CDP6038+MTX treatment groups, with the exception of the CDP6038 1mg/kg iv+MTX group, VEGF levels remained reduced, compared to predose values, at Day 84.

Reductions in SAA levels from predose were seen in all of the CDP6038+MTX treatment groups postdose. There was no clear dose-dependency, with the greatest reductions observed in the CDP6038 1mg/kg sc+MTX group, although this group also had the highest

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predose SAA levels. In all of the CDP6038+MTX treatment groups SAA levels remained suppressed, compared to predose, at Day 84. In the placebo+MTX group SAA levels remained relatively stable throughout the Treatment Period.

There was a rapid suppression of fibrinogen levels in each of the CDP6038+MTX dose groups during the first 72 hours postdose with further suppression seen up to Day 14. Fibrinogen levels remained suppressed compared to predose levels for the remainder of the study in each of the CDP6038+MTX groups except the lowest dose group, CDP6038 0.1mg/kg iv+MTX, where levels had returned to predose values by Day 84.

All CDP6038+MTX treatment groups showed a marked reduction in IL-6 levels (to 0.5pg/mL, the LLOQ of the IL-6 assay) at the first postdose assessment on Day 28. For all CDP6038+MTX treatment groups, IL-6 levels remained suppressed to the end of the study, although in the lowest dose group (CDP6038 0.1mg/kg iv+MTX) there was an indication of a slight recovery in IL-6 levels. Interleukin-6 levels remained relatively stable in the placebo+MTX group.

There was no obvious change in sIL-6R or sgp130 levels following CDP6038+MTX treatment at any of the doses or routes tested.

Clinical variable results: There were no meaningful changes in DAS28(CRP) in the placebo+MTX overall group. In the CDP6038+MTX overall group there was an indication of a slight reduction in DAS28(CRP) from Baseline (ie, an improvement) (maximum mean change from Baseline -0.906 on Day 56), which was maintained during the study, however, there was no clear dose-dependency, with the greatest reductions seen in the CDP6038 1mg/kg sc+MTX group (maximum mean change from Baseline -1.573 on Day 56).

However, it should be noted that for the overall study population the majority of subjects (57.5%) had low disease activity (ie, DAS28[CRP] ≤3.2), with 37.5% of subjects with moderate disease activity (DAS28[CRP] >3.2 to 5.1) and 5.0% of subjects with high disease activity (DAS28[CRP] >5.1) (1 subject in each of the placebo iv+MTX and CDP6038 1mg/kg sc+MTX groups). A post hoc analysis was therefore performed looking at DAS28(CRP) in subjects with a Baseline score >3.2, ie, moderate to high disease activity. Seventeen subjects in the PPPC fell into this category (3 subjects in the placebo+MTX overall group and 14 subjects in the CDP6038+MTX overall group), although 1 subject in the CDP6038 1mg/kg sc+MTX group withdrew from the study after Day 7, and so for all other time points data are only available from 16 subjects. Despite the small number of subjects with a Baseline DAS28(CRP) >3.2 there appeared to be a more definite indication of a treatment-related reduction in DAS28(CRP) in the CDP6038+MTX

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overall group (maximum mean reduction from Baseline -1.178 on Day 56), with the greatest and most sustained reduction observed in the CDP6038 1mg/kg sc+MTX group (maximum mean reduction from Baseline -1.975 on Day 56).

Safety results:

Adverse events: There were no deaths during the study. Two subjects (1 subject in the placebo iv+MTX group and 1 subject in the CDP6038 1mg/kg sc+MTX group) experienced SAEs: Grade 2 Bowen's disease and worsening of RA, respectively. Neither event was considered related to study drug by the Investigator. One subject in the placebo+MTX overall group withdrew from the study as a result of exacerbation RA. The incidence of treatment-emergent AEs (TEAEs) did not increase with increasing dose of CDP6038+MTX administered, although a slightly higher number of AEs were experienced by subjects in the 2 CDP6038+MTX sc treatment groups (16 subjects [94.12%] 101 events) compared to the 2 CDP6038+MTX iv treatment groups (13 subjects [100%], 54 events).

The most commonly reported TEAEs in the CDP6038+MTX overall group were in the system organ classes of infections and infestations, investigations, nervous system disorders, gastrointestinal disorders, skin and sc tissue disorders, and general disorders and administration site conditions.

