

# Population Pharmacokinetics of Olokizumab in Healthy Volunteers and Rheumatoid Arthritis Subjects



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## Introduction

- Interleukin-6 (IL-6) plays a central role in rheumatoid arthritis (RA). Olokizumab (OKZ) is a humanized monoclonal antibody targeting IL-6 and may theoretically exhibit nonlinear pharmacokinetics due to target-mediated processes<sup>1,2</sup>. Its clinical development included intravenous and subcutaneous administration across Phase I–III studies in healthy volunteers and RA patients, generating heterogeneous datasets.

The objective was to develop a unified population pharmacokinetic model, evaluate structural assumptions and quantify sources of interindividual variability in exposure.

## Methods

- Pooled PK data were compiled from eight clinical studies of OKZ encompassing Phase I–III trials (N=1115)<sup>3-11</sup>:

TABLE 1. Olokizumab clinical study details.

| Study Number                    | Regimens and subject amount                                                                                                                                                                                                                                                                                       |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| RA0001 (Phase I)                | 0.001 mg/kg i.v. (3), 0.01 mg/kg i.v. (3), 0.03 mg/kg i.v. (3), 0.1 mg/kg i.v. (3), 0.1 mg/kg s.c. (3), 0.3 mg/kg i.v. (3), 0.3 mg/kg s.c. (3), 1 mg/kg i.v. (3), 1 mg/kg s.c. (3), 3 mg/kg i.v. (3), 3 mg/kg s.c. (3), 10 mg/kg i.v. (3), Placebo (34)*<br>* was not included into analysis; <b>Total N = 67</b> |
| RA0010 (Phase I/II)             | 0.1 mg/kg i.v. (6), 1 mg/kg i.v. (7), 1 mg/kg s.c. (8), 3 mg/kg s.c. (9), Placebo (10)<br><b>Total N = 40</b>                                                                                                                                                                                                     |
| RA0074 (Phase I)                | 0.3 mg/kg s.c. (4), 1 mg/kg s.c. (4), 3 mg/kg s.c. (4), 6 mg/kg s.c. (4), Placebo (4)*,<br>* was not included into analysis <b>Total N = 20</b>                                                                                                                                                                   |
| RA0056 (Phase II)               | 60 mg Q4W s.c. (22), 60mg Q2W s.c. (20), 120 mg Q4W s.c. (23), 120 mg Q2W s.c. (22), 240 mg Q4W s.c. (22), 240 mg Q2W s.c. (23), Placebo (44)<br><b>Total N = 176</b>                                                                                                                                             |
| RA0083 (Phase II)               | 60 mg Q4W s.c. (32), 60mg Q2W s.c. (15), 120 mg Q4W s.c. (16), 120 mg Q2W s.c. (13), 240 mg Q4W s.c. (13), Placebo (29)<br><b>Total N = 118</b>                                                                                                                                                                   |
| CL04041022 (CREDO-1, Phase III) | 64 mg Q4W s.c. (64), 64 mg Q2W s.c. (56), Placebo (142)<br><b>Total N = 262</b>                                                                                                                                                                                                                                   |
| CL04041023 (CREDO-2, Phase III) | 64 mg Q4W s.c. (186), 64 mg Q2W s.c. (172), Placebo (242)<br><b>Total N = 600</b>                                                                                                                                                                                                                                 |
| CL04041025 (CREDO-3, Phase III) | 64 mg Q4W s.c. (151), 64 mg Q2W s.c. (136), Placebo (64)<br><b>Total N = 351</b>                                                                                                                                                                                                                                  |

Abbreviations: i.v. = intravenous infusion, s.c. = subcutaneous injection, N = number of subjects in the study

- Evaluation of models was conducted using Akaike Information Criterion (AIC), shrinkage diagnostics, precision of parameter estimates (RSE <51%), and goodness-of-fit plots.. For handling concentrations below the limit of quantification, the M3 method was applied<sup>12</sup>.
- Baseline continuous covariates were log-transformed and implemented as power functions normalized to median values. Covariate selection employed a stepwise forward inclusion (p <0.05) and backward elimination (p <0.01) procedure. Correlated or biologically implausible covariates were excluded prior to selection<sup>13</sup>.
- Graphical evaluation included visual inspection of diagnostic plots (DV vs PRED/IPRED, PWRES/IWRES), η-shrinkage, and prediction-corrected VPCs. Covariate effects were simulated using 200 parameter replicas modified at the 5th–95th percentile, with exposure metrics (C<sub>max</sub>, C<sub>min</sub>, AUC) summarized versus a typical patient.
- Models were developed in Monolix 2020 R1 incorporating SAEM and Importance Sampling optimization procedure. Model diagnostics was produced in SimuRg package in R.

