YOUR LOGO

POPULATION PHARMACOKINETIC ANALYSIS REPORT

<PRODUCT/PROJECT> / POHXXXX

<Title of the study>

Test Facility : <Institution>
99999 City
<Country>

Author : <Name1>
Reviewer : <Name2>

Document Reference : Final Study Report – POHXXXX

Date : 2021-08-09

Total number of pages : 66 + 1 page for Electronic Signatures

STUDY REPORT REVIEW AND APPROVAL

We, the undersigned, confirm that this report accurately reflects the findings and conclusions of study POHXXXX.

Author:	
<Name1> <Jobtitle> <Group> <Department>	Signed electronically

Reviewer:	
<Name2> <Jobtitle> Head of <Group> <Department>	Signed electronically

Approval:	
<Name3> Head of <Department>	Signed electronically

SUMMARY

This is an example report created from the LaTeX template introduced in the main paper. This example report serves as a guide through conducting the report generation using the proposed template structure. It is reproducible by following the supplied supplemental materials.

The non-linear mixed effect modeling (NONMEM) Tutorial Part I by Robert J. Bauer, CPT PSP 2019 [1], serves as a basis for the creation of example figures and tables. All model code and data are available in the aforementioned publication.

By using the supplied materials and following the instructions in the main article, the reader should at least be able to:

- Compile the single LaTeX text chunks into a single report,
- Link figures and tables generated in R within the report,
- Work in the proposed folder structures that feed into the reporting template.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS, TERMS, AND SYMBOLS

CL	clearance
V	volume of distribution
η	random effect
ω	variance describing between-subject variability
σ	variance of residual variability
BLQ	below limit of quantification
CI	confidence interval
CWRES	weighted residuals evaluated at individual conditional estimates
DV	dependent variable
EVID	event identification
FOCE/INTERACTION	first order conditional estimation method with interaction between ω and σ
IIV	inter-individual variability
IPRED	individual predicted data based on individual empirical Bayes parameter estimates
IWRES	absolute individual weighted residuals
MDV	missing dependent variable
N	number
NM-TRAN	NONMEM translator (non-interactive pre-processor)
NONMEM	non-linear mixed effect modeling
NPDE	normalized prediction distribution errors
OFV	objective function value
PK	pharmacokinetics
PopPK	population pharmacokinetics
PRED	predicted data based on population parameter estimates
PREDPP	package of NONMEM subroutines to compute predictions for population PK data
RSE	relative standard error
SD	standard deviation
SE	standard error
WT	body weight

1 INTRODUCTION

This sample report demonstrates how to include essential output of a population pharmacokinetic (PopPK) analysis. Data and models are taken from a previous NONMEM tutorial [1].

The structure of this report is essentially based on the proposed structure of the regulatory guidelines compared in the Supplementary Material S1 of the main article. Depending on the region, adjustments may need to be made to the section headings.

2 OBJECTIVES

By following the instructions from the main paper a report describing the findings from the modeling exercise in [1] can be compiled.

3 DATA

3.1 Description of clinical studies

The key elements of the study example [1] are described in Table 1.
In a Phase 2 study in 60 adult patients, an anesthetic was given at 1, 2 and 4 mg doses via intravenous infusion over 5 hours. Plasma samples were collected at 1, 5, 12 and 24 hours post dose.

Table 1: Key design elements of clinical studies included in the analysis

Study Number	Phase	Title/Design	Treatment	Study Population	Sampling Times
504	2	text[1]	1 mg, 2 mg, or 4 mg dose of an anesthetic over a 5-hour constant-rate intravenous infusion	N = 60 surgical patients	Individual, plasma samples were obtained at four time points after the start of the infusion (1, 5, 12, and 24 hours postinitiation)

[1] Your footnote text [2] Your footnote text

3.2 Dataset creation

The data set ’501.csv’ was obtained from Supplementary Materials S2 in [1]. In order to comply with the requirements of post-processing tools mentioned in the report, that facilitate automation across the established folder structures, the NONMEM variables event identification (EVID) and missing dependent variable (MDV) were added.

3.3 Bioanalysis

No information on the underlying bioanalysis is available for the study example. This section can be adapted as suitable.

4 METHODS

4.1 Overview of model development process

Ideally, a PopPK analysis follows a prespecified PopPK Analysis Plan (PAP), which is then made available in an Appendix.

4.2 Population pharmacokinetic modeling

In this example PopPK modelling was conducted using NONMEM 7.4.1.

4.2.1 Structural model

The structural model is given by the base model supplied by Bauer et al. [1].

4.2.2 Statistical model

The statistical model was not further adapted from the base model.

4.2.3 Covariate model

To illustrate the workflow through the proposed templates a covariate analysis using the literature model is demonstrated.

4.2.4 Statistical methods for nonlinear mixed effect models

The first order conditional estimation method with interaction between ω and σ (FOCE/INTERACTION) estimation algorithm was used to fit the model. The objective function value (OFV), which is statistically minus two times the log likelihood of the data, was calculated for each model fit within NONMEM. The OFV on inclusion of a parameter was assumed to be χ^2 distributed with number of degrees of freedom equal to the number of parameters added to the nested model. Nested models were accepted as a better model if the objective function was 3.84 points lower ($P < 0.05$) when including a new parameter.

4.2.5 Model evaluation

Evaluation of the quality of the model was based on likelihood ratio test (OFV), goodness-of-fit plots, and η-shrinkage.

4.2.5.1 Goodness-of-fit plots

Goodness-of-fit was graphically evaluated as recommended in [2]. The observed versus predicted observations (PRED and IPRED) were investigated to determine if the model described the data accurately. For each observation, weighted residuals evaluated at individual conditional estimates (CWRES) and absolute individual weighted residuals (IWRES) were calculated. The plots of IWRES or CWRES versus IPRED and PRED were used to detect potential bias in individual and population predictions, respectively. The graph of CWRES versus time was plotted to assess a potential time dependency. No bias was concluded if data points were (more or less) scattered evenly around the horizontal zero-line. Histograms and/or quantile-quantile probability plots (Q-Q plots) were drawn to assess the normality of a given distribution.

The distribution of the individual PK parameters was also evaluated by drawing density plots of random effects (ηs). An absence of a trend in the plots of ηs versus covariates would support an adequate consideration of covariates in the model.

The descriptive performance of the model was evaluated by calculation of normalized prediction distribution errorss (NPDEs) in NONMEM [3, 4]. Subsequently, NPDEs were evaluated in R to determine if the model described the data observed adequately. The NPDEs should follow a $\mathcal{N}(0,\ 1)$ distribution. Plots of NPDEs versus observations and versus time were also evaluated to determine that no trends were present.

4.2.5.2 Eta-shrinkage

The extent of Bayesian shrinkage (η-shrinkage) was evaluated using Equation (1) [5]:

$$\eta - shrinkage = \left(1 - \frac{SD_{\eta_{EBE,P}}}{\omega_P}\right) \cdot 100\% \tag{1}$$

with EBE as Empirical Bayes Estimates, given for a parameter P. Large values of η-shrinkage, e.g., values > 50%, would be associated with generally poor individual estimates of that parameter.

4.3 Simulations

No simulations were performed for the example report. Please adapt this section as suitable. …

4.4 Software and hardware

Data were analyzed using NONMEM software version 7.4.1 (ICON, Development Solutions, Elliot City, MD, USA). NONMEM and its modules NM-TRAN and PREDPP were compiled with the GNU Compiler Collection for Fortran 90/95 (GCC 4.8, [6]) running under openSUSE Linux (x86_64), on a computer cluster based upon Intel® multi-processor workstations/servers from HP® or Fujitsu® [7].

