Other Clinical Report

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Additional reports:	**Page:** 1 of 34

Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI proprietary name: Drug name (BI 123456)		**EudraCT number(s):** 2017-123456-12	
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Title

A nice title

Publications

Not applicable

Clinical phase(s): I

Objectives

- Objective 1
- Objective 2

Methodology

Some methods

Diagnosis

Some diagnosis

BI investigational product: Drug name (BI 123456)

Dose: 10, 20, 30 mg

Mode of administration: Intravenous infusion

Duration of treatment

Until disease progression or drop-out from the trial

Results

Some cool results

Conclusions

Some relevant conclusions

EXECUTIVE SUMMARY

Text

More Text.

The statistically significant covariates identified in the model were as follows:

- xxx
- xxx
- xxx

More Text.

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ABBREVIATIONS, TERMS, AND SYMBOLS

ΔOFV	Change in the objective function value
ADA	Antidrug antibodies
AIC	Akaike information criterion
BIC	Bayesian information criterion
BMI	Body mass index
BOV	Between-occasion variability
BSV	Between-subject variability
CI	Confidence interval
CL/F	Apparent clearance
cm	Centimeter
CRP	C-reactive protein
CV	Coefficient of variation
CWRES	Conditional weighted residuals
DV	Dependent variable
eGFR	Estimated glomerular filtration rate
FOCE	First order Conditional Estimation method
FOCE-I	First order Conditional Estimation method with eta-epsilon interaction
h	Hour(s)
IIV	Inter-individual variability
IOV	Inter-occasion variability
IPRED	Individual predicted values
IQR	Interquartile range
k_a	First order absorption rate constant
kg	Kilogram
LBW	Lean body weight
LRT	Likelihood-ratio test
m	Meter
mg	Milligram
ng	Nanogram
nmol	Nanomol
NONMEM	NONlinear Mixed Effects Modelling software
OFV	Objective function value
OMEGA	Variance parameter for between-subject or between-occasion random effects

pcVPC	Prediction corrected visual predictive check
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic
PRED	Population predicted values
PsN	Perl-speaks-NONMEM
Q/F	Apparent inter-compartmental clearance
QQ	Quantile-quantile
RSE	Relative standard error
RUV	Residual unexplained variability
s.c.	Subcutaneous
SE	Standard error
V_c/F	Apparent central volume of distribution
V_p/F	Apparent peripheral volume of distribution
VPC	Visual predictive check
WT	Body weight

1. INTRODUCTION

Some text.

1.1 SUB SECTION EXAMPLE

Some more text followed by 2 double spaces after the line.

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1.1.1 Subsubsection example

Refer to Section 1.1.

2. OBJECTIVES

The overall objective of the analysis was xxx. To achieve this, the following sub-objectives were set:

- xx
- xx
- xx

3. DATA

3.1 DATA MANAGEMENT

See Table 1.

Table 1 PopPK analysis dataset

Study Name	Phase	N	Dose (Q2W, subcutaneous (s.c.))	PK Sampling
BI xxxxxx versus Humira in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel group, exploratory trial comparing efficacy, endoscopic improvement, safety, and immunogenicity	III	72 (BI xxxxxx) 75 (Humira)	Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg and every 2 weeks thereafter until week 48 At week 24, all patients in the Humira arm were switched to receive BI xxxxxx	Pre-dose on Day 1, Day 29 (Week 4), Day 169 (Week 24), Day 337 (Week 48/EoT)

3.1.1 Missing Data

3.1.2 Outliers

4. METHODS

4.1 MODELING PLAN

Some text.

4.2 SOFTWARE

Model development was performed using a nonlinear mixed-effects modeling approach with a qualified installation of the NONlinear Mixed Effects Modelling software (NONMEM) software, Version 7.4.3 or higher. (R24-1740) The first order conditional estimation method with eta-epsilon interaction (FOCE-I) was used for parameter estimation.

