Safety and Pharmacokinetics of Olokizumab, an Anti-IL-6 Monoclonal Antibody, Administered to Healthy Male Volunteers: A Randomized Phase I Study

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Interleukin-6 (IL-6) is implicated in the pathophysiology of several inflammatory conditions. Olokizumab, a humanized anti-IL-6 monoclonal antibody, selectively blocks the final assembly of the IL-6 signaling complex. A randomized, double-blind, placebo-controlled, phase I dose-escalation study assessed the safety and tolerability of escalating single doses of olokizumab administered intravenously (iv) or subcutaneously (sc) to 67 healthy male volunteers. The pharmacokinetics, pharmacodynamics and immunogenicity of olokizumab were also assessed. Olokizumab was tolerated at doses up to 3.0 mg/kg sc and 10.0 mg/kg iv; the maximum tolerated dose was not reached. No serious adverse events or withdrawals as a result of treatment-emergent adverse events were reported. Pharmacokinetic analysis showed that both maximum serum concentration and area under the concentration-time curve increased linearly with increasing dose. Mean terminal half-life was 31.5 days (standard deviation 12.4 days). The bioavailability of the sc doses ranged from 84.2% to 92.5%. Rapid decreases in C-reactive protein concentrations were observed, with no dose dependency.

Keywords
anti-IL-6, first in human, olokizumab, pharmacokinetics, safety
in RA. This suggestion is supported by a mathematical-model system.

Olokizumab is a humanized anti-IL-6 monoclonal antibody that selectively blocks the final assembly of the IL-6 signaling complex. A phase I study was designed to assess the safety, tolerability, and pharmacokinetics (PK) of olokizumab (ClinicalTrials.gov, NCT01276119).

Methods

Study Design

This was a phase I, single-center, randomized, double-blind, placebo-controlled, single-dose, dose-escalation study of olokizumab in 11 cohorts of six healthy male volunteers.

The starting dose was determined by considering the most recent recommendations, and regulatory guidelines. Specifically, the starting dose (0.001 mg/kg) was an order of magnitude below both the pharmacologically active dose for olokizumab in the human IL-6-induced serum amyloid A bioassay in mice and the maximum recommended starting dose calculated from the no adverse event level (NOAEL) from a toxicology study (NOAEL established at 50 mg/kg by weekly, iv or sc, negative-controlled administration of olokizumab for 4 weeks in male and female cynomolgus monkeys, unpublished data). Furthermore, ligand occupancy calculations for anticipated maximum olokizumab concentration in plasma, based on the activity of olokizumab in an in vitro whole human blood assay (IL-6-induced STAT3 phosphorylation), predicted ligand occupancy of 25% for a dose of 0.001 mg/kg (unpublished data). Thus, overall, the 0.001 mg/kg dose was deemed a safe starting dose for the study, based on the integration of all available pertinent data.

Subjects were randomized (1:1) to one of 11 doses of olokizumab or placebo: iv dosing, infused over 120 min, started at 0.001 mg/kg and increased to 10.0 mg/kg using eight dose steps (0.001, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg); sc dosing was at 0.3, 1.0, or 3.0 mg/kg. Dose escalation was staggered. To allow for an appropriate observation after each dose, the time interval between doses within a cohort was at least 48 hours for iv and 96 hours for sc administration.

Escalation of the iv dose, or change to the sc route of administration were recommended by the Safety Review Committee based on review of ≥7 days of safety data after the last administered dose, as well as on dose and study procedure adjustments.

The study site was: PAREXEL International GmbH, Institut für Klinische Pharmakologie, on the premises of DKF Kliniken Berlin Westend, D - 14050 Berlin, Germany. The study protocol was reviewed and approved by the German regulatory authority and the Independent Ethics Committee (IEC), and complied with the principles of Good Clinical Practice and the Declaration of Helsinki.

The IEC name and address were: Landesamt für Gesundheit und Soziales Ethik-Kommission des Landes Berlin, Sächsische Strasse 28, D - 10707 Berlin, Germany.

