Model-Based Optimal Design and Execution of the First-Inpatient Trial of the Anti-IL-6, Olokizumab

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The first-in-patient study for olokizumab (OKZ) employed model-based, optimal design and adaptive execution to define the concentration–C-reactive protein (CRP) suppression response. Modeling and exploratory statistics activities involved: reverse engineering of first-in-class (tocilizumab) pharmacokinetic/pharmacodynamic (PK/PD) models, adaptation of models to OKZ with a priori knowledge and preclinical data translation, application of multidimensional Desirability Index for optimal study design, sample size reestimation based on new information, optimization of second study part via Bayesian analysis of interim data, and interim and final analysis for PK/PD objective attainment. Design work defined a dose window (0.1–3 mg/kg) for CRP suppression exploration and suggested 72 patients in five single-dose levels would suffice. During execution, new information resulted in reestimating the study size to half. Halting the first part and conducting interim analysis for second part optimization followed. Second interim and final analyses confirmed attainment of study objective, illustrating efficiency and optimality of the study.

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Olokizumab (OKZ) is a humanized monoclonal antibody, directed against interleukin-6 (IL-6), a pleiotropic cytokine that has been implicated in the pathophysiology of rheumatoid arthritis (RA). IL-6 has been linked with C-reactive protein (CRP), an acute inflammation protein whose production from hepatocytes is regulated by IL-6 signaling. CRP, in turn, is a marker of disease activity and therapeutic response in RA.

TCZ is the first in the class of IL-6 signaling inhibitors, a humanized monoclonal antibody directed against the IL-6 receptor (IL-6R), developed by Chugai-Roche and approved for the treatment of RA. In addition to these external clinical data and model, preclinical in vitro and in vivo animal study data were available. Importantly, these preclinical investigations provided comparative data between OKZ and an in-house anti-IL-6R antibody (Supplementary Figure S1). Integration of all available data led to reverse engineering of the published TCZ model and its translation to OKZ in the form of three potential PK/PD model parameterizations (Supplementary Table S1). These three models were employed to perform simulations of different clinical trial scenarios perturbing a six-dimensional design space. The assessment of each potential design was driven by the need to reduce the uncertainty of the common-link function between the PK and PD parts of the three considered models: a logistic function of CRP levels as a function of OKZ concentration. The quality of each potential design was evaluated by considering estimates of bias and precision of the logistic function’s parameters for each of the three models within a global desirability analysis to identify the optimal one: linear desirability functions were defined first, to ensure target bias at 0 and minimal SE with predefined maximal acceptable CV%, respectively. The desirability functions were combined using a weighted geometric mean, with different weights for each potential model, to obtain a global Desirability Index which translated the objectives of the study (acceptable precision and bias for two PK/PD parameters) and allowed investigation of the interactions and trade-offs between the various design elements quantifying their combinatorial impact (see Methods).

During Cohort 1 recruitment, integration of pertinent data (first-in-human PK, TCZ published information) led to...
RESULTS
Reverse engineering of TCZ models and adaptation to OKZ
The reverse-engineered version of the published\textsuperscript{12} TCZ PK/PD model provided the scaffold for knowledge-based adaptation to OKZ based on translation of preclinical pharmacology and disease target biology data. This adaptation, given the uncertainty stemming from translating preclinical and literature-based data, yielded three different model parameterizations. The model “adjusted PK” pertained to a parameterization for which OKZ linear clearance and maximum rate of nonlinear clearance ($V_{\text{max}}$) were lower than TCZ with all other parameters remaining the same (based on relative abundance of IL-6 vs. IL-6R and difference in antibody subtype). Conversely, the model “adjusted potency” pertained to a parameterization for which OKZ had lower half-maximal concentration for CRP suppression (EC$_{50}$) with all other parameters remaining the same (based on preclinical in vivo and in vitro comparative data). The model “adjusted PK and potency” referred to a parameterization combining the elements of the previous two. Specific parameters for each model/scenario and knowledge-based rationale for the adaptation of all the PK and PD parameters are given in Supplementary Material online. Prestudy simulations (Figure 1) quantified overall OKZ PD span/uncertainty between scenarios and indicated that potential OKZ attributes such as lower clearance and/or higher potency in suppressing CRP could result in a study dose range of 0.1–3 mg/kg i.v., spanning from an active, minimally effective dose to a maximally effective one. This was different from the TCZ dose range (2–8 mg/kg i.v. (ref. 11)).