All NONMEM runs were stored on the file server under unique archive numbers.

Graphical analysis, descriptive statistics, and evaluation of NONMEM outputs were conducted using R [8]. The used R scripts are documented in Appendix C.1. The version of R and package dependencies are documented in Appendix C.2.

5 RESULTS

5.1 Data disposition and subject population summary

In total, there were 240 pharmacokinetic (PK) samples from 60 subjects available for analysis. Table 2 presents an overview of the concentrations. None of the concentrations were excluded from the analysis, e.g., due to below limit of quantification (BLQ) status. Concentration versus time plots exhibit a monophasic decline, which is indicative of a one-compartment model (Figure 1).

Table 2: Overview of PK samples (statistics in µg/mL)

	MDV	N	Missing	Mean	SD	Min	Q1	Median	Q3	Max
DV	0	240	0	27.87	30.30	0.92	8.36	17.52	33.67	198.33
	1	0	60							

The gender ratio of the subjects included in the data set is roughly balanced, with 53% females and 47% males. (Table 3). Descriptive statistics of covariates age and weight are presented in Table 4.

Table 3: Number and percentage of subjects by sex

	Level	N	%
SEX	female	32	53.3
	male	28	46.7

Table 4: Summary statistics of continuous covariates

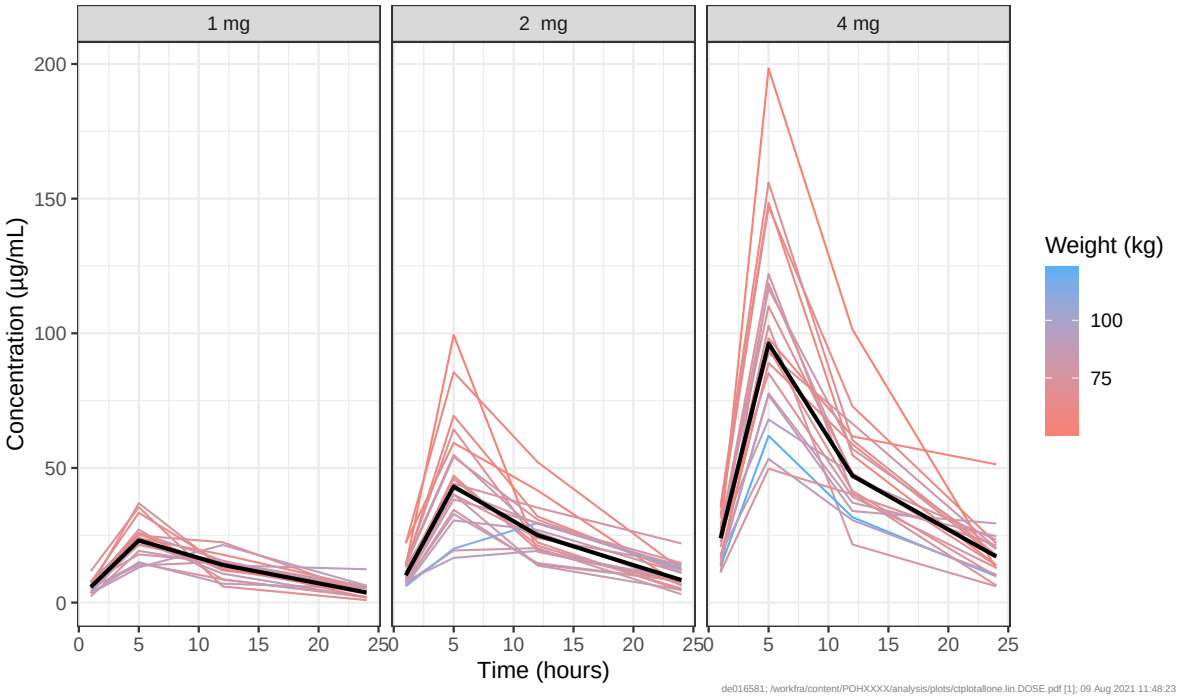
	N	Mean	SD	Min	Q1	Median	Q3	Max
Age (years)	60	50.78	12.42	25.00	41.00	51.00	60.00	75.00
Weight (kg)	60	76.91	13.64	50.30	69.60	77.35	85.35	123.00

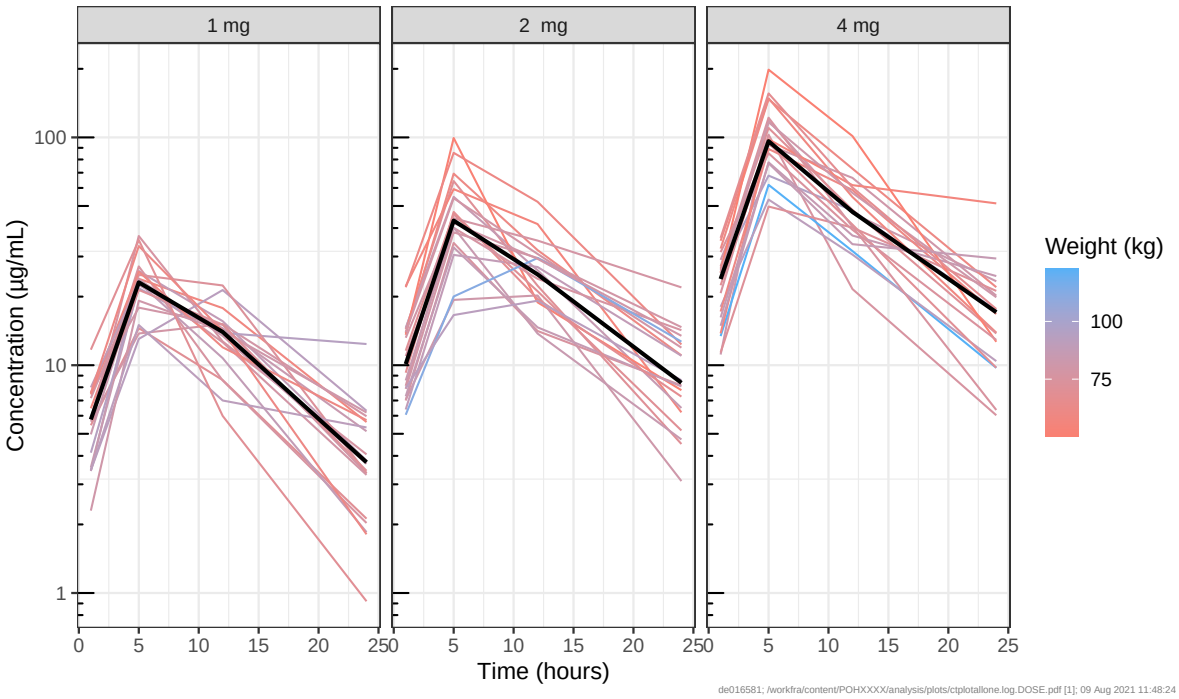
Men and women are about the same age, with the men being slightly heavier than the women (Table 5).

Table 5: Summary statistics of continuous covariates by sex

Covariate	Sex	N	Mean	SD	Min	Q1	Median	Q3	Max
Age(y)	female	32	50.9	10.1	38.0	44.0	48.5	57.0	72.0
Age(y)	male	28	50.6	14.9	25.0	36.8	53.0	60.0	75.0
Weight (kg)	female	32	74.1	12.8	50.3	65.7	72.0	85.9	96.3
Weight (kg)	male	28	80.1	14.1	58.4	75.7	79.3	84.8	123.0

Figure 1: Concentrations versus time facetted by dose and colored by body weight on linear (upper panel) and semi-logarithmic scale (lower panel). The thick black line represents the median





5.2 Population pharmacokinetic modeling results

5.2.1 Base model

Run №1117171 is the base model as derived from the model 504 described in [1, p. 536]. The data were fit to a one-compartment constant-rate infusion model with the parameters clearance (*CL*) and volume of distribution (*V*). Inter-individual variability (IIV) was estimated on both *CL* and *V*. The residual unknown variability is proportional as the drug assay has a constant coefficient of variation as concentrations increase. Model parameters are summarized in Table 6. Goodness-of-fit plots are presented in Figures 2 and 3.