## Results

### Model building and diagnostics

- The final population PK model was selected from the list of more than 150 candidates. It represented a two-compartment model with first order absorption for s.c. administration, first order elimination, and a combined residual error.
- Inter-individual variability (IIV) was retained on CL and V<sub>c</sub>, with a positive correlation between them (cor = 0.2). Bioavailability (F) differed between early phase studies and CREDO Phase III studies: F<sub>non-CREDO</sub> = 0.73 and F<sub>CREDO</sub> = 0.88. η-shrinkage for all parameters with IIV did not exceed 51%:

TABLE 2. OKZ final PK model parameters.

| Parameter                                | value | s.e.   | RSE (%) |
|------------------------------------------|-------|--------|---------|
| Fixed Effects                            |       |        |         |
| k <sub>a</sub> (d <sup>-1</sup> )        | 0.22  | 0.0075 | 3.45    |
| CL/F (L/d)                               | 0.18  | 0.0025 | 1.44    |
| β <sub>CL_logBALB</sub>                  | -1.09 | 0.17   | 15.6    |
| β <sub>CL_logBHDLC</sub>                 | -0.34 | 0.05   | 14.9    |
| β <sub>CL_logBWGT</sub>                  | 0.63  | 0.057  | 9.16    |
| V <sub>1</sub> /F (L)                    | 4.1   | 0.15   | 3.74    |
| β <sub>V1_logBALT</sub>                  | -0.19 | 0.058  | 30.3    |
| β <sub>V1_logBWGT</sub>                  | 1.09  | 0.12   | 10.8    |
| Q/F (L/d)                                | 0.59  | 0.046  | 7.70    |
| V <sub>2</sub> /F (L)                    | 2.33  | 0.078  | 3.34    |
| Standard Deviation of the Random Effects |       |        |         |
| ω <sub>CL</sub>                          | 0.42  | 0.011  | 2.63    |
| ω <sub>V1</sub>                          | 0.73  | 0.027  | 3.72    |
| Correlations                             |       |        |         |
| cor(V <sub>1</sub> , CL)                 | 0.2   | 0.046  | 22.6    |
| Residual Error                           |       |        |         |
| a (μg/mL)                                | 0.091 | 0.0098 | 10.8    |
| b                                        | 0.23  | 0.0032 | 1.42    |

Abbreviations: s.e. = standard error, RSE = relative standard error, BALB = baseline albumin level, BHDLC = baseline high density lipoproteins level, BWGT = baseline body weight, BALT = baseline alanine aminotransferase.

- Time-varying covariates were also assessed in the model. However, longitudinal covariate changes were quite minor, and algorithm convergence was not achieved.
- The final model adequately described the data:

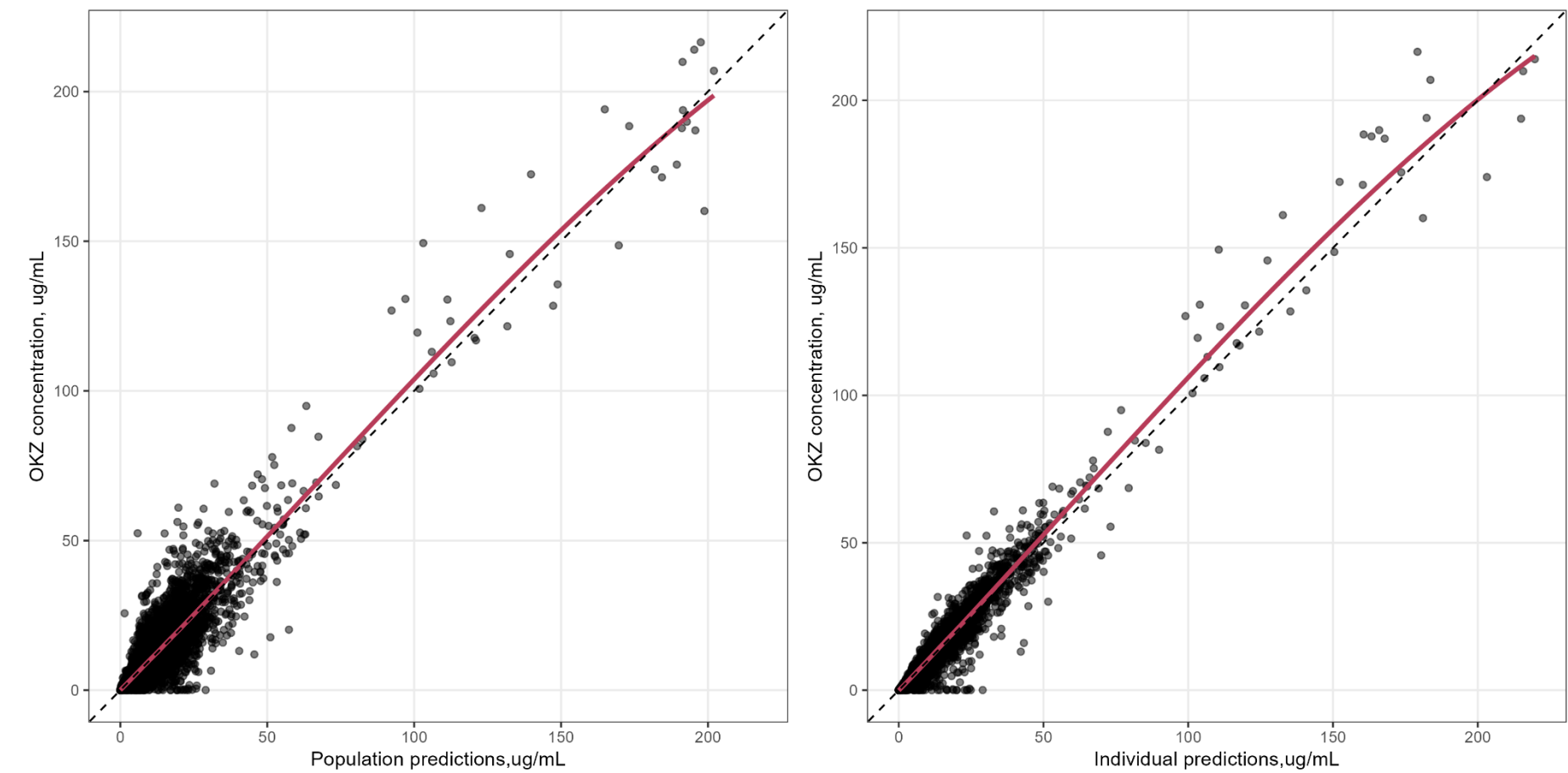


FIGURE 1. Observations vs. predictions diagnostic plots for the final model. Red – spline smoothing line, Black dashed – unity line.