Perl-speaks-NONMEM (PsN) Version 4.6.0 (or higher) was used for automation and post processing. R Version 3.5.3 (or higher) was used for model evaluation as well as graphical and tabular displays. All computation was performed on a validated Linux cluster (Scientific Linux 7.9 (Nitrogen)).

4.3 EXPLORATORY DATA ANALYSIS

A graphical analysis was conducted prior to fitting any models to understand and explore the available data. This exploratory analysis was used to assess whether the disposition appeared to be mono- or biexponential, the PK was linear across the evaluated dose range, or if there was an impact of potentially relevant covariates. The graphical analysis also helped identify any gross errors during the compilation of the datasets and potential outliers.

Figures generated included plots of individual and median plasma concentration time-profiles, per study, dose, product, and other potential covariates.

4.4 BASE MODEL DEVELOPMENT

The population PK model was developed following an iterative model building process using a nonlinear mixed effects approach. In brief, nonlinear mixed effects models aim to characterize PK profiles at the population and individual levels via fixed and random effects. More details are provided below in Sections 4.4.2, 4.4.3, and 4.4.4.

4.4.1 Structural Model

4.4.2 Inter-Individual Variability

Inter-individual variability (IIV), or between-subject variability (BSV), was estimated using the following model:

$$P_j = TVP \cdot e^{\eta_j} \quad (1)$$

where P_j represents the individual PK parameter for the j^{th} individual, TVP is the typical value of the parameter, and η_j represents the independent random variable with a mean of zero and variance ${\omega_p}^2$. This model assumes a log normal distribution for the P_j values and a normal distribution of η_j values. If the η_j were not normally distributed (based upon graphical techniques discussed in Section 4.3), appropriate transformations such as a Box-Cox transformation were evaluated. Estimates of the between-subject variance in P were presented as the square root of ${\omega_p}^2$ multiplied by 100%, which is an approximation of the percent coefficient of variation (CV%) for a log-normally distributed quantity. Off-diagonal elements for the variance parameter for between-subject or between-occasion random effects (OMEGA) matrix were included in the base model where possible.

4.4.3 Inter-Occasion Variability

Inter-occasion variability (IOV), also termed between-occasion variability (BOV) were estimated using the following model, where applicable:

$$P_{j,k} = TVP \cdot e^{(\eta_j + \eta_k)} \tag{2}$$

where $P_{j,k}$ represents the individual PK parameter for the j^{th} individual's k^{th} occasion, η_j represents the independent random variable with a mean of zero and variance ${\omega_p}^2$, and η_k represents the occasion independent random variable with a mean of zero and variance ${\omega_p}^2$. This model assumes a log-normal distribution for the $P_{j,k}$ values and a normal distribution of η_j and η_k values. If the η_j and/or η_k were not normally distributed (based upon graphical techniques discussed in Section 4.3), appropriate transformations such as a Box-Cox transformation were evaluated. Estimates of inter-occasion variance in P were presented as the square root of ${\omega_p}^2$ multiplied by 100%, which is an approximation of the %CV for a log-normally distributed quantity.

4.4.4 Residual Variability

Residual unexplained variability (RUV) was tested as either an additive error, proportional error, or combined additive and proportional error, such that:

$$C_{ij} = \hat{C}_{ij} \cdot e^{\varepsilon_{ij_1}} + \varepsilon_{ij_2} \tag{3}$$

where C_{ij} is the i^{th} observation in the j^{th} individual, $\hat{C}_{ij}$ is the model prediction for the i^{th} observation in the j^{th} individual, ε_{ij_1} is the proportional RUV and ε_{ij_2} is the additive RUV with means of zero and variances of ${\sigma_1}^2$ and ${\sigma_2}^2$, respectively. If indicated during the graphical analysis, separate error terms were explored for e.g. different study groups. Moreover, the log transformation of both sides (LTBS) was considered, where RUV was modeled as an additive error on the log scale, which corresponds to a proportional error on normal scale such that:

$$ln(C_{ij}) = ln(\hat{C}_{ij}) + \varepsilon_{ij} \tag{4}$$

4.5 COVARIATE MODEL DEVELOPMENT

The influence of antidrug antibodies (ADA) (time-varying), age, sex, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), and serum albumin were tested for their statistical significance on PK parameters in the model. Table 2 reports the covariates that were assessed on each parameter.