Optimal study design and sample size reestimation
Analysis of the simulations that perturbed the design space (see Methods) showed that desired levels of precision ($\leq$30 coefficient of variation (CV)) and bias on the PK/PD model parameters for CRP suppression (EC$_{50}$ and sigmoidicity factor, $\gamma$) summarized into a Desirability Index\textsuperscript{15} could be achieved with 9–10 patients on active treatment per dose assuming a lower limit of quantification (LLOQ) for the OKZ PK assay of 0.03 µg/ml and with four dose levels to a maximum dose of 3 mg/kg, with the %CV of the CRP assay fixed at 15%. The interplay and sensitivity of the various factors affecting the desirability

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Simulated ($n = 1,000$) dose/response relationship between OKZ doses and % change of CRP from baseline (mean) at a 4-week time point following a single OKZ i.v. dose with use of the three model parameterizations based on adaptation of TCZ model to OKZ. Simulation of respective TCZ/CRP relationship included for comparison. CRP, C-reactive protein; OKZ, olokizumab; TCZ, tocilizumab.}
\end{figure}
outcome is presented in Figure 2. The lower and upper limit of baseline CRP had limited impact on the estimated quality of the model. Results indicated that satisfactory precision and bias for EC\textsubscript{50} and $\gamma$ were also likely to be achieved in the case of CRP baseline distribution, which is uniform or resembles a historical one for mild RA patients who are easier to recruit. The latter was provided by a clinical site that would undertake part of the study. The LLOQ of the OKZ PK assay (unconfirmed at the time of initial study design) appeared an impactful design parameter. With LLOQ equal to 0.03 µg/ml (Figure 2a), the desirability value was high and robust to any change of the other design elements, within the range envisaged. With LLOQ equal to 0.1 µg/ml, the desirability index decreased; it became more sensitive to baseline CRP values and could be improved by an (undesirable) increase of the number of subjects (Figure 2b). The nonintuitive LLOQ importance can be explained by considering the estimate of EC\textsubscript{50} (Table 1; 0.415 µg/ml). A PK LLOQ close to the EC\textsubscript{50} would have resulted in pertinent OKZ concentrations being unquantified, and thus, in a suboptimal study in terms of characterizing the PK/PD relationship. The results

Figure 3 (Original) study design CDP6038, olokizumab.
codetermined the study design along with strategic and operational considerations. The study design (Figure 3) involved two sequential cohorts ($n = 36$ per cohort with $n = 27$ on active treatment). Cohort 1 would consist of two i.v. doses (0.1 and 1 mg/kg), a s.c. dose (1 mg/kg) and respective placebo subsets. The optimal doses and route of administration for Cohort 2 were to be proposed after evaluation of PK/PD and safety data from Cohort 1. During Cohort 1 recruitment, pertinent information became available (OKZ first-in-human PK, publication of refined TCZ model, definition of PK assay LLOQ, and CRP baseline of recruited patients). This triggered a sample size reestimation based on refined model structure and parameterizations (see Methods). Under the revised model, distribution of both $EC_{50}$ and $\gamma$ estimates with $n = 27$ subjects on active treatment for the whole study appeared comparable to those that would have been achieved with the originally planned $n = 54$ on active treatment. In addition, the interquartile difference (75–25%) or the %CV of the parameter estimates appeared similar for all sizes envisaged and acceptable for the purpose of meeting the objectives of the study (targeted %CV–30% for $EC_{50}$ and $\gamma$), whatever the sample size, assuming that the first two randomization blocks ($n = 12$ block) of Cohort 1 had been completed as planned (see Supplementary Table S2 online).