The incidence of infections and infestations and nervous system disorders was higher in the CDP6038+MTX treatment group overall compared to the placebo+MTX group overall. Within the system organ class of infections and infestations, 16.7% of subjects in the CDP6038+MTX overall group had nasopharyngitis and upper respiratory tract infections compared to no subjects in the placebo+MTX overall group. None of the incidences of nasopharyngitis were considered related to study drug by the Investigator. Within the system organ class nervous system disorders, headache was the most commonly reported TEAE with 30% of subjects in the CDP6038+MTX overall group reporting the event compared to 10% of subjects in the placebo+MTX overall group.

According to CTCAE grading the majority of subjects (60.0% in the CDP6038+MTX overall group and 70.0% in the placebo+MTX overall group) had AEs that were CTCAE Grade 1. Eleven subjects (36.7%) in the CDP6038+MTX overall group and 3 subjects (30.0%) in the placebo+MTX overall group had 24 and 3 Grade 2 events, respectively. No subjects had Grade 3 or Grade 4 events. While the number of CTCAE Grade 1/Grade 2 events was higher in the CDP6038+MTX overall group compared to the placebo+MTX overall group, there was no clear dose relationship in the incidence of these events among the different CDP6038 treatment groups.

Fifteen subjects (50.0%) in the CDP6038+MTX overall group experienced 36 events that

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were considered by the Investigator to be related to IMP, in comparison to 12 events experienced by 4 subjects (40.0%) in the placebo+MTX overall group.

Clinical laboratory evaluations: For the majority of hematology parameters, there were no clinically significant differences in mean values between the placebo group and the different CDP6038 dose groups, and no clinically significant fluctuations in mean values over time. For leukocytes, and neutrophils, however, there were apparent reductions from Baseline following CDP6038 treatment. According to CTCAE grading there were no shifts from Baseline in any hematology parameter to Grade 4 during the study. One subject in the CDP6038 3mg/kg sc+MTX group had a 3 grade shift in neutrophil count from normal at Baseline to Grade 3 on Day 84. The Grade 3 neutropenia in this subject was not associated with any infection or fever, although the subject did have a urinary tract infection shortly after Day 35 when the subject's neutrophil count was low (Grade 2). Five subjects (3 in the CDP6038 1mg/kg sc+MTX group, and 1 in each of the CDP6038 0.1mg/kg iv and CDP6038 3mg/kg sc+MTX groups) had AEs of infection with an apparent temporal relationship to incidences of neutropenia.

There was no clear relationship between changes in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels over time and dose of CDP6038 administered. Increases AST and ALT levels from Baseline were seen in the first 7 to 14 days postdose, thereafter they were seen to return to near Baseline levels with the exception of the CDP6038 1mg/kg iv+MTX group where mean levels remained slightly elevated to the end of the study. The elevations in AST and ALT in the CDP6038 1mg/kg iv+MTX group were primarily driven by 1 subject who had Grade 1 and Grade 2 elevations in AST and ALT, respectively reported as AEs on Day 7 and intermittently high levels thereafter to study end. There were no CTCAE Grade 3 or 4 shifts in AST or ALT during the study.

Bilirubin levels in the placebo+MTX group were seen to fall during the study. In the CDP6038 0.1mg/kg iv, CDP6038 1mg/kg iv, and CDP6038 1mg/kg sc dose groups bilirubin levels were seen to increase from Baseline from Day 7 although there was no clear relationship between dose level and effect. Maximum postdose increases were 26.86% on Day 21 in the CDP6038 0.1mg/kg iv+MTX group, 20.89% on Day 28 in the CDP6038 1mg/kg iv+MTX group, and 28.04% on Day 42 in the CDP6038 1mg/kg sc+MTX group. Bilirubin levels in the CDP6038 3mg/kg sc group followed a saw-tooth pattern of alternating increases and decreases from Baseline. There were no shifts to Grade 3 or 4 in bilirubin levels in any of the treatment groups. One subject in the CDP6038 3mg/kg sc+MTX group, had a shift in her bilirubin levels from Grade 1 at Baseline (Day -1) to Grade 2 post Baseline, but this shift was not associated with any changes in the

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subject's ALT or AST levels which were in normal range throughout the study.