Table 2 Covariates to be Assessed in the Population PK Analysis

Covariate	Code	Value	Parameters
Time-varying ADA (titer)	ADAI	Categorical	CL/F
Sex	SEX	Categorical	CL, V_c/F
Body weight* (kg)	WT	Continuous	CL/F, V_c/F, Q/F, V_p/F
Age (y)	AGE	Continuous	CL, V_c/F
C-reactive protein (mg/L)	CRP	Continuous	CL/F
eGFR (mL/min/1.73m^2)	EGFR	Continuous	CL/F
Serum albumin (g/L)	ALB	Continuous	CL/F

*Included *a priori* with an exponent of 0.75 for clearance terms and 1.0 for volume terms and not estimated.
CL/F = apparent clearance, V_c/F = apparent central volume of distribution, V_p/F = apparent peripheral volume of distribution, eGFR = estimated glomerular filtration rate

4.5.1 Covariate Models

To enable full exploration of potential covariate relationships, all covariance terms were removed from the model prior to the covariate model development. Covariates were modeled as changes in the parameter of interest from the reference subject. The reference subject was defined as the subject with demographic factors equal to the median for continuous covariates (weight, age, etc.) or most prevalent for categorical covariates (sex, race, etc.). Continuous covariates were normalized to the population median values using the general equation:

$$TVP_i = P_{pop} \cdot \left(\frac{cov_i}{cov_{med}} \right)^{\theta} \tag{5}$$

where TVP_i represents the model predicted PK parameter (e.g. apparent clearance (CL/F) or apparent central volume of distribution (V_c/F)) for the typical individual, i, with covariate value cov_i, P_{pop} represents the population central tendency for the PK parameter TVP, cov_{med} represents the population median value of the covariate, and θ represents a scale factor. With this type of model, if $\theta = 0$, the influence of the covariate could be dropped from the model; if $\theta = 1$, a direct proportional relationship is specified; and if θ is less than or greater than 1, a non-linear relationship is specified. Negative θ values specify a nonlinear inverse relationship. Diagnostic plots were examined during development of the model to assess the appropriateness of covariate models.

Categorical covariates, such as race and sex were modeled in the following manner:

$$TVP_i = P_{pop} \cdot \theta^{cov_i} \quad (6)$$

With this type of model, θ describes the change in parameter relative to the reference subgroup, for example, for females (cov_i = 1) relative to males (cov_i = 0). Categorical covariates with more than two categories were binarized in a similar fashion, e.g. caucasian (cov_i = 1) or not caucasian (cov_i = 0).

If two or more covariates are highly correlated, then the most clinically/biologically and practically relevant covariate was tested on a parameter in the analysis, and the other covariate(s) was discarded. This practice was applied for covariates such as body weight (WT), body mass index (BMI) and lean body weight (LBW).

4.5.2 Covariate Model Building

Following development of the base model and graphical assessment of covariate-eta (η) relationships, the covariate model was built according to the following steps:

1. If the η-shrinkage for the parameter of interest was not substantial (i.e. <35%) and a visually apparent relationship is identified for the parameter-covariate pairs specified in Table [-@tbl-covariates], covariates were added to the model in a stepwise forward manner. If the η-shrinkage was substantial (≥35%), a graphical assessment of covariate-η relationships was not performed and all specified covariates were tested on that parameter.
2. In the forward selection process, covariates were identified as statistically significant if change in the OFV (ΔOFV) ≥6.64 ($p < 0.01$ for 1 degree of freedom).
3. The covariate effect with the largest ΔOFV was included in the model, and the other covariates previously identified as significant were then re-tested for significance. Note - covariates that were not identified as significant on a given parameter were not re-tested during subsequent steps of forward selection.
4. Once no more covariate effects were identified as significant, a backwards elimination process was then performed, where covariates were deleted singly from the full model in a backward elimination process and the ΔOFV computed from the full model. Covariates that could be deleted from the full model without an associated increase in objective function value (OFV) ≥10.8 ($p < 0.001$ for 1 degree of freedom) were sorted by OFV and the covariate with the smallest ΔOFV was removed from the model. This process was repeated until no more covariates could be removed from the model, resulting in the final population pharmacokinetic (PopPK) model.