Volunteers

Eligible volunteers were men, 18–60 years of age. Main exclusion criteria included: clinically significant concomitant chronic or acute illness; history of significant adverse reaction to biological products; live or attenuated vaccination within the previous 3 months; and having received immunoglobulins within the previous 6 months.

Assessments

The intent-to-treat (ITT) population, used for safety and tolerability assessments, was defined as randomized subjects who had received at least one dose of olokizumab or placebo. The per-protocol (PP) population, used for secondary assessments, was defined as subjects in the ITT population who had no major protocol deviations affecting PK variables.

The safety variables evaluated were: AE recording (nature, frequency, severity, and relationship to investigational drug); safety laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis); vital signs; physical examination; and standard 12-lead electrocardiogram. Safety assessments were carried out at scheduled visits from Day −1 to Day 8, and at follow-up visits every 2 weeks from Day 15 to Day 99. Adverse events were assessed throughout the study by the investigating physician and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.0).

PK measurements included: concentration–time profiles of olokizumab in plasma; standard non-compartmental PK parameters (maximum plasma concentration [Cmax], area under the concentration–time curve from time 0 up to the time of the last sample with a quantifiable level [AUC0–t], time of maximum plasma drug concentration [tmax], terminal elimination half-life [t1/2], apparent total body clearance [CL/F], apparent volume of distribution [V/F] and anti-olokizumab antibodies in plasma. PD measurements included: plasma concentrations of CRP, haptoglobin, serum amyloid A protein, serum amyloid P, IL-6, and soluble IL-6R and gp130. The assays for IL-6 (Biosource [Invitrogen] Human IL-6 Ultrasensitive ELISA, K11C0063), IL-6R (R&D Human sIL-6R Immunoassay, DR600), and gp130 (R&D Human soluble gp130 Quantikine kit, DGP00) were validated with a range of olokizumab concentrations, up to 100 µg/mL. The sIL6R and gp130 assays were unaffected by addition of olokizumab. The assay chosen to determine IL-6 levels was shown to be inhibited by olokizumab. As a result, only baseline IL-6 levels were free (unbound) IL-6. For post-dose samples the assay detected IL-6 in the presence of drug as the IL-6/olokizumab complex.
Blood samples for determination of plasma concentrations of olokizumab and PD measurements were taken pre-dose on Day 1; 1 hour post-dose for subjects in the iv dose step 1 only; 2 hours post-dose for subjects in iv dose steps 2–8 only; 4 hours post-dose for all iv dose groups; and 6 and 12 hours post-dose on Days 2–8 and Days 15, 29, 43, 57, 71, 85, and 99 for all subjects. Plasma concentrations of olokizumab were measured using an electrochemiluminescence assay. Briefly, olokizumab in the sample bound to biotinylated human IL-6, and the complex was subsequently immobilized on 96-well standard-bind, Streptavidin-coated Meso Scale Discovery (MSD) plates. A wash step removed any unbound antibodies. A SULFO-TAG\textsuperscript{TM} anti-human kappa antibody detected the immobilized complex; MSD read buffer was then added, which reacted with the SULFO-TAG\textsuperscript{TM}, completing the chemiluminescent reaction. The light emitted was quantified using the MSD Sector Imager 6000 system. The light signal was proportional to the amount of olokizumab in the sample. The dynamic range of the calibration curve used was 0.015–0.500 mg/mL, allowing for sample dilution.

Anti-drug/olokizumab antibodies (ADAs) in plasma were measured in samples collected for PK analysis pre-dose, and from 168 hours post-dose onwards. ADAs were measured by enzyme-linked immunosorbent assay. ADAs in the sample bound to olokizumab immobilized on a 96-well plate. Biotinylated olokizumab was introduced and bound to the captured anti-olokizumab. Streptavidin-horseradish peroxidase (SA-HRP) was subsequently bound to the biotinylated olokizumab. A 3,3',5,5'-tetramethylbenzidine substrate reacted with bound SA-HRP and the color generated was measured by absorbance. Color development was proportional to the amount of ADAs present in the sample. The dynamic range of the calibration curve used was 0.015–0.500 µg/mL, allowing for sample dilution.