The results implied that the study could potentially be stopped after dose optimization and completion of the first randomization block of Cohort 2. By the time the reestimation step was complete, a total of 27 subjects had been randomized to Cohort 1 (active and placebo, 2 randomization blocks of 12 + 3 additional subjects). Recruitment was halted, and the first interim analysis was implemented to determine the optimized dose for exploration in 1 block of 12 patients in Cohort 2.

**First interim analysis and dose optimization of Cohort 2**

The first interim analysis following sample size reestimation involved CRP and OKZ plasma concentration data from 18 patients from Cohort 1 for at least 4 weeks postdose (4 at placebo, 3 at 0.1 mg/kg i.v., 4 at 1 mg/kg i.v., and 7 at 1 mg/kg s.c.). The first-in-human PK data were combined with the PK data available from the current study to support this interim analysis. A two-compartment PK model, with linear elimination and first-order absorption for the s.c. administration adequately described the OKZ plasma concentration–time data. In terms of PK/PD modeling, as anticipated, 16 a lag time was observed between the maximum OKZ plasma concentration and the time to the maximum CRP inhibition; an effect compartment model was used to evaluate the CRP–OKZ plasma concentration relationship. The resulting PK and PK/PD parameters are shown in Table 1.

![Table 1 Population PK and PK/PD parameter estimates for the three different modeling occasions of study data (first interim, second interim, and final analyses)](image)

The highest level of desirability was obtained for the combination with a Cohort 2 dose equal to 3 mg/kg. Given the project’s intent to develop a s.c. formulation, the optimal dose proposed for Cohort 2 was 3 mg/kg s.c.

**Second interim and final analysis**

The second interim analysis occurred 4 weeks after the first and involved all available data from Cohorts 1 and 2. The PK and PK/PD analyses were consistent with findings from the first interim analysis (Table 1). The updated PK/PD model was employed as in the first interim analysis. Estimates
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(mean and precision) of EC\textsubscript{50} and \(\gamma\) from the second interim analysis compared to the “desired” ones during the sample-size reestimation step (Table 2), revealed that the mean and precision of EC\textsubscript{50} were only slightly improved, reflecting the valid estimates and use of prior knowledge during reestimation. In terms of both EC\textsubscript{50} and \(\gamma\), the precision outperformed even the one anticipated for the sample reestimation scenario pertaining to a greater number of patients enrolled. Based on this information, it was determined that the PK/PD objectives of the trial were met in terms of precision of PD parameters (<30\%CV).

Final PK/PD analyses of all week-12 data from all patients yielded parameter estimates marginally different from the ones estimated in the second interim analysis. The precision of the parameter estimates was reasonable and high interindividual variability was observed in all parameters (Table 1). For the PK model, body weight was a significant covariate of clearance and central volume of distribution. For the PK/PD model, endogenous anti-IL-6 was not significant as covariate for EC\textsubscript{50} and \(\gamma\). A plot of the individual observed CRP data and respective prediction with the final PK/PD model vs. the concentration in the effect compartment is presented in Figure 4, highlighting the complete response curve that was explored in the study.

**DISCUSSION**

The first inpatient study for OKZ was tailored to play a bridging role between the first-in-human and a subsequent phase Ib study in moderate-to-severe RA. CRP was chosen as target engagement biomarker relevant to the disease under the premise that characterization of the dose–exposure–response relationship for suppressing an IL-6 effect in the liver (CRP production regulated by IL-6 (ref. 4)) could provide PD (potency) insights useful in the subsequent clinical development, especially since there were similar outcomes reported for TCZ. Baseline CRP was part of the randomization procedure/eligibility to ensure elevated levels (median: 3.37 µg/ml; range: 0.6–27.2 µg/ml) with a reasonable spread that allowed robust characterization of the PD effect in a mild-to-moderate RA patient group and translatability to a more severe methotrexate-inadequate responder RA population.