4.6 MODEL EVALUATION

Model evaluation techniques to assess the quality of model fit included statistical tests, diagnostic plots, and consideration of scientific plausibility. Some of these were during model development for important intermediate models as needed, while final base and covariate models were subjected to all techniques described in this section.

4.6.1 Numerical Techniques

The following numerical techniques were implemented:

- The change in objective function value ΔOFV was used to perform a likelihood-ratio test (LRT) with n degrees of freedom to determine the statistical significance between the fits of two nested models (under the assumption that the ΔOFV is chi-square distributed), where n is the difference in number of parameters between the models. For this analysis, a ΔOFV of $\geq$3.84 ($p < 0.05$ on 1 degree of freedom) was considered significant when $n = 1$ and using the first order conditional estimation (FOCE) in NONMEM. The LRT is not applicable for inclusion of variance terms.
- The Akaike information criterion (AIC) and Bayesian information criterion (BIC), to compare both nested and non-nested models, following the principle that the lower the AIC and/or BIC are, the better the model is.
- Successful convergence of the minimization procedure, with at least 3 significant digits in parameter estimates.
- Generation of acceptable relative standard errors (RSEs) for the parameter estimates, using $\leq$35% for fixed effects and $\leq$50% for variability parameters as a general guide.

4.6.2 Graphical Techniques

Graphical techniques included plotting of:

- The observed dependent variable (DV) vs. the population predicted valuess (PREDs).
- The observed DV vs. the individual predicted valuess (IPREDs).
- The observed DV, PREDs. and IPREDs vs. time.
- Residuals and conditional weighted residuals (CWRES) vs time after first and previous dose.
- CWRES vs. the PREDs.
- CWRES vs. the IPREDs.
- Histograms and/or quantile-quantile (QQ) plots of the individual random effects distributions (as frequencies) to check for normality/symmetry and determine if any shrinkage to the mean occurs.
- Histograms and/or QQ plots of CWRES.
- Correlations of the individual random effects.
- Scatterplots of the individual random effects vs. continuous covariates or boxplots of individual random effects vs. categorical covariates.

Additional plots were generated as needed, e.g., to compare predictions of competing models or to further explore bias observed in the observed DV vs PREDs plot due to possible nonlinearity or censoring (mirror plots).

4.6.3 Collinearity and Model Stability

Evidence of collinearity and a model's stability was assessed by computation of the condition number, which is the ratio of the largest to the smallest eigenvalue. A condition number of less than 1000 indicates that there is minimal collinearity between parameter estimates and that the variance-covariance matrix is well conditioned. A condition number that is in excess of 10000 indicates that the model may be unstable due to high collinearity. If the condition number was greater than 10000, the model was simplified by reducing the number of structural and/or random effect parameters, and re-evaluated using the methods described in Section 4.6. If the condition number fell between 1000 and 10000, further assessment of the model was made using additional diagnostic criteria as described in Section 4.6.

4.6.4 Parameter Uncertainty

The covariance step in NONMEM (MATRIX=S option) was implemented (as run times permitted) to evaluate precision of the parameter estimates. Models with parameter estimates with high associated RSEs (i.e., >35% for fixed effects and >50% for random effects) were re-evaluated. Additionally, asymptotic 95% CIs of the parameter estimates were computed using the standard errors (SEs).