**Statistical Analysis**

**Statistical Methods Software.** Statistical evaluation was performed using SAS software package version 9.1 (SAS Institute, Inc., Cary, NC). Standard non-compartmental PK parameters were calculated using WinNonlin\textsuperscript{8} version 5.2 (Pharsight, Mountain View, CA).

**Pharmacokinetic Analyses.** Descriptive statistics included n, n ≥ LLOQ, mean, standard deviation, coefficient of variation, median, minimum and maximum, geometric mean, and geometric coefficient of variation. A linear model, with ln(dose) as fixed effect, was estimated for each route of administration separately to assess the dose proportionality for AUC\textsubscript{0–t}, AUC, and \(C_{max}\). Dose dependence for \(V_z/F\), \(CL/F\), and \(t_{1/2}\) was also investigated for each route of administration separately.

The \(C_{max}\) and \(t_{max}\) were derived by observing the olokizumab time–concentration profiles. Linear regression was used to estimate the terminal elimination rate constant (\(\lambda_z\)) and \(t_{1/2}\) was subsequently estimated as being equal to \(\ln(2)/\lambda_z\). The AUC\textsubscript{0–t} was calculated by applying the linear up/log down trapezoidal rule. The area under the concentration–time curve from time zero to infinity (AUC\textsubscript{0–inf}) was determined as AUC\textsubscript{0–t} + \(C_t/\lambda_z\), where \(C_t\) is the last measurable concentration at time \(t\). The total clearance (CL or CL/F, F being the fraction of dose absorbed for sc administration) was calculated as dose/\(AUC_{0–inf}\).

The volume of distribution for the elimination phase (\(V_z\) or \(V_z/F\)) was calculated as dose/(\(\lambda_z AUC_{0–t}\)).

Absolute bioavailability was estimated for the 0.3, 1.0, and 3.0 mg/kg doses using the following formula:

\[
F = \frac{AUC_{sc} \cdot Dose_{sc}}{AUC_{iv} \cdot Dose_{iv}}
\]

where \(AUC_{sc}\) is the area under the curve following sc administration and \(AUC_{iv}\) is the area under the curve following iv administration. \(Dose_{sc}\) is the dose (mg/kg) following iv administration, and \(Dose_{sc}\) is the dose following sc administration.

**Results**

**Study Population**

Sixty-five of 67 randomized subjects completed the study (Supplementary Figure S1). Two subjects in the placebo group withdrew for personal reasons not related to AEs after dosing had been initiated. All 67 treated subjects were included in both ITT and PP populations. Demographic characteristics were generally similar between treatment groups (Supplementary Table S1).

**Safety**

**Adverse Events.** The overall occurrence of treatment-emergent AEs (TEAEs) with placebo (18 subjects; 52.9%) and olokizumab (11 subjects; 33.3%) is presented in Supplementary Table S2 and Supplementary Figure S2a. No deaths or serious AEs were reported, and no subjects withdrew from the study as a result of TEAEs. There was no dose-dependent increase in reported TEAEs for either iv or sc dose ranges of olokizumab, with one TEAE occurring in each of the 0.001, 0.01, 0.03, 0.1, and 10.0 mg/kg iv and 1.0 and 3.0 mg/kg sc groups, and two in the 0.3 mg/kg iv and sc groups (Supplementary Figure S2b).

Most TEAEs reported with olokizumab or placebo were Grade 1 or 2 (Supplementary Figure S3a). One subject in the olokizumab 0.3 mg/kg iv group had a Grade 3 increase in aspartate aminotransferase (AST) and Grade 4 elevated creatine kinase (see next section). The incidence of Grade 3 or 4 TEAEs did not increase with increasing doses of olokizumab (Supplementary Figure S3b). The only TEAE
considered to be related the study drug was mild headache (one in each of the placebo iv and the olokizumab 0.3 mg/kg iv groups). No deaths or serious TEAEs, and no discontinuations due to TEAEs occurred during the study.