Plots of ηs versus covariates indicate moderate correlation between age and *CL*, weight and *V* and a low correlation between weight and *CL* (Figure 9).

The NONMEM control stream and report file is presented in Appendix B.1.

Table 6: Parameter estimates and standard errors from model no. 1117171

	Estimate (%RSE)	95% CI	Shrinkage(%)
Structural Model:			
TVCL	3.09 (3.7)	2.86 - 3.32	
TVV	35.1 (4.69)	31.8 - 38.4	
Inter-individual Variability (ω):			
ETCL:ETCL	0.252 (10.8)	0.19 - 0.301	9.42
ETV:ETV	0.319 (9.08)	0.255 - 0.373	9.27
Residual Error (σ):			
(PERR:PERR)	0.222 (7.15)	0.188 - 0.252	20.6

TVCL, clearance; TVV, volume of distribution
RSE = relative standard error, SD = standard deviation; SE = standard error; CI = confidence interval calculated as 95% CI = Point estimate ±2· SE; NA = not applicable.
RSE of parameter estimate is calculated as 100 × (SE/typical value).
RSE of inter-individual variability (ω) and residual variability (sigma) magnitude is presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.
Shrinkage is calculated as 100 × (1 – SD of post hocs/ω), with ω = sqrt(variance estimate).

Figure 2: Goodness-of-fit plots of model no. 1117171 (1/2)

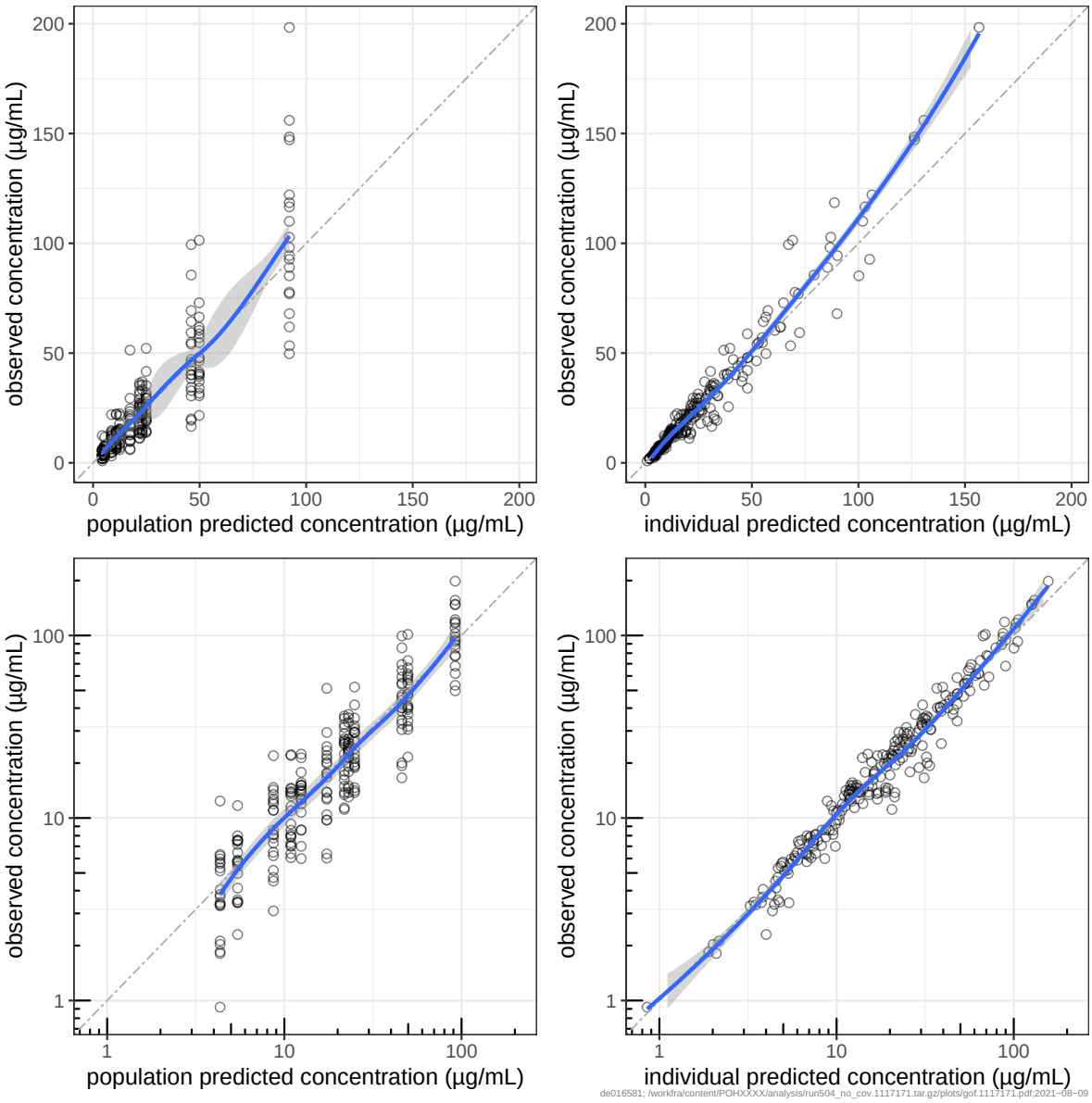
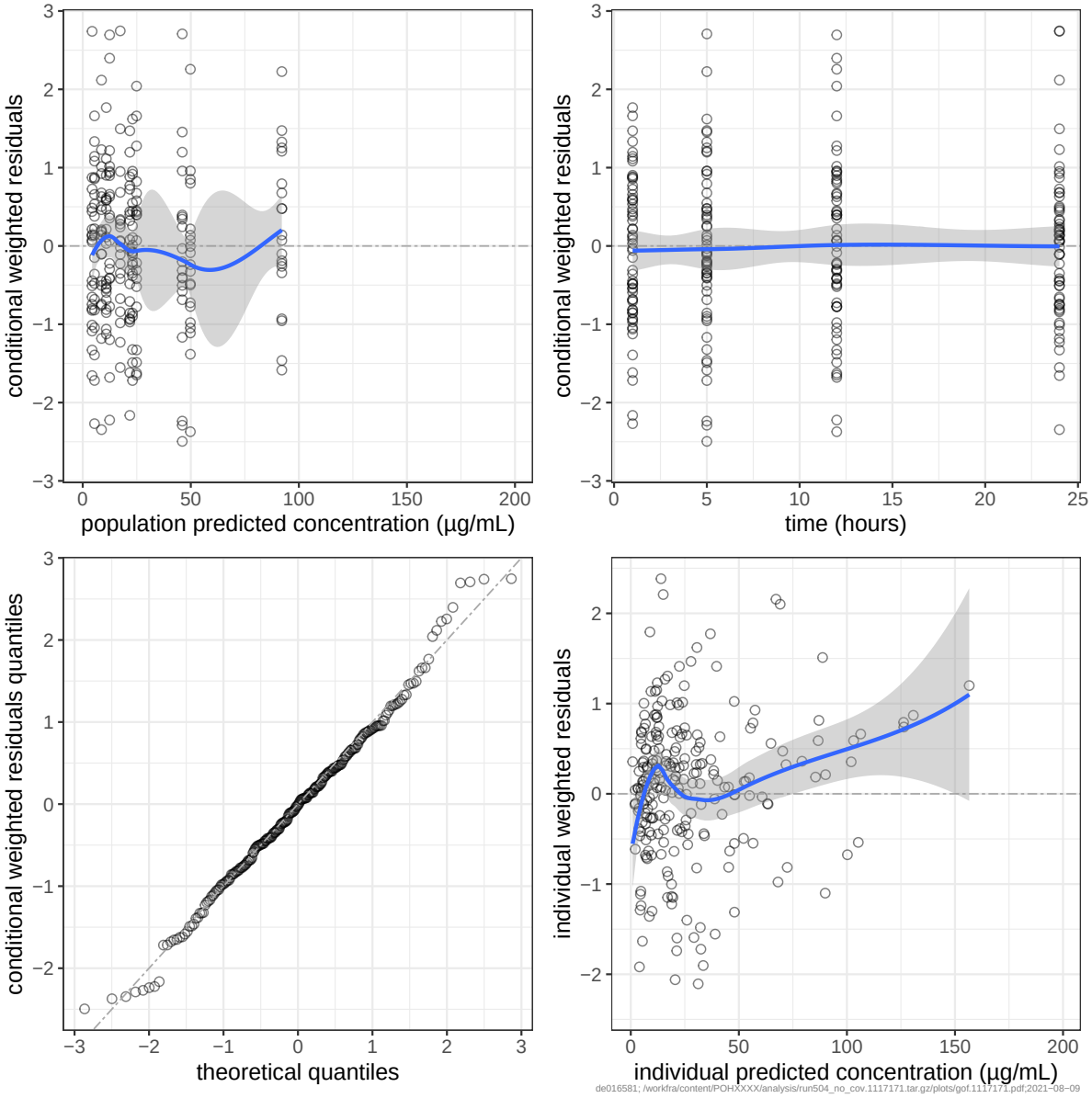