4.6.5 Visual Predictive Checks

Visual predictive checks (VPCs) were performed to assess a model's simulation properties. The basic premise is that a model derived from an observed data set should be able to produce simulated data that are similar to the original observed data. The VPCs were performed by simulating 500 replicates of the concentration-time data from the posterior distribution of the model to compute empirical 95% confidence intervals (CIs) for the 10^{th}, 50^{th}, and 90^{th} percentiles of the simulated data. The observed data were then overlaid, along with the corresponding percentiles (i.e., 10^{th}, 50^{th}, and 90^{th}). Also, prediction corrected visual predictive checks (pcVPCs) were generated. (R13-0300) If a strong covariate effect was included in the model, the VPCs and/or pcVPCs were stratified by that covariate as appropriate. If a model has acceptable simulation properties, the observed and simulated percentiles should be closely aligned.

4.6.6 Individual Profiles

Individual plots with observed data, individual predictions and population predictions were produced. Due to the large number of subjects included in the present analysis, only a representative subset of individuals were shown. Different occasions for the same individual were shown on the same plot, using time after dose.

5. ASSUMPTIONS

Table 3 Model Assumptions

Assumptions	Justification	Status	Approach	Evaluation
Assumption1	Justification1	Status1	Test Approach1	Evaluation1
Assumption2	Justification2	Status2	Test Approach2	Evaluation2
Assumption3	Justification3	Status3	Test Approach3	Evaluation3
Assumption4	Justification4	Status4	Test Approach4	Evaluation4
Assumption5	Justification5	Status5	Test Approach5	Evaluation5
Assumption6	Justification6	Status6	Test Approach6	Evaluation6

6. RESULTS

6.1 EXPLORATORY GRAPHICAL ANALYSIS

6.2 POPULATION PHARMACOKINETIC MODEL DEVELOPMENT

6.2.1 Summary of the Final Population PK Model

6.2.2 Evaluation of the Final Population PK Model

Some text.

7. DISCUSSION

Paragraph 1.

Paragraph 2. To be added. Some more text.

Paragraph 3.

8. CONCLUSIONS

To be added.

Some more text.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R24-1740 SL Beal et al. *NONMEM 7.4.3 users guides*. Accessed 2024-05-08. 2019. URL: https://nonmem.iconplc.com/%5C#/nonmem743.

R13-0300 Bergstrand M, Hooker A, Wallin J, et al. 'Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models'. In: *The AAPS journal* 13.2 (2011), pp. 143–151.

9.2 UNPUBLISHED REFERENCES

10. APPENDICES

10.1 DATA SPECIFICATION

The data specification document is available internally (See Section 3.1).

10.2 POPULATION PK MODEL DEVELOPMENT

10.2.1 Base Model Development

The following section describes the pivotal models evaluated during development of the base model for drug scientific name. A summary of pivotal models evaluated in this section is shown in Table 4 with the highlighted yellow row showing the best base model to fit the data. Initially, the model development began with using the HV model from the literature and a Bayesian feedback was performed (with no parameter estimation, i.e. MAXEVAL=0). In the second run (run2), the effect of ADA on CL/F was removed, which had a negative effect on the model with a OFV increase of over 200 points. Parameter estimation proceeded with run21, where the RUV model was simplified by removing additive error, and the η terms for apparent inter-compartmental clearance (Q/F), apparent peripheral volume of distribution (V_p/F), first order absorption rate constant (k_a) were removed as the data was not informative to estimate these parameters. Run21 was found to be stable after these changes, and model development then proceeded to covariate model development. Parameter estimates of the base model are shown in Table 5.

Table 4 Pivotal Model Building Steps – Base Model

Run #	Ref #	OFV	ΔOFV	Minimisation	Covariance Step	Description
1	-	3986.5	-	-	No	Literature model, adpated for 1297.4 ADA effect included as-is from original model (MAX EVAL 0)
2	1	4187.4	200.9	Yes	No	Removed ADA positive covariate. Default CL assumes everyone is negative.
21	2	1721.1	-2466.3	Yes	Yes	Prop. error only, removed ETA for Q/F, Vp/F, ka. Estimating corr between CL/F-Vc/F

The highlighted yellow row represents the final base model. OFV = objective function value.