### Olokizumab PK prediction distribution

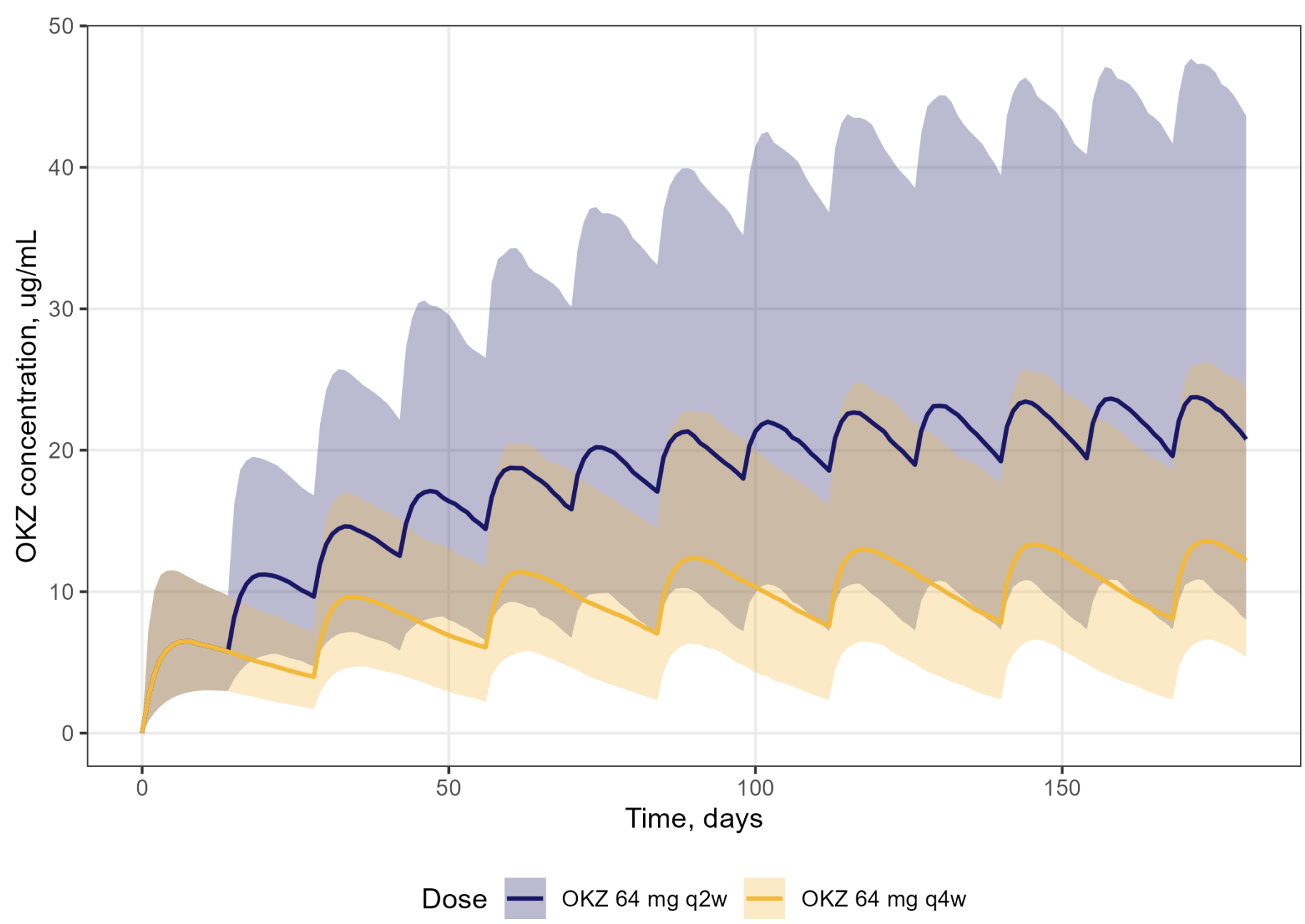
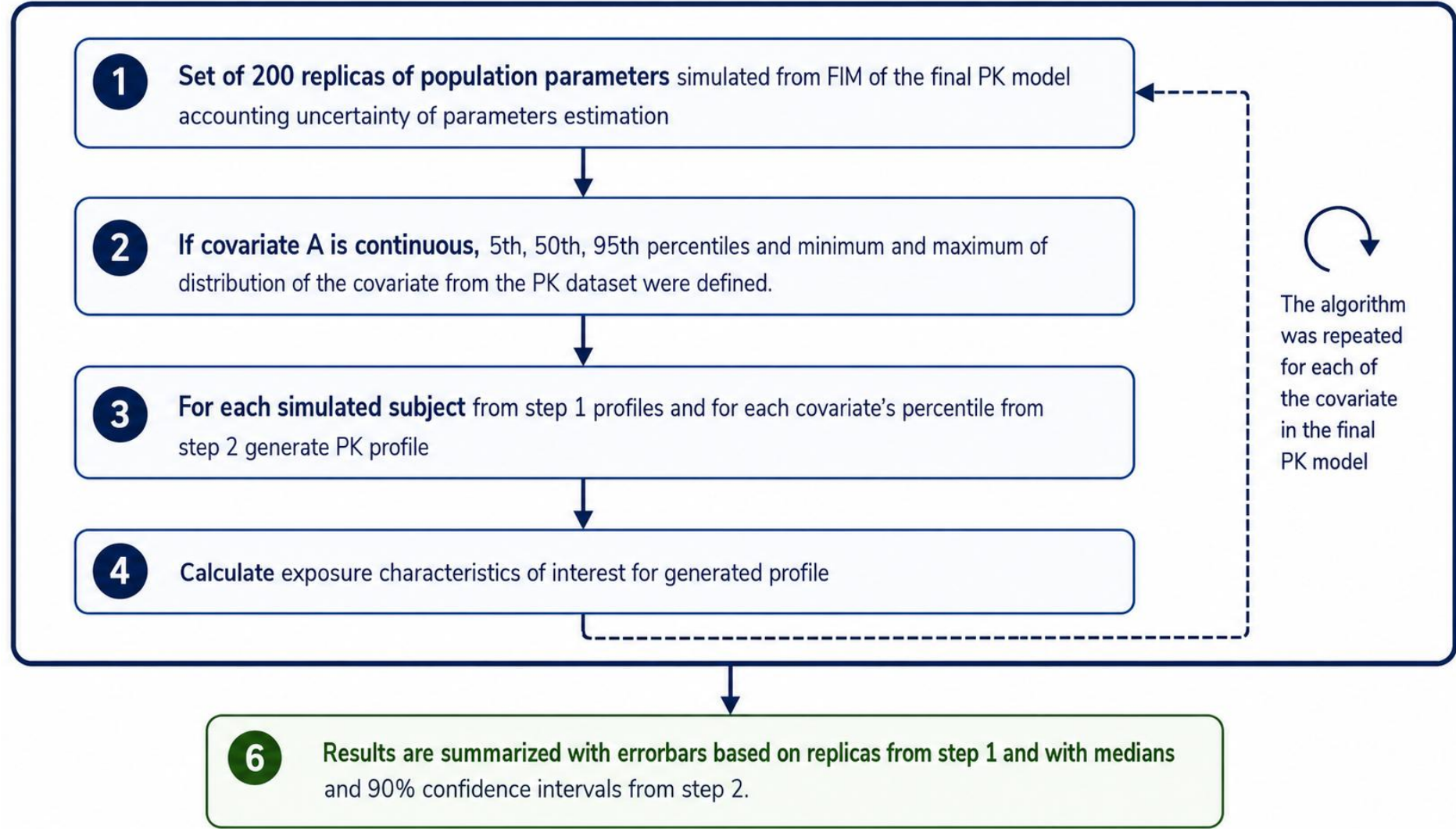