The above considerations called for a model-based, real-time analysis with subsequent trial adaptation, with a Bayesian mindset that utilized all available data (external, preclinical, and clinical) and knowledge (first-in-class PK/PD models, translation based on target biology). Translation of preclinical comparative data and knowledge of target biology (IL-6 vs. IL-6R) led to the prestudy use of three different PK/PD parameterizations managing the considerable uncertainty. The parameterization corresponding to OKZ being more potent and with longer, linear kinetics was initially weighted more than the others in simulations and turned out to be the actual OKZ profile. Results indicate that the PK/PD response surface for OKZ for CRP suppression was optimally explored. A high level of precision in both EC \textsubscript{50} and \(\gamma\), the primary study objectives, were achieved with the final model (23.4 and 17.4\%), respectively. The PK/PD analysis of study data yielded an EC\textsubscript{50} value roughly fourfold lower than the respective TCZ one, a less steep slope for the exposure–response curve and an effect compartment rate constant roughly fourfold lower.\textsuperscript{16}

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**Table 2** Quantiles and precision of EC\textsubscript{50} and \(\gamma\) estimates at second interim analysis compared with envisioned performance during sample reestimation.

| Stage | Patients\(^a\) | 10\% | 25\% | Median | 75\% | 90\% | IQL\(^b\) |
|-------|---------------|------|------|--------|------|------|--------|
| EC\textsubscript{50} | Interim 2 | 27 | 0.35 | 0.44 | 0.54 | 0.64 | 0.72 | 0.2 |
|       | “Adjust PK and potency” | 27 | 0.33 | 0.43 | 0.55 | 0.65 | 0.78 | 0.22 |
| \(\gamma\) | Interim 2 | 27 | 0.82 | 0.96 | 1.12 | 1.28 | 1.42 | 0.32 |
|       | “Adjust PK and potency” | 27 | 0.92 | 1.14 | 1.52 | 2.68 | 3.22 | 1.54 |

| Stage | Patients\(^a\) | Mean | SD | %CV |
|-------|---------------|------|----|-----|
| EC\textsubscript{50} | Interim 2 | 27 | 0.54 | 0.15 | 27.31 |
|       | “Adjust PK and potency” | 27 | 0.55 | 0.18 | 30.03 |
| \(\gamma\) | Interim 2 | 27 | 1.12 | 0.24 | 21.43 |
|       | “Adjust PK and potency” | 27 | 1.96 | 0.68 | 34.85 |

CV, coefficient of variation; IQL, interquartile range.

\(^a\)Total number of patients on active treatment in Cohorts 1 and 2. \(^b\)Interquartile (75–25\%) range. \(^c\)Results during sample size reestimation.

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**Figure 4** Individual observed C-reactive protein plasma concentration vs. olokizumab effect compartment concentration. Blue area and line represent 90\% prediction interval and median from the final PK/PD model.
The visual predictive checks (Supplementary Material online) for the PK/PD model showed that the effect compartment model was able to reasonably describe the data. However, some model misspecification was noticed, particularly at the lowest dose level. Due to the exploratory nature of the study and to facilitate comparison with TCZ, no further model development was performed. Other model options, such as an indirect response model, might help to describe the data better across the full dose range.

The overall result was a study that met its objectives considerably ahead of schedule and with significant cost savings since only half of the envisaged sample size sufficed. The study also demonstrated the synergistic effect of PK/PD modeling, exploratory statistics, and systems pharmacology and the complementarity of these competences.

Limitations of the study include its inability to yield a direct understanding of the OKZ relationship with efficacy, in part, due to its small-size and single-dose nature.

METHODS
Reverse engineering of TCZ models
The published12 TCZ phase III PK/PD model consisted of a population PK model with two disposition compartments and two parallel elimination pathways (linear and nonlinear) describing the serum concentration–time course of TCZ and a PK/PD model describing the relationship between the serum concentrations of TCZ and CRP via a direct sigmoidal model. The model was reconstructed and evaluated using Berkeley Madonna software, version 8.3.14 (Berkeley Madonna, Berkeley, CA). Simulations were performed and summaries of data generated to ensure that appropriate assumptions were made and that the published TCZ metrics were matched (Supplementary Material online). All simulations were performed within Berkeley Madonna software, and output was summarized in Excel and SPLUS.