Figure 3: Goodness-of-fit plots of model no. 1117171 (2/2)



5.2.2 Covariate analysis

Run №1117172 is the full covariate model as described in [1, p. 536]. Covariates included age, weight and sex on each *CL* and *V*. Table 7 indicates that the model could be simplified by recognizing that the parameters estimating the effects of sex on *CL* and *V* are both estimated to be near 1, the effect of age on *V* is near 0, and the effect of weight on *CL* is near 0.75 (an allometric weight coefficient that is consistent with literature for allometric relationships between *CL* and weight for many small molecules) [1].

Goodness-of-fit plots are presented in Figures 4 and 5. The NONMEM control stream and report file is presented in Appendix B.2.

Table 7: Parameter estimates and standard errors from model no. 1117172

	Estimate (%RSE)	95% CI	Shrinkage(%)
Structural Model:			
TVCL	3.03 (3.83)	2.8 - 3.26	
TVV	32.4 (4.88)	29.2 - 35.5	
WTCLEXP	0.66 (24.3)	0.34 - 0.98	
WTVEXP	1.32 (15.3)	0.918 - 1.72	
AGECLEXP	-0.534 (19.3)	-0.74 - -0.328	
AGEVEXP	0.0523 (247)	-0.206 - 0.311	
SEXCLEXP	0.904 (5.68)	0.801 - 1.01	
SEXVEXP	0.947 (7.13)	0.812 - 1.08	
Inter-individual Variability (ω):			
ETCL:ETCL	0.175 (14.9)	0.111 - 0.221	16.1
ETV:ETV	0.216 (14.8)	0.138 - 0.273	17.1
Residual Error (σ):			
(PERR:PERR)	0.224 (6.72)	0.192 - 0.253	17

TVCL, clearance; TVV, volume of distribution; covariate relationships: WTCLEXP, CL ~WT; WTVEXP, V ~WT; AGECLEXP, CL ~AGE; AGEVEXP, V ~AGE; SEXCLEXP, CL ~SEX; SEXVEXP, V ~SEX
RSE = relative standard error, SD = standard deviation; SE = standard error; CI = confidence interval calculated as 95% CI = Point estimate ±2· SE; NA = not applicable.
RSE of parameter estimate is calculated as 100 × (SE/typical value).
RSE of inter-individual variability (ω) and residual variability (sigma) magnitude is presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.
Shrinkage is calculated as 100 × (1 – SD of post hocs/ω), with ω = sqrt(variance estimate).

Figure 4: Goodness-of-fit plots of model no. 1117172 (1/2)