FIGURE 2. Final PK model prediction distribution (solid line -median, filled area between 5-95 prediction percentiles).

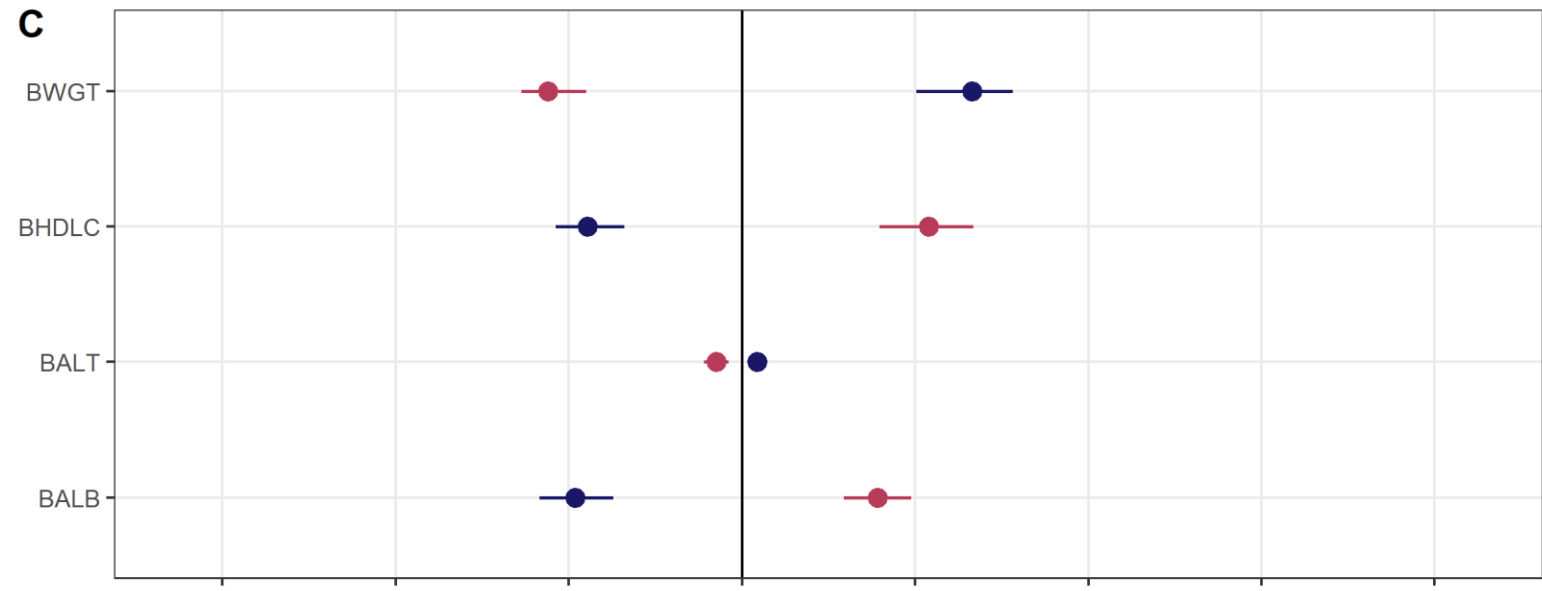
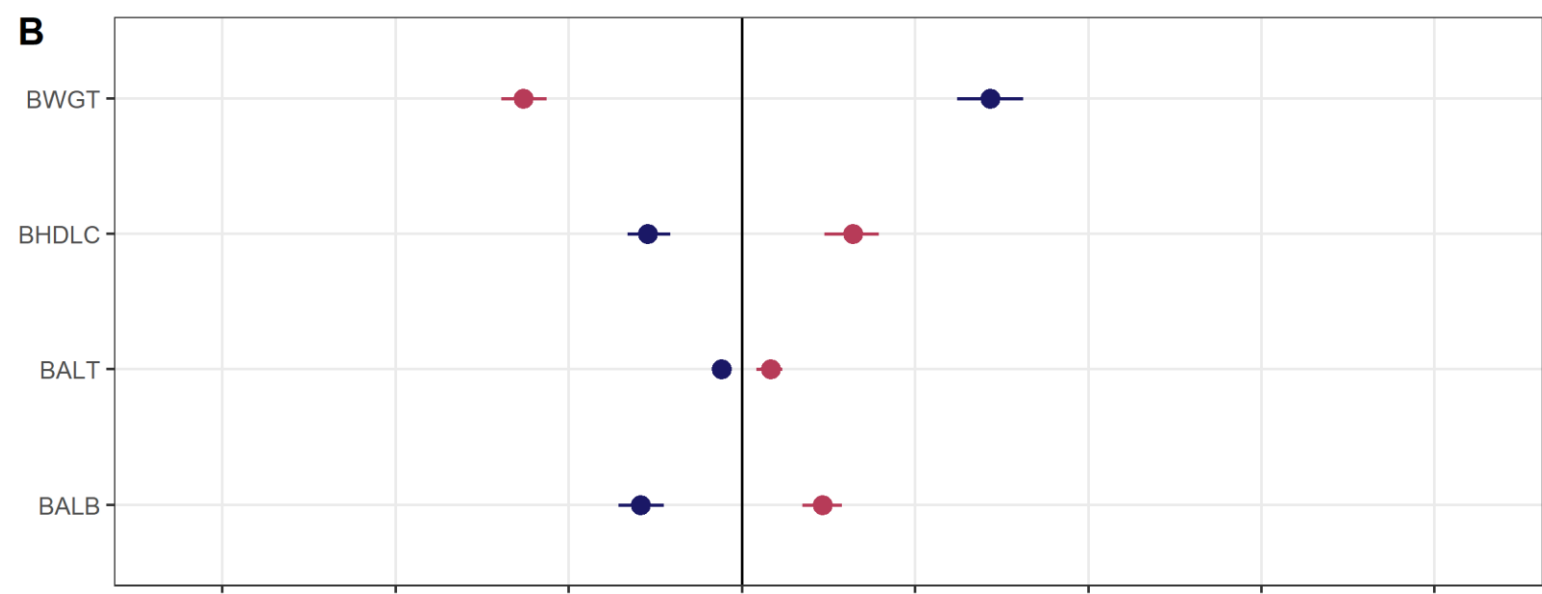
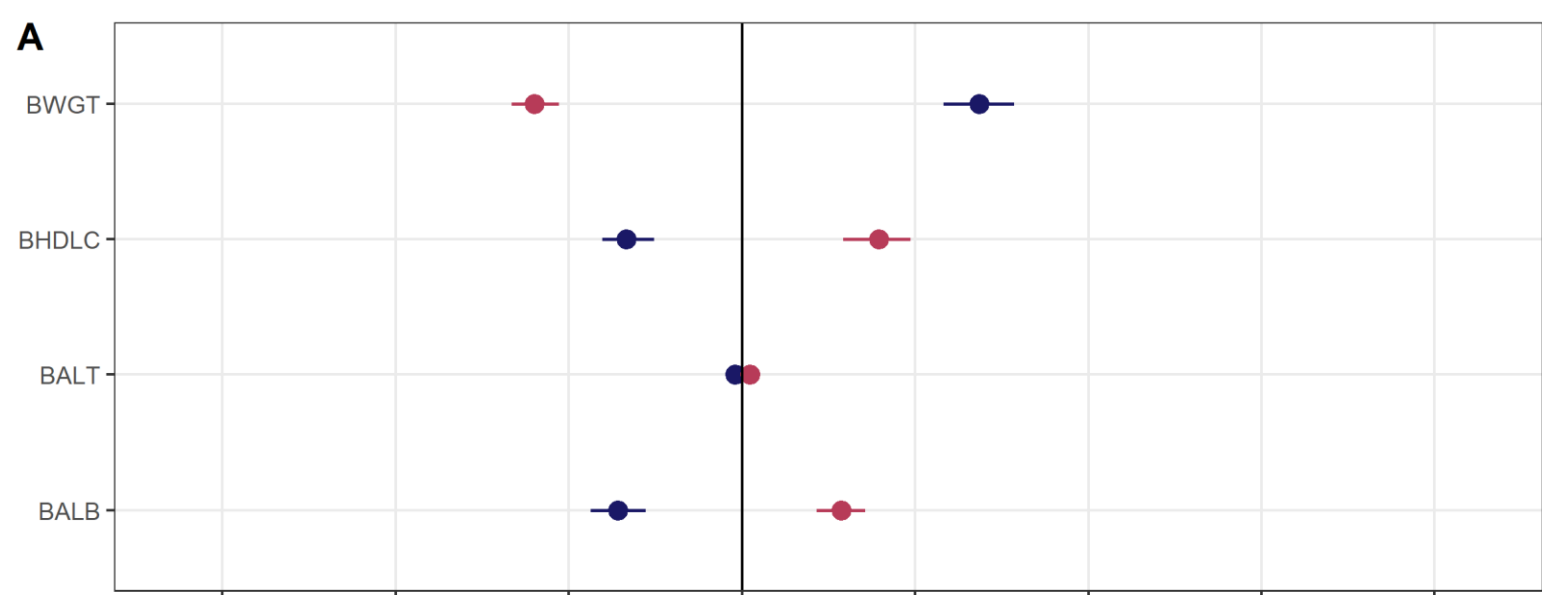
### Covariate impact assessment