Optimal study design and sample size reestimation
The design elements of the trial considered relevant and potentially optimizable were:

- Sample size: 5, 10, or 15 patients/dose
- Number of dose levels: 3, 4, or 5
- Dose range: 0.1–3 or 0.1–5 mg/kg
- Baseline CRP range: lower limit varied from 0 to 30 µg/ml and upper limit from 30 to 150 µg/ml
- LLOQ of PK assay: varied from 0.03 to 0.3 µg/ml (the latter being the LLOQ of the assay at the time of study design)
- Precision of the CRP assay (fixed at 15%CV)

In addition, possible CRP baseline distributions were considered (Supplementary Material online). The combination of these six design elements, with two or three levels each, led to 1,152 different scenarios. For each scenario, 500 study trials were simulated with all three OKZ/CRP model parameterizations to investigate the trade-offs.14 Simulations were performed in the R software (version 2; The R Foundation for Statistical Computing, Vienna, Austria) and analyzed with JMP version 7.0. The quality of each design was based on the bias and precision of estimates of EC_{50} and γ, parameters of a logistic function of the CRP levels as a function of the OKZ concentration. The bias and precision of EC_{50} and γ for each of the three potential models, totaling 12 estimates, were considered into a global desirability analysis to identify the optimal clinical trial scenario. Desirability linear functions were defined first, to ensure target bias at 0 with maximal departure of 30% from the true value and, second, to minimize the SE with a maximal CV% acceptable value of 100% for EC_{50} and 200% for γ. A global Desirability Index combined the desirability functions with the simulations from the three OKZ/CRP model parameterizations weighted differently. The “adjusted PK and potency” parameterization was given weight five times larger than the other two based on available data. The final outcome was the optimal design, i.e., the combination of the elements that maximize the global Desirability Index. The study protocol (NCT01009242) was approved by the Institutional Review Board/Independent Ethics Committee as defined in local regulations and performed according to the Declaration of Helsinki. All patients provided written consent.

During the study, prior to planned interim analysis, pertinent information became available that was considered informative enough to reestimate the sample size. The information considered was:

- Confirmation of the OKZ PK LLOQ assay (0.027 µg/ml)
- Characterization of the OKZ PK from the first-in-human study (indicating that only two model parameterizations were possible, “adjusted PK” and “adjusted PK and potency”)
- Publication of a refined PK/PD relationship for TCZ that included a lag-time of effect between TCZ concentration and CRP suppression15
- Characterization of baseline CRP range (95% of study patients already recruited had baseline CRP ranging from 0.5 to 30 µg/ml).
- Realized Cohort 1 randomization (two i.v. doses, 0.1 and 1 mg/kg, and one s.c. dose, 1 mg/kg).

Following a protocol amendment detailing how the study and analyses may adapt, a reestimation of the sample size commenced with use of a new model with a revised structure,16 new OKZ PK parameters from the first-in-human PK model, and adapted PK/PD parameter estimates based on preclinical in vivo and in vitro data for resimulation (two parameterizations receiving equal weight). The aforementioned methodology leading to a Desirability Index was followed with the newly simulated CRP concentration–time profiles based on the refined models. This process was repeated by considering actual dose levels tried in Cohort 1 and potential Cohort 2 dose level combinations.

PK/PD modeling of study data
The PK/PD modeling of study data was performed sequentially using a population approach within the NONMEM software, version VI, level 2.0 (ICON Development Solutions, Ellicott City, MD), with interface PsN 3.2.12. A pooled PK analysis combining data from the first-in-human and first-in-patient studies was performed. A two compartment model with linear elimination and first-order absorption for the s.c. route was used. Intersubject variability was assessed on each of the pharmacokinetic parameters using an exponential model. Proportional, additive, and combined (proportional and additive error) structures were evaluated for the residual
error. The effect of endogenous anti-IL-6 levels was included as an additive term in the error model. Body weight, age, and gender were tested as covariates in the PK model. Goodness of fit plots, visual predictive checks, and parameter estimates were considered as model evaluation criteria.