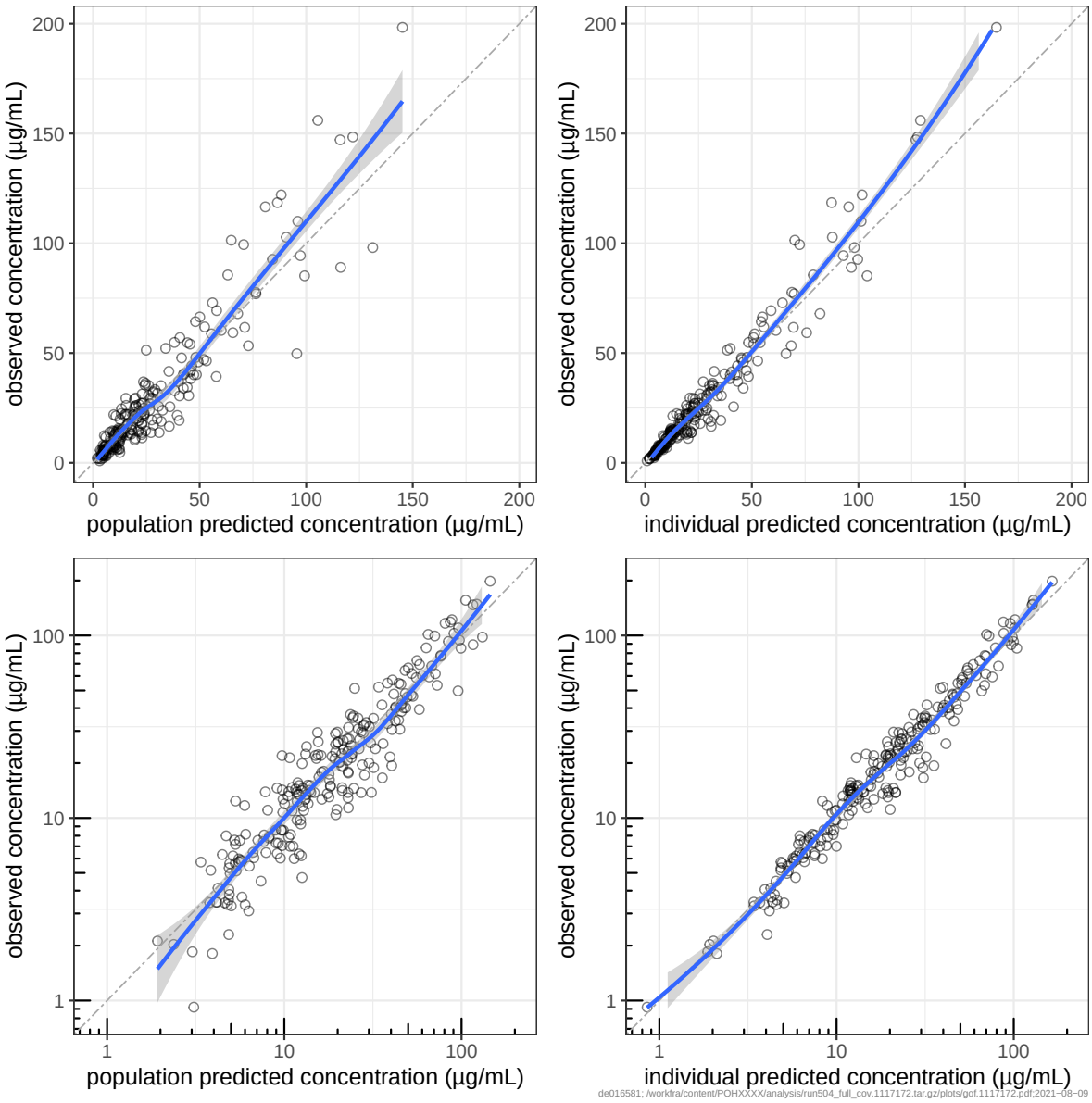
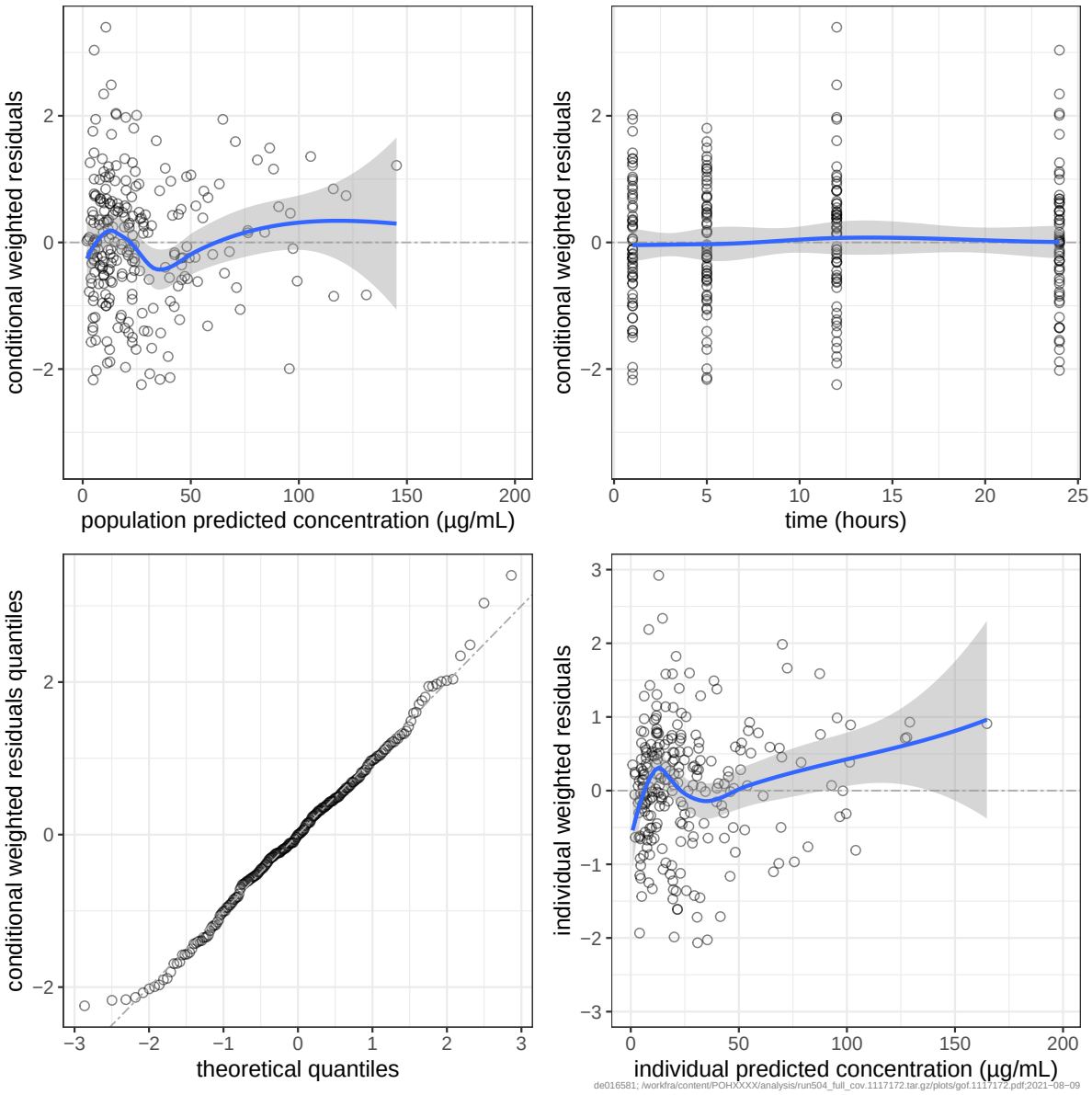


Figure 5: Goodness-of-fit plots of model no. 1117172 (2/2)



5.2.3 Final model

Model №1117172 was conveniently and reversibly simplified by fixing the appropriate THETAs to 1 and 0.75, respectively. Model parameters are summarized in Table 8. Goodness-of-fit plots are presented in Figures 6 and 7. Individual goodness-of-fit plots are shown in Figures 11 and 12. The NONMEM control stream and report file is presented in Appendix B.3.

Table 8: Parameter estimates and standard errors from model no. 1117173

	Estimate (%RSE)	95% CI	Shrinkage(%)
Structural Model:			
TVCL	2.88 (3.1)	2.7 - 3.06	
TVV	32.3 (3.78)	29.9 - 34.8	
WTCLEXP	0.75 (NA)	NA - NA	
WTVEXP	1 (NA)	NA - NA	
AGECLEXP	-0.529 (18)	-0.72 - -0.339	
SEXCLEXP	1 (NA)	NA - NA	
SEXVEXP	1 (NA)	NA - NA	
Inter-individual Variability (ω):			
ETCL:ETCL	0.185 (16.5)	0.108 - 0.238	15
ETV:ETV	0.225 (14.8)	0.143 - 0.284	16.2
Residual Error (σ):			
(PERR:PERR)	0.224 (7.41)	0.187 - 0.255	17.5

TVCL, clearance; TVV, volume of distribution; covariate relationships: WTCLEXP, CL ~WT; WTVEXP, V ~WT; AGECLEXP, CL ~AGE; AGEVEXP, V ~AGE; SEXCLEXP, CL ~SEX; SEXVEXP, V ~SEX
RSE = relative standard error, SD = standard deviation; SE = standard error; CI = confidence interval calculated as 95% CI = Point estimate ±2· SE; NA = not applicable.
RSE of parameter estimate is calculated as 100 × (SE/typical value).
RSE of inter-individual variability (ω) and residual variability (sigma) magnitude is presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.
Shrinkage is calculated as 100 × (1 – SD of post hocs/ω), with ω = sqrt(variance estimate).

Simulation-based diagnostics of the final PK model №1117173 (Figure 8) demonstrated the mean of NPDE to be 0.08 with a variance of 1.04, indicating no bias and an ability of the model to reasonably capture the underlying variability. There were also no major trends in the plots of NPDE versus predicted data based on population parameter estimates (PRED) or time, therefore, the overall NPDE results indicated adequate performance of the model to describe the data.

The scatter plot matrix presented in Figure 10 shows no more correlation between the post-hoc estimates of ηs and covariates, indicating that covariate effects have been adequately considered in the model.

An overview of the three models is shown in Table 9.