Table 5 Parameter Estimates for the Base Population PK Model

Name	Value	RSE(%)
Clearance (CL/F, L/h)	0.0195	1.4
Central Volume (V_c/F, L)	2.49 FIX	-
Inter-compartmental Clearance (Q/F, L/h)	0.0709 FIX	-
Peripheral Volume (V_p/F, L)	3.74 FIX	-
First-order absorption rate (ka, /h)	0.0108 FIX	-
Zero-order absorption duration (D_1, h)	2.96 FIX	-
Exponent of weight effect on CL/F and Q/F (-)	0.75 FIX	-
Exponent of weight effect on V_c/F andV_p/F (-)	1.0 FIX	-
BSV on CL/F	0.425	10.8
BSV on V_c/F	2.36	15.2
BSV Correlation CL/F-V_c/F	-0.463	15.2
Proportional RUV	0.319	0.14

%RSE = percent relative standard error. Standard errors obtained via covariance step in NONMEM.
Source: /pmx_bip/Projects_PMx/BI695501/CLINICAL/ANALYSES/1297_4/MODELS/run21/

10.2.1.1 Evaluation of the Base Population PK Model

Plots of observed versus population predicted plasma concentrations and observed versus individual predicted plasma concentrations are presented below in Figure 1. Plots of the observed versus population predicted concentrations demonstrated moderate bias, with the majority of data evenly scattered around the line of unity. Additionally, the apparent bias at the high population observed values was evaluated separately using VPCs (Figures 7). It can be seen that there was moderate underprediction for the median percentile, however the model has adequate predictive performance at the 5^{th} & 95^{th} percentiles with no obvious bias.

Plots of the observed concentrations versus the individual predicted concentrations, which account for random effects, were more tightly scattered around the line of unity. Additional diagnostic plots of CWRES are shown in Figures 3 – 4, which highlight that the base model fitted the data with minimal bias.

Density histograms of the BSV individual random effects are presented in Figure 5. All BSV terms were distributed around zero. Individual estimates of shrinkage for CL/F and V_c/F were 16.4% and 24.9%, respectively. A correlation was observed between CL/F and V_c/F, which was accounted for in the model by implementing a correlation term between CL/F and V_c/F, shown in Figure 6.

All standard errors, which were obtained by the covariance step in NONMEM (Table 5), for both the structural fixed effect and random effects parameter estimates were considered to be acceptable (<31%), with the exception of the correlation between CL/F and V_c/F.

To evaluate the model further, pcVPCs were constructed and are shown in Figure 7. Overall, it can be seen that the model described the observed concentrations adequately with an even

distribution of observations above and below the 10^{th} and 90^{th} prediction intervals (Figure 7). It can also be seen that the simulated median values agreed closely with the observed data (Figure 7).

Figure 1 Observations vs Population Predictions for the Base Population PK Model

The solid grey line represent the line of unity, the solid blue represent the trend in the data (Loess smooth).

Figure 2 Observations vs Individual Predictions for the Base Population PK Model

The solid grey line represent the line of unity, the solid blue represent the trend in the data (Loess smooth).

Figure 3 CWRES vs Time Plot for the Base Population PK Model

The solid grey line represent the line of unity, the solid blue represent the trend in the data (Loess smooth).

Figure 4 CWRES vs Time After Dose Plot for the Base Population PK Model

The solid grey line represent the line of unity, the solid blue represent the trend in the data (Loess smooth).

Figure 5 BSV Random Effects Distributions for the Base Population PK Model

The short vertical lines near the X-axis represents individual counts, and the vertical black line show the expected mean of zero. η-shrinkage is shown at the top for CL/F (ETA(1)) and V_c/F (ETA(2)), respectively.

Figure 6 Correlations Between Parameters for the Base Population PK Model

Each black dot represents each individual's η-correlation, with the overall correlation coefficient shown in the plot. Note: ETA-V2 refers to ETA for V_c/F.