Following graphical evaluation of CRP/time (Supplementary Figure S2 online) and CRP/OKZ data in SPLUS/R, the relationship between CRP and individual predicted OKZ plasma concentrations was analyzed using a population approach in NONMEM software. An effect compartment model was evaluated and was consistent with the data. Intersubject variability was assessed on all PD parameters, testing both an additive and an exponential error structure. Exponential, additive, and combined error structures were evaluated for the residual error terms. Once the structural and statistical PK/PD model was ascertained, the effect of baseline endogenous IL-6 autoantibodies (detected by the OKZ PK assay) was explored on the PK/PD parameters, EC50, and γ. Goodness of fit plots, visual predictive checks (Supplementary Figures S3 and S4 online), and parameter estimates were considered as model evaluation criteria.

Dose optimization of Cohort 2

The developed PK/PD model at first interim analysis was used to simulate a virtual set of patients for an assessment of the optimal Cohort 2 dose/route. Both interindividual variability and estimate uncertainty around the population PK and PD parameter estimates were accounted for the use of an R algorithm, which drew from the joint distribution of interindividual variability and uncertainty around the point estimate for each parameter. Thus, a set of PK and PD parameters defining each virtual patient was drawn and used to sequentially simulate OKZ concentration–time profiles in plasma and effect compartment as well as CRP concentration–time profiles. For the CRP concentration predictions, the residual error was added to make the simulated CRP concentrations being used as observed CRP for the PK/PD model estimation.

Profile/data pools of 200 virtual patients were generated this way for 28 dose and route combinations. Profiles were randomly selected from these pools for a Bayesian analysis of actual study data coupled with partial simulated data for Cohort 1 patients whose complete data were not yet available and with future Cohort 2 data for the various dose/route combinations considered. The relationship between CRP and OKZ effect compartment concentration for each of the resulting Cohort 1 and Cohort 2 Bayesian datasets was analyzed in R (version 2.5.1) and WinBugs (version 1.4.3) adaptation of the developed population PK/PD model. The prior distributions used in the process were predefined based on literature and previous clinical data (see Supplementary Material online).

In order to identify the optimal dose/route combination(s), an iteration process was applied (Fedorov procedure). Starting from an initial set of doses, the process identified the next set of doses to be tested in order to find the combination that minimizes an objective function. This surface objective function, quantified as the 75% percentile of the surface between the 2.5 and 97.5% percentiles of the Emax relationship between CRP and OKZ effect compartment concentration quantified “holistic” PD uncertainty. The process stopped after a maximum of nine iterations or if the diminution of the predicted surface was less than 2%. The process explored up to three Cohort 2 randomization blocks for a range of three doses combination (1 i.v. and 2 s.c.).

In addition to the surface objective function, other functions (bias and variance of PD parameters) were calculated. The minimization of the weighted combination determined the final recommendation for Cohort 2 dose (Supplementary Table S3 online).

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Conflict of Interest. K.K., M.Z., O.H., S.S., and R.O. are UCB employees. A.J. and B.B. were UCB employees during design, execution, and analysis.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Robustness and translatable early clinical results are often hindered by small sample sizes and “standard” study designs leading to suboptimal characterization of pharmacology and ill-informed decisions.

WHAT QUESTION DID THIS STUDY ADDRESS?

The PK/PD profile of olokizumab for CRP suppression in a disease relevant population was fully and precisely characterized with a minimal number of patients allowing further clinical development.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

A combination of PK/PD, exploratory statistics, and translational research methodology paved a crossdisciplinary methodology resulting in an optimal study design, agility in execution, and attainment of study objectives ahead of schedule and with half the patients originally envisaged.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

Model-based study design and execution with true integration of PK/PD modelers, exploratory statisticians, and systems pharmacologists driven by a Bayesian, “systems” mindset can result in faster, cheaper, and more informative clinical studies.
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