Table 9: Comparison of models

ARCHIVE	PROBLEM	nPSE	OBJ	OBJdiff	ETCL	ETV
1117171	base model	6.0	1118.3	0.0	0.252	0.319
1117173	fixed covariates	7.0	1065.4	-53.0	0.185	0.225
1117172	all covariates estimated	12.0	1058.3	-60.0	0.175	0.216

OBJ, Objective Function value; OBJdiff, difference of OBJ to the base model; nPSE, number of model parameters; ETCL, IIV on *CL*; ETV, IIV on *V*

Inclusion of covariates reduced the objective function by 60 units (fit №1117172). The final model №1117173 has a 7 units higher objective function than the full covariate model (№1117172), which is not statistically significant with 5 degrees of freedom, which is the difference in the number of parameters (Table 9). The reduction in IIV due to inclusion of covariates is -36.2% for *CL* and -41.8% for *V* (model №1117173 versus №1117171).

Figure 6: Goodness-of-fit plots of model no. 1117173 (1/2)

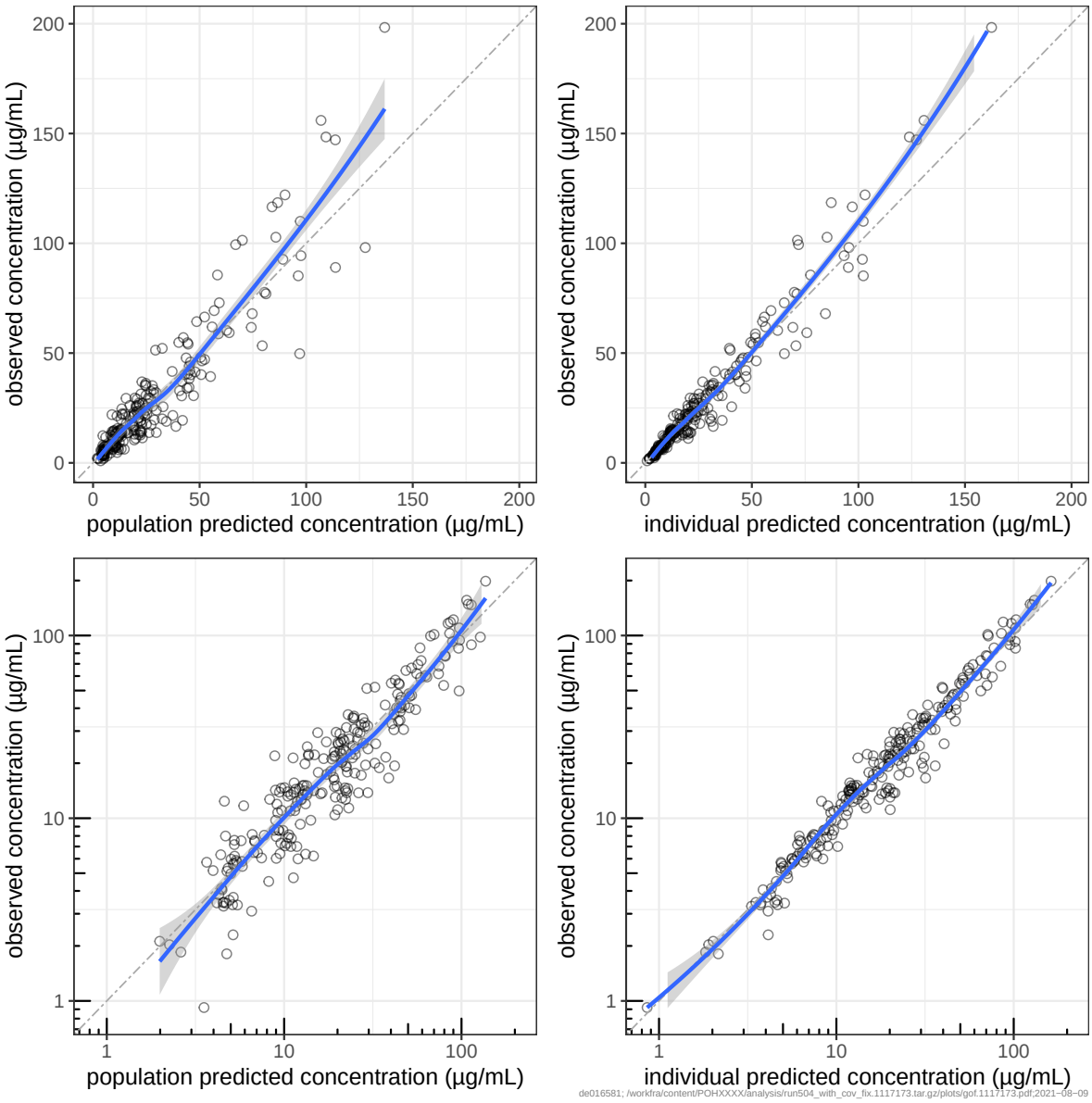


Figure 7: Goodness-of-fit plots of model no. 1117173 (2/2)