Clinical Biochemistry and Hematology. Overall, changes in mean serum AST concentrations in the olokizumab groups were similar to those seen in the placebo groups. An increase in AST concentration, considered unrelated to the investigational drug, was observed in the aforementioned subject in the olokizumab 0.3 mg/kg iv group (4.6 times the upper limit of the normal range; Grade 3 TEAE). This subject also had increases in alanine aminotransferase (ALT; 1.43 times the upper limit of the normal range) and creatine kinase (16659.7 U/L; Grade 4 TEAE). The subject reported having undertaken physical activity in the days before the scheduled visit on Day 29. Follow-up assessment showed return to normal ranges for all parameters, within 8 days for creatine kinase and AST, and within 14 days for ALT.

Overall, serum ALT concentrations increased slightly in the olokizumab groups, with a maximum mean value of 78.7 IU/L on Day 29, but there was no clear dose-dependent effect.

Increased mean serum total bilirubin concentrations were observed at the higher olokizumab dose levels (up to 24.10 μmol/L for 10.0 mg/kg iv). These increases were not associated with elevations in AST or ALT.

Mean decreases in plasma fibrinogen concentrations from baseline (maximum reductions of 19.2% and 1.5% in the olokizumab and placebo groups, respectively) were not associated with AEs. No subject had abnormally high fibrinogen levels during the study and, overall, 24 (72.7%) subjects administered olokizumab had abnormally low fibrinogen levels, compared with only one (2.9%) subject in the placebo groups. In total, 15 (45.5%) subjects in the olokizumab groups had a shift in their fibrinogen levels from baseline to Grade 2 after treatment administration, compared with no subjects in the placebo groups.

Mean total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol plasma concentrations remained stable throughout the study. Small increases in mean triglyceride plasma concentrations from baseline were observed in all olokizumab and placebo groups by Day 8 post-dose (maximum increases: from 0.117 mmol/L in the olokizumab 3.0 mg/kg sc group to 1.220 mmol/L in the olokizumab 3.0 mg/kg iv group).

Reductions in leukocyte counts from baseline were observed with olokizumab overall compared with placebo overall, with maximum mean reductions of 22.6% on Day 2 (to 4.589 g/L) maintained until Day 85, versus 10.9% on Day 85 (to 5.331 g/L), respectively. Neutrophil counts also decreased from baseline with olokizumab overall compared with placebo overall, with maximum mean reductions of 28.9% on Day 2 (to 2.150 g/L) versus 12.2% on Day 85 (to 2.767 g/L), respectively. Overall, there was no apparent dose or time dependency associated with neutrophil count abnormalities and no association with AEs.

Immunogenicity
ADAs were detected in the plasma of two subjects (in the 0.3 mg/kg iv and 1.0 mg/kg sc groups). However, both subjects tested positive for ADAs only in their pre-dose

| PK parameter | 0.3 mg/kg sc (n = 3) | 1.0 mg/kg sc (n = 3) | 3.0 mg/kg sc (n = 3) |
|--------------|----------------------|----------------------|----------------------|
| C_{max} (μg/mL) | 2.99 (0.271) | 6.97 (0.313) | 22.3 (4.48) |
| t_{max} (hours) | 120 (96.0, 168) | 336 (168, 337) | 168 (144, 168) |
| AUC_{0-τ} (h μg/mL) | 2.704 (886) | 8.273 (1843) | 24,723 (2145) |
| AUC_{0-inf} (h μg/mL) | 2.988 (1.124) | 9.990 (3.881) | 30,444 (4.913) |
| τ_r (days) | 24.2 (11.1) | 33.3 (16.3) | 39.2 (10.4) |
| CL/F (L/day) | 0.204 (0.083) | 0.193 (0.040) | 0.178 (0.042) |
| V_z/F (L) | 6.23 (1.36) | 8.68 (2.66) | 9.71 (1.70) |
| Bioavailability (F) | 85.7% | 92.5% | 84.2% |

Data are presented as the arithmetic mean (SD). AUC_{0-inf} area under the concentration–time curve extrapolated to infinity; AUC_{0-τ} area under the concentration–time curve from time = 0 up to the time of the last sample with a quantifiable level; CL/F, apparent total body clearance; t_{max}, maximum plasma drug concentration; F, bioavailability; τ_r, terminal elimination half-life; t_{τ}, time of maximum plasma drug concentration; V_z/F, apparent volume of distribution.