Figure 7 pcVPC for the Base Population PK Model: Overall

Open circles = individual observed, dashed black lines = observed 5^{th} & 95^{th} percentiles of the observed data, solid black line = observed median concentration, solid blue line = median of the model predictions, solid red line = median of the 5^{th} & 95^{th} percentiles of the simulated data, shaded areas = 95% prediction interval around the model predicted 5^{th}, 50^{th}, & 95^{th} percentiles, green lines = bin limits. Note: time after dose is shown. Source: /pmx_bip/Projects_PMx/BI695501/CLINICAL/ANALYSES/1297_4/MODELS/run21/vpc_run21/

10.2.2 Covariate Model Development

From reviewing the graphical analysis of the concentration-time profiles (see Section 4.3), the η-covariate plots (Appendices 10.3.1), and based on physiological plausibility, the potential covariate effects of sex, ADA, CRP, eGFR, and serum albumin were evaluated on CL/F. Covariate analysis were performed according the pre-defined ΔOFV thresholds as described in Section 4.5, and the pivotal models are shown in Table ??.

The highlighted yellow row represents the final (covariate) model. The highlighted cyan rows represent models that were not pursued further.

OFV = objective function value.

10.3 SUPPLEMENTARY FIGURES

10.3.1 Additional Diagnostic Plots for the Base Model

Figure 8 Effect of Race on CL/F for the Base Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. interquartile range (IQR)), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 9 Effect of Sex on CL/F for the Base Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 10 Effect of Race on V_c/F for the Base Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 11 Effect of Sex on V_c/F for the Base Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 12 Effect of Age, Weight, BMI, BSA, eGFR, CRP, and ADA on CL/F for the Base Model

The dots represent each individual post-hoc estimate, the solid grey line line represents zero, and the dashed blue line represents the trend in the data (Loess smooth).

Figure 13 Effect of Age, Weight, BMI, BSA, eGFR, CRP, and ADA on V_c/F for the Base Model

The dots represent each individual post-hoc estimate, the solid grey line line represents zero, and the dashed blue line represents the trend in the data (Loess smooth).

Figure 14 Example Individual Fits for the Base Model

The solid blue lines show the individual model prediction (IPRED), the dashed blue lines show the population model prediction (PRED), and the grey circles show the observations (DV).

10.3.2 Additional Diagnostic Plots for the Final Model

Figure 15 Effect of Race on CL/F for the Final Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25^{th} and 75^{th} percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 16 Effect of Sex on CL/F for the Final Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25^{th} and 75^{th} percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 17 Effect of Race on V_c/F for the Final Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25^{th} and 75^{th} percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 18 Effect of Sex on V_c/F for the Final Model

The dashed line represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25^{th} and 75^{th} percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. *N* denotes the number of subjects in each subcategory. Note: baseline-values are shown.

Figure 19 Effect of Age, Weight, BMI, BSA, eGFR, CRP, and ADA on CL/F for the Final Model

The dots represent each individual post-hoc estimate, the solid grey line line represents zero, and the dashed blue line represents the trend in the data (Loess smooth).

Figure 20 Effect of Age, Weight, BMI, BSA, eGFR, CRP, and ADA on V_c/F for the Final Model

The dots represent each individual post-hoc estimate, the solid grey line line represents zero, and the dashed blue line represents the trend in the data (Loess smooth).

Figure 21 Example Individual Fits for the Final Model (1)

The solid blue lines show the individual model prediction (IPRED), the dashed blue lines show the population model prediction (PRED), and the grey circles show the observations (DV).

Figure 22 Example Individual Fits for the Final Model (2)

The solid blue lines show the individual model prediction (IPRED), the dashed blue lines show the population model prediction (PRED), and the grey circles show the observations (DV).

Figure 23 Example Individual Fits for the Final Model (3)

The solid blue lines show the individual model prediction (IPRED), the dashed blue lines show the population model prediction (PRED), and the grey circles show the observations (DV).

10.4 MODEL CODE

10.4.1 NONMEM Control Stream for the Base Model

10.4.2 NONMEM Listing File for the Base Model

10.4.3 NONMEM Control Stream for the Final Model

10.4.4 NONMEM Listing File for the Final Model