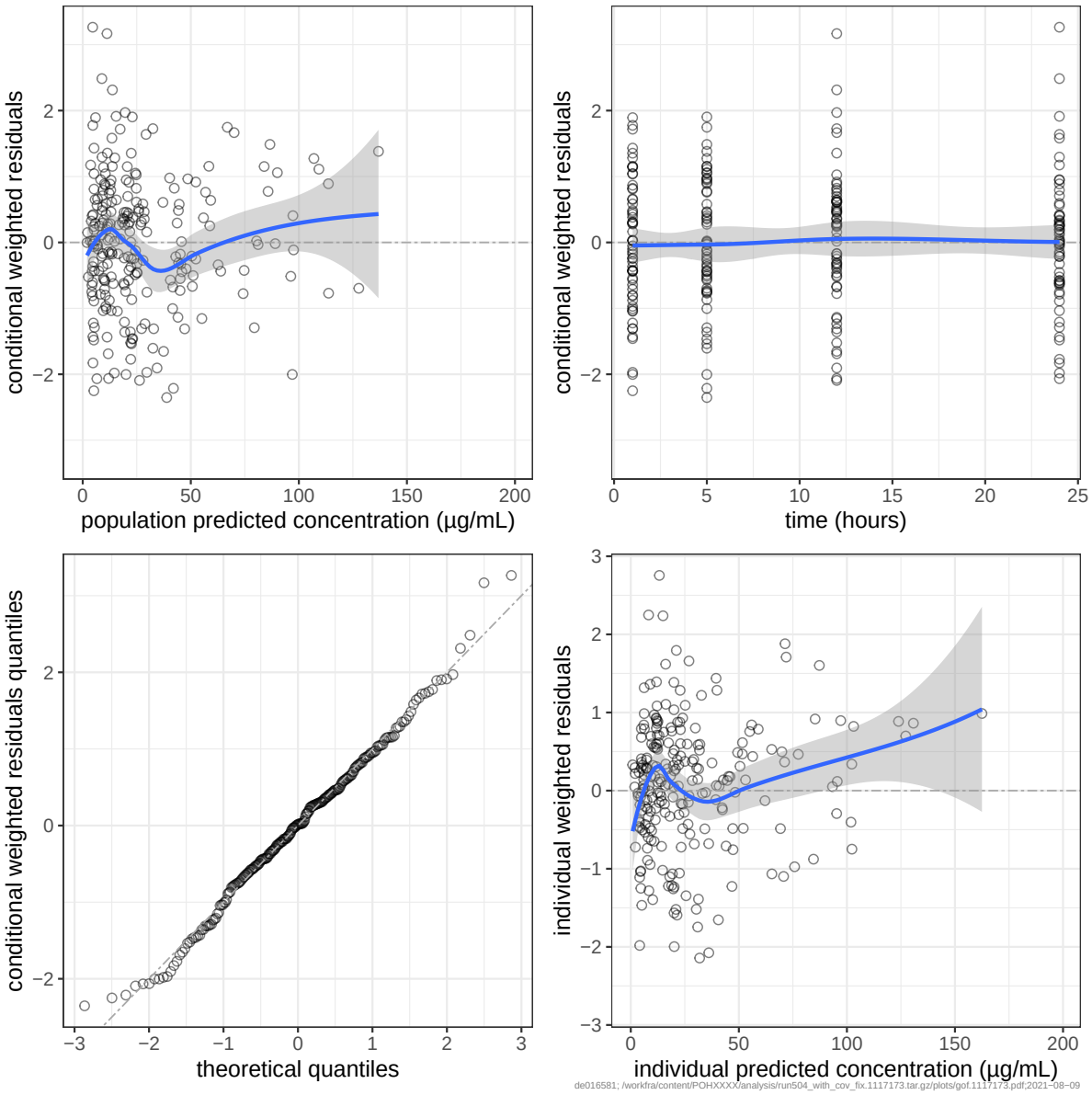
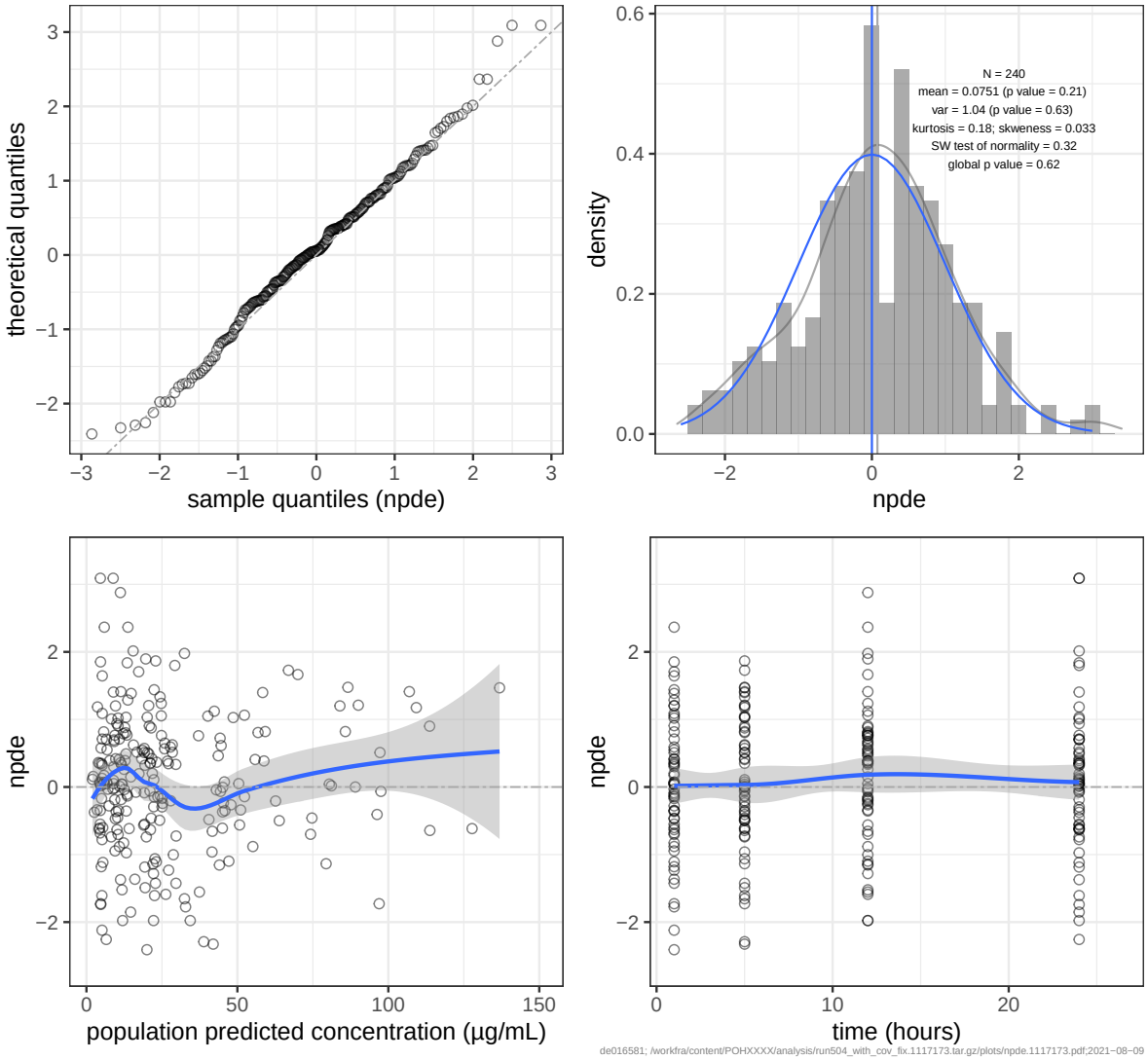


Figure 8: Normal Q-Q plot of NPDE, plot of NPDE vs. time after dose and PRED, and histogram of NPDE with the probability density function of the overlaid standard Gaussian distribution, fit №1117173



6 DISCUSSION

This example report shows how the proposed LaTeX structure can be successfully implemented. An example study was used to visualize the model building process, mainly focusing on the covariate inclusion and visualization of intermediate steps along with final model evaluation. These LaTeX report templates and automatically created folder structures can serve as the backbone of an automation process for modeling report generation, with already all necessary elements on board. Figures and tables are generated on a case-by-case basis and as needed, but are retractable and can be automatically included through this system. Text chunks, that are repetitive across different reports can already be supplied, which leads to an increase in speed for report generation and higher reproducibility.

7 CONCLUSIONS

By using the supplied materials and following the instructions in the main article, the reader should at least be able to:

- Compile the single LaTeX text chunks into a single report,
- Link figures and tables generated in R within the report,
- Work in the proposed folder structures that feed into the reporting template.

8 REFERENCES

1. Bauer RJ. NONMEM Tutorial Part I: Description of Commands and Options, with Simple Examples of Population Analysis. CPT Pharmacometrics Syst Pharmacol 2019;8:525–37.
2. Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model Evaluation of Continuous Data Pharmacometric Models: Metrics and Graphics. CPT Pharmacometrics Syst Pharmacol 2017;6:87–109.
3. Comets E, Brendel K, and Mentre F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed 2008;90:154–66.
4. Nguyen TH, Comets E, and Mentre F. Extension of NPDE for evaluation of nonlinear mixed effect models in presence of data below the quantification limit with applications to HIV dynamic model. J Pharmacokinet Pharmacodyn 2012;39:499–518.
5. Savic RM and Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J 2009;11:558–69.
6. GNU Compiler Collection. `https://gcc.gnu.org`, accessed 16.11.2015. 2015.
7. Speth H. A Linux cluster for population pharmacokinetic analyses. Int J Clin Pharmacol Ther 2004;42:189–90.
8. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria, 2019.

9 TABLES

This section is intended to provide additional tables, which do not necessarily need to be shown in the main body of the report.

10 FIGURES

This section is intended to show additional displays, which do not necessarily need to be shown in the main body of the report.