*Median value (range).

The extrapolated AUC_{0-inf} was more than 20% for one subject in the 1.0 mg/kg group and one subject in the 3.0 mg/kg group.

The time interval used to estimate the τ_r was less than 2 t_{τ} for one subject in the 1.0 mg/kg group and one subject in the 3.0 mg/kg group; with half-lives reported equal to 50.6 and 49.5 days, respectively.
sample, and there was no evidence of lower plasma concentrations of olokizumab post-dose compared with other subjects in their respective dose groups.

**Pharmacokinetics**

The PK parameters are summarized in Tables 1 and 2. Mean plasma concentration–time profiles increased linearly with escalating doses of olokizumab (Figure 1, Tables 1 and 2). An initial slower rise in mean plasma concentration–time profiles was observed for the three sc doses compared with the iv doses. The $t_{\text{max}}$ for the sc doses ranged from 4 to 14 days. Mean AUC$_{0-\text{inf}}$ (where estimated), AUC$_{0-t}$, and C$_{\text{max}}$ increased linearly with escalating doses, regardless of the route of administration (Supplementary Figure S4).

For the olokizumab group overall (iv and sc dosing), the mean $t_{\text{1/2}}$ was 31.5 days (standard deviation 12.4 days). Mean CL was 0.149 L/day in the olokizumab iv groups overall, and CL/F was 0.186 L/day in the sc groups overall. The $t_{\text{1/2}}$, volume of distribution, and clearance were all independent of olokizumab dose and route of administration (Supplementary Figure S5). Absolute bioavailability, which was measured for the three sc doses, ranged from 84.2% to 92.5% (Table 1).

**Pharmacodynamics**

Mean serum CRP concentrations were reduced both after iv and sc administration of olokizumab. The extent and duration of reduction as well as time to maximum reduction varied widely across groups. Higher reductions compared to placebo were seen in higher dose groups.

Mean serum haptoglobin concentrations were not affected in any of the olokizumab sc dose groups or the lower olokizumab iv dose groups (up to 0.1 mg/kg iv) compared with placebo. In the higher olokizumab iv dose groups ($\geq$0.3 mg/kg iv), mean haptoglobin concentrations were reduced compared with placebo from Day 15–29 until Day 99.

Due to insufficient data it was not possible to determine whether there were meaningful or consistent differences in serum amyloid A or P concentrations compared with placebo. Low number of subjects per group and variability preclude any further interpretation for any of the aforementioned PD assessments.

Mean total IL-6 concentrations (sum of free and complexed with olokizumab) increased with increasing olokizumab dose and reached a plateau around Day 15 post-dose. The elevated IL-6 levels were maintained through to Day 99. No changes in IL-6R or gp130 concentrations were observed.

**Discussion**

These data provide evidence that olokizumab, a humanized anti-IL-6 monoclonal antibody, is tolerated
at doses of up to 3.0 mg/kg sc and 10.0 mg/kg iv in healthy male volunteers, with bioavailability data supporting sc dosing. The occurrence of TEAEs was generally lower in the olokizumab treatment groups than in the placebo groups. In addition, in this population of healthy subjects, olokizumab was not associated with an increased incidence of upper respiratory tract infections, as has been observed with other immune-targeted biological agents.8–10,19–21 In fact, nasopharyngitis and rhinitis were less common in the olokizumab groups than in the placebo groups (one vs. three events and zero vs. three events, respectively). Ongoing clinical studies will confirm whether olokizumab has any impact on respiratory infections in patients with RA.