TABLE 3. The simulation scenarios for the assessment of covariate effects on PK parameters and OKZ exposure characteristics.



The scheme is applicable for C<sub>max</sub>, C<sub>min</sub> and AUC after first dose and at the steady state. Each covariate can have effect on exposure characteristics through one or several parameters depending on a tested covariate.

- Five interactions of baseline covariates with model parameters were included and tested in the model: log-transformed serum albumin, high-density lipoprotein cholesterol and body weight (BWGT) for CL; log-transformed alanine aminotransferase and BWGT for V<sub>c</sub>.
- Simulated exposure metrics varied within ±25% across observed covariate ranges, however this impact needs to be assessed in safety, exposure-response and PKPD analysis.



Abbreviations: AUC = area under curve, C<sub>max</sub> = peak concentration, C<sub>min</sub> = minimal concentration before next dose, BALB = baseline albumin level, BHDLC = baseline high density lipoproteins level, BWGT = baseline body weight, BALT = baseline alanine aminotransferase, ss = steady-state.

FIGURE 3. Covariate effects on s.c. OKZ 64 mg Q4W exposure parameters: A) AUC<sub>ss</sub>, B) C<sub>max</sub><sub>ss</sub>, C) C<sub>min</sub><sub>ss</sub> – for 90% CI covariate range, which were calculated on steady-state regime (112-140 days interval).

## Conclusions

- A robust two compartment population PK model for olokizumab was developed based on the pooled dataset from phase I–III clinical studies.
- The model adequately described the data. Body weight was the primary driver of variability in clearance and central volume parameters that was assessed by means of steady-state exposure characteristics.
- Finally, the developed model is aimed to inform exposure–response and PKPD predictions, supporting long-term evaluation of olokizumab efficacy.

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