There were no changes in levels of total cholesterol, low density lipoprotein cholesterol (LDL), or high density lipoprotein cholesterol (HDL), following CDP6038 administration compared to placebo. However, 1 NCEP category shifts in total cholesterol (60.0% of CDP6038+MTX subjects vs 20.0% of placebo+MTX subjects) and LDL (30.0% of CDP6038+MTX subjects vs 10.0% of placebo+MTX subjects) were seen post Baseline which occurred in a higher percentage of CDP6038+MTX-treated subjects compared to placebo+MTX-treated subjects. Small increases in mean triglyceride levels from Baseline were seen in all CDP6038+MTX treatment groups, with the exception of the CDP6038 0.1mg/kg iv+MTX group. Maximum increases from Baseline ranged from 0.43mmol/L in the CDP6038 1mg/kg sc+MTX group (37.5% on Day 28) to 0.74mmol/L in the CDP6038 1mg/kg iv+MTX group (67.43% on Day 3). In general, the mean increases in triglyceride levels were maintained to Day 84. According to NCEP classification, no subjects in either treatment group had a 3 category shift in their triglyceride levels post Baseline and 2 NCEP category shifts in triglycerides were only seen in the CDP6038+MTX group (23.3% of subjects).

Overall, dose-related reductions in mean complement C3 and C4 levels were seen by Day 4 following CDP6038+MTX administration compared to placebo+MTX. For all but the CDP6038 0.1mg/kg iv+MTX group, which showed some recovery, these reductions were maintained to the end of the study but none were considered clinically significant by the Investigator.

There were no clinically significant changes in urinalysis parameters.

Vital signs: Vital sign parameters (respiration rate, pulse rate, body temperature, and blood pressure) and ECGs remained relatively stable throughout the study across the placebo and CDP6038 treatment groups. However, increases in SBP >10mmHg from Baseline were seen in a higher percentage of CDP6038+MTX treated subjects (76.7%) compared to placebo+MTX treated subjects (40.0%).

Conclusions: The PK and PD objectives of the study were met:

- Dose-dependent and sustained (through Day 84 [with the exception of the CDP6038 0.1mg/kg iv+MTX group]) suppression of CRP levels was seen following all doses of CDP6038+MTX compared to placebo+MTX.
- No significant evidence of target mediated clearance of CDP6038 was observed based on evaluation of the plasma concentration-time data and the derived parameters.

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- The maximum concentration of CDP6038 following sc administration was achieved within a median of 7 to 13 days following 3mg/kg and 1mg/kg, respectively.
- An estimate of the terminal elimination half-life across the doses and routes of administration was 31 days (median, range 12 to 63 days).
- Bioavailability determined from the nonlinear mixed effects PK/PD modeling, pooling data from RA0001 and RA0010, was 75.6%. Noncompartmental analysis of the data from RA0010 yielded a bioavailability of 66.2%.
- For the CRP-CDP6038 plasma concentration relationship, the final estimates of the PK/PD parameters EC50 and γ were 0.415µg/mL and 0.87, with a desired precision 23.4% and 17.4%, meeting the objectives of the study.
- Anti-CDP6038 antibodies were detectable in the plasma of 1 subject in the CDP6038 1mg/kg iv+MTX group alone but, with the exception of an upper respiratory tract infection, were not temporally related to the incidence of any AEs.

Exploratory biomarker and clinical variable analysis revealed:

- The antagonistic effects of CDP6038 on IL-6 were clearly demonstrated by the marked reductions in IL-6 levels observed in each of the CDP6038+MTX dose groups. The specificity of this action was shown by the lack of effect on the key components of the IL 6 receptor signaling complex: sIL-6R or sgp130.
- In line with the corresponding reduction in IL-6 levels, the acute phase proteins SAA and fibrinogen were also seen to be reduced following CDP6038+MTX administration although there was no clear dose-dependency.
- The data for the biomarkers CTX-I, PINP, CTX-II, and PIIANP were highly variable, and together with the short treatment duration preclude any meaningful assessment of CDP6038's effects on bone and cartilage turnover.
- The high variability of the data for the synovial abnormality biomarker, MMP3, also prevents conclusions being drawn (predose % CV 85.47% in the placebo+MTX overall group and 52.35% in the CDP6038+MTX overall group). However, the decreases in VEGF levels seen in each of the CDP6038+MTX dose groups do indicate a possible reduction in the activity (inflammation) in the synovium and show a potential for disease modification occurring in the pannus.
- There was an indication of the efficacy of CDP6038 in the subpopulation of subjects

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with a Baseline DAS28(CRP) of >3.2, ie, those with moderate to high disease activity. Although the number of subjects falling into this moderate to high category was small, improvements in DAS28(CRP) were seen following CDP6038+MTX administration, especially in the CDP6038 1mg/kg sc+MTX group.