Targeting the IL-6 signaling complex has the potential to affect liver function owing to its role in metabolic processes of the liver,3 which might be manifested as increases in AST, ALT, and bilirubin concentrations; increases in lipids; and decreases in CRP and other acute-phase proteins and fibrinogen concentrations.7,8 Clinical evidence with tocilizumab has shown transient increases in mean hepatic aminotransferase concentrations, although these were not associated with concomitant increases in bilirubin (an important marker of potential liver toxicity) or with any clinical symptoms of hepatic dysfunction.8–10 In the present study, AST concentrations were generally unaffected by olokizumab administration, and overall, slight increases in ALT concentrations were observed in the olokizumab groups, although with no clear dose dependency. Increases in bilirubin concentrations were observed at the higher olokizumab dose levels (3.0 mg/kg sc and iv and 10.0 mg/kg iv) but there was no indication that this change was dose dependent. It is unclear why inhibition of IL-6 signaling might be associated with isolated hyperbilirubinemia and this will need to be examined further in clinical studies.

IL-6 decreases hepatic synthesis and secretion of lipoproteins, which leads to a reduction in serum low-density lipoprotein cholesterol concentrations.2 IL-6 decreases hepatic synthesis and secretion of lipoproteins, which leads to a reduction in serum low-density lipoprotein cholesterol concentrations.2 In this study, plasma lipid concentrations remained stable after a single administration of olokizumab, with only small increases in mean triglyceride concentrations from baseline observed in all olokizumab and placebo groups by Day 8 post-dose.

Overall, low number of subjects per cohort and study variability hindered interpretation and analysis of PD data. CRP and serum amyloids A and P are markers of the acute-phase response.5 CRP levels were reduced at all doses of olokizumab compared with placebo, with the largest reductions observed at the highest doses, whereas serum amyloid A and P concentrations seemed to remain stable throughout the study, based on the data collected. It is important to note, however, that these latter markers may be relatively insensitive in a healthy volunteer population, and further examination in clinical studies will provide greater insights.

The stimulation of fibrinogen synthesis during an acute-phase reaction is mediated by cytokines; IL-6 directly upregulates fibrinogen gene expression and, therefore, has an important role in the increase of fibrinogen synthesis.22,23 In this study, inhibition of IL-6 signaling by olokizumab was associated with a dose-dependent reduction in fibrinogen in these healthy subjects, although these changes were not
associated with events of bleeding or clotting parameter abnormalities.

Neutrophils are important mediators of inflammation in RA, because of their ability to secrete proteolytic enzymes and reactive oxygen intermediates.7 Transient decreases in absolute neutrophil counts have been observed in clinical trials of tocilizumab in patients with RA,5,10 as inhibition of IL-6 function is known to margenate neutrophils, leading to a decrease in the number of circulating neutrophils.24 In the present study, mild drug-related reductions in neutrophil counts were observed after administration of all olokizumab dose levels, with no apparent dose–response relationship.

The rate of clearance of endogenous cytokines, such as IL-6, from the circulation is several-fold greater than that of whole immunoglobulin G antibodies. As a result, the clearance rate of the olokizumab/IL-6 complex (which is incapable of signaling), would be expected to be closer to that of olokizumab than that of endogenous IL-6 alone. Consistently with this, in the present study, serum concentrations of total IL-6 (i.e., sum of free IL-6 and IL-6 complexed with drug), increased with increasing doses of olokizumab administered and accumulated over time, before reaching a steady-state on Day 15.

Finally, PK analyses showed that both Cmax and AUC increased linearly with increasing dose. There was no apparent indication of target-mediated clearance, in contrast to what was observed in the tocilizumab studies.25 This finding is consistent with a previous report of another anti-IL6 antibody, sirukumab26 and can be attributed to the qualitative and quantitative differences between the two targets, IL-6 and IL-6R.27,28

Currently available biological therapies, especially anti-TNF agents, represent a significant advance in the treatment of RA.3 However, some patients do not show an adequate response or do not maintain a response to treatment with these agents, or experience prohibitive AEs. Therefore, a need remains for additional agents with proven efficacy and a favorable safety and tolerability profile.4 The findings of this study support the ongoing clinical evaluation of olokizumab in patients with moderate to severe RA.

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Declaration of Conflicting Interests
Kosmas Kretos, Suzanne McCabe, Stevan Shaw, Joby Jose, Ruth Oliver are UCB employees. Astrid Jullion and Matthew Hickling were UCB employees at time of presented work. Georg Golor has no disclosures.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site.