Safety analysis showed that CDP6038 was tolerated at doses of up to 3mg/kg sc.

- One subject in each of the placebo+MTX and CDP6038 1mg/kg sc+MTX groups had SAEs: Grade 2 Bowen's disease and worsening of RA, respectively. Neither event was considered related to study drug by the Investigator.
- One subject in the placebo+MTX overall group withdrew from the study as a result of exacerbation of RA.
- The majority of AEs were of mild or moderate intensity.
- There were no CTCAE Grade 3 or Grade 4 TEAEs. Two subjects in the CDP6038 0.1mg/kg iv+MTX group experienced events of severe intensity (headache and vomiting), but both events were considered to be unlikely related to study drug by the Investigator.
- Treatment-related AEs were experienced by 40.0% of subjects in the placebo+MTX overall group and 50.0% of subjects in the CDP6038+MTX overall group.
- The most frequently reported TEAEs (occurring in ≥2 subjects in any treatment group) included headache experienced by 30.0% of subjects in the CDP6038+MTX overall group compared to 10.0% of placebo+MTX-treated subjects, and nasopharyngitis, and upper respiratory tract infection both experienced by 16.7% of subjects in the CDP6038+MTX overall group compared to no subjects in the placebo+MTX group. None of the incidences of nasopharyngitis were considered related to study drug by the Investigator.
- Drug-related decreases in neutrophils (>32% of Baseline) and leukocyte counts (>26% of Baseline), which were maintained to Day 84, were observed following administration of all CDP6038 dose levels but there was no clear dose-dependency. Five subjects (3 in the CDP6038 1mg/kg sc+MTX group, and 1 in each of the CDP6038 0.1mg/kg iv and CDP6038 3mg/kg sc+MTX groups) had AEs of infection with an apparent temporal relationship to incidences of neutropenia.
- Dose-dependent reductions in complement (C3 and C4) levels were also seen. The

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reductions were not considered clinically significant by the Investigator.

- Increases in bilirubin levels (>20% of Baseline) were observed following an initial drop from Baseline in the CDP6038 0.1mg/kg iv, 1mg/kg iv, and 1mg/kg sc+MTX groups but there was no clear relationship between dose level and effect, and the elevations were not maintained to the end of the study. Increases in ALT (>25% of Baseline) and AST (>16% of Baseline) were seen in the first 7 to 14 days postdose in the CDP6038 0.1mg/kg iv, 1mg/kg iv, and 1mg/kg sc+MTX groups, but levels only remained slightly elevated to the end of the study in the CDP6038 1mg/kg iv (AST and ALT) and CDP6038 1mg/kg sc+MTX (ALT) groups. There was no clear dose-response.
- With the exception of triglycerides where small mean increases from Baseline were observed in all but the lowest CDP6038 dose group (range 37.5% in the CDP6038 1mg/kg sc+MTX group to 67.4% in the CDP6038 1mg/kg iv+MTX group), there was little change in the mean lipid values over time. However, 1 NCEP category shifts in total cholesterol (60.0% of CDP6038+MTX subjects vs 20.0% of placebo+MTX subjects) and LDL (30.0% of CDP6038+MTX subjects vs 10.0% of placebo+MTX subjects) were seen post Baseline and 2 NCEP category shifts in triglycerides were only seen in the CDP6038+MTX group (23.3% of subjects).
- Vital sign parameters and ECGs remained relatively stable throughout the study. Increases in SBP >10mmHg from Baseline were seen in a higher percentage of CDP6038+MTX treated subjects (76.7%) compared to placebo+MTX (40.0%), however due to the small numbers of subjects in each group no conclusions can be drawn.

Report date: 29 Mar 2011