Figure 9: Correlation of random effects and covariates for model no. 1117171

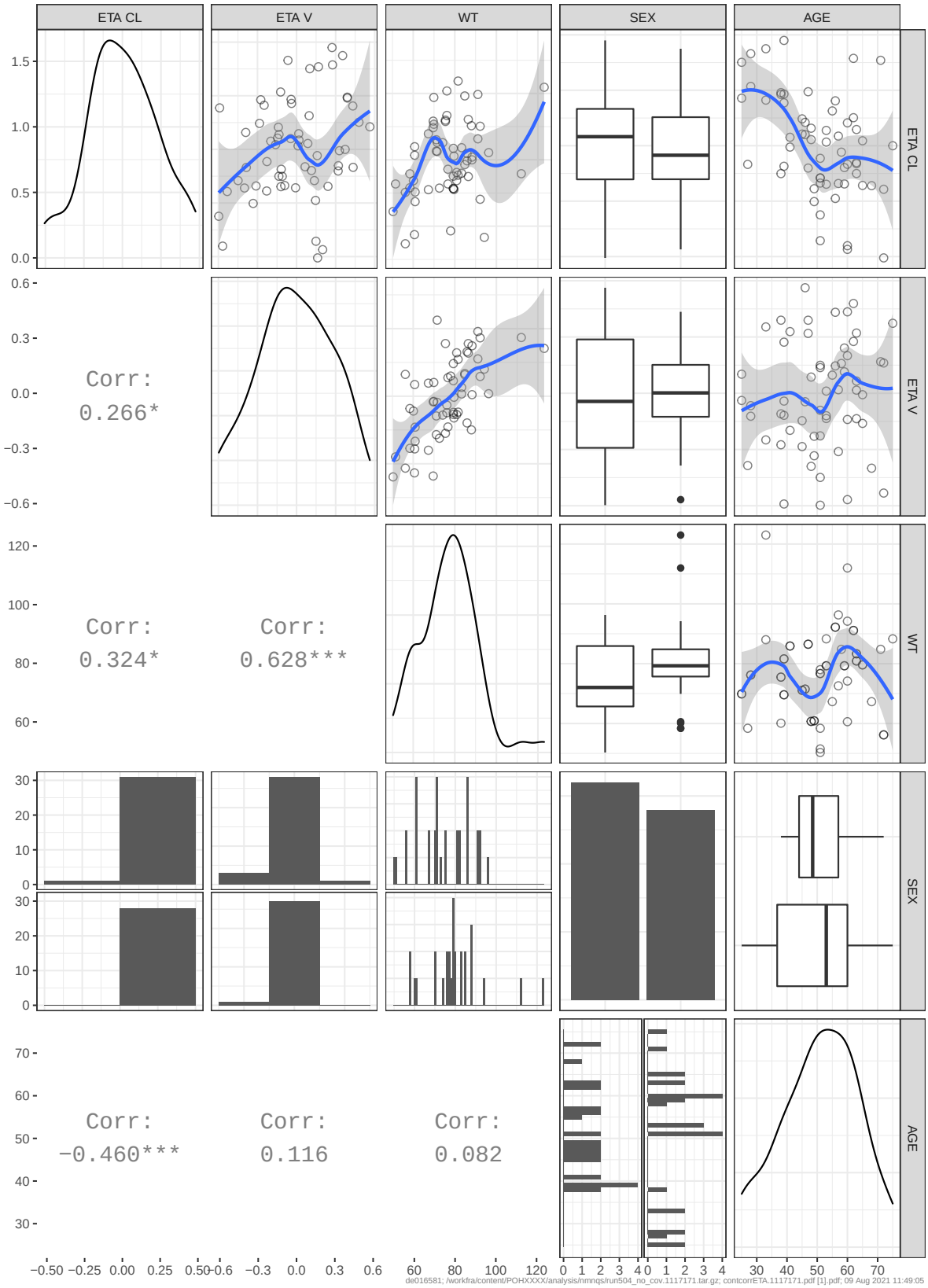


Figure 10: Correlation of random effects and covariates for model no. 1117173

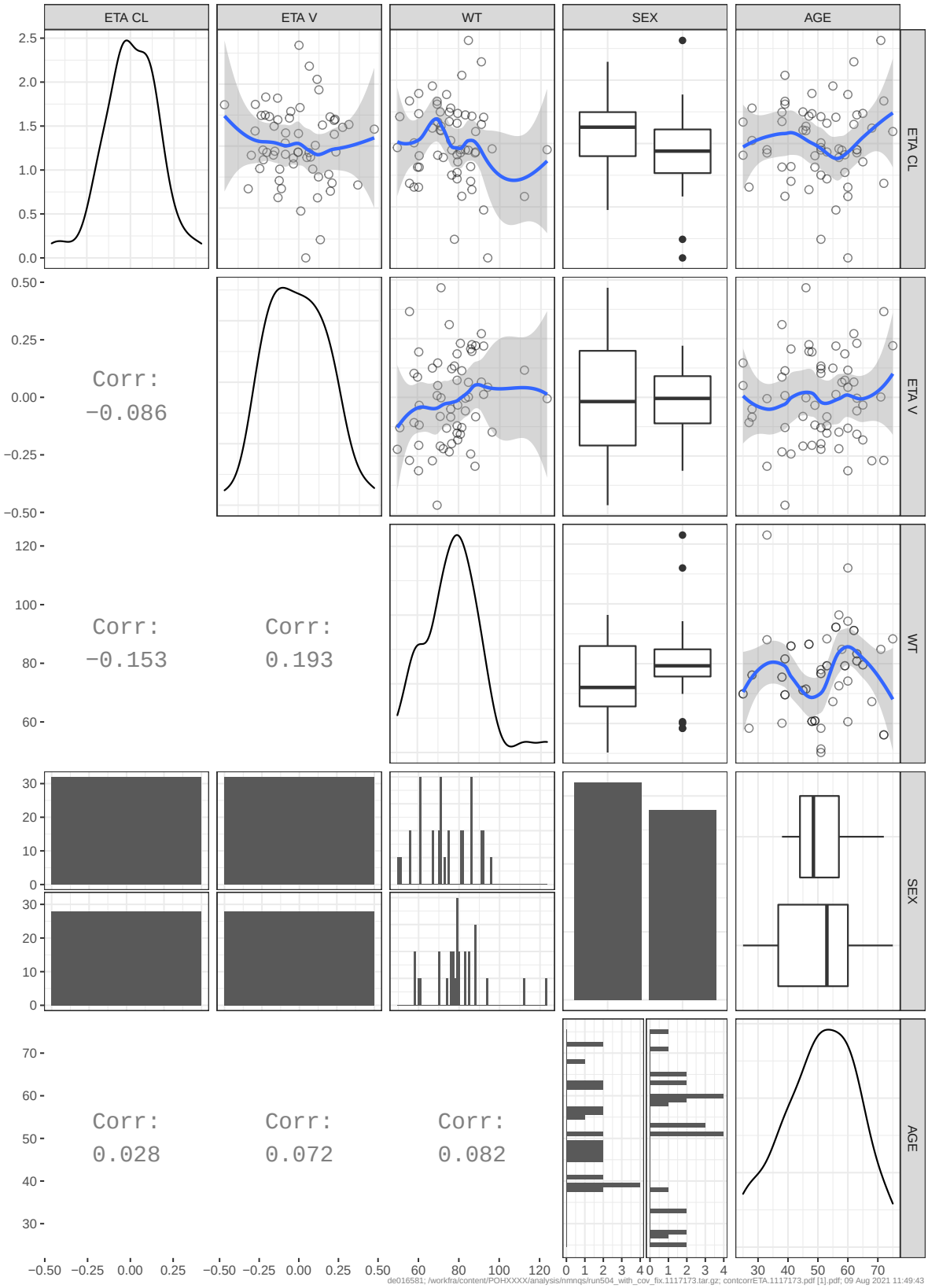


Figure 11: Observed, individual (blue), and population predicted concentrations (red) versus time (model №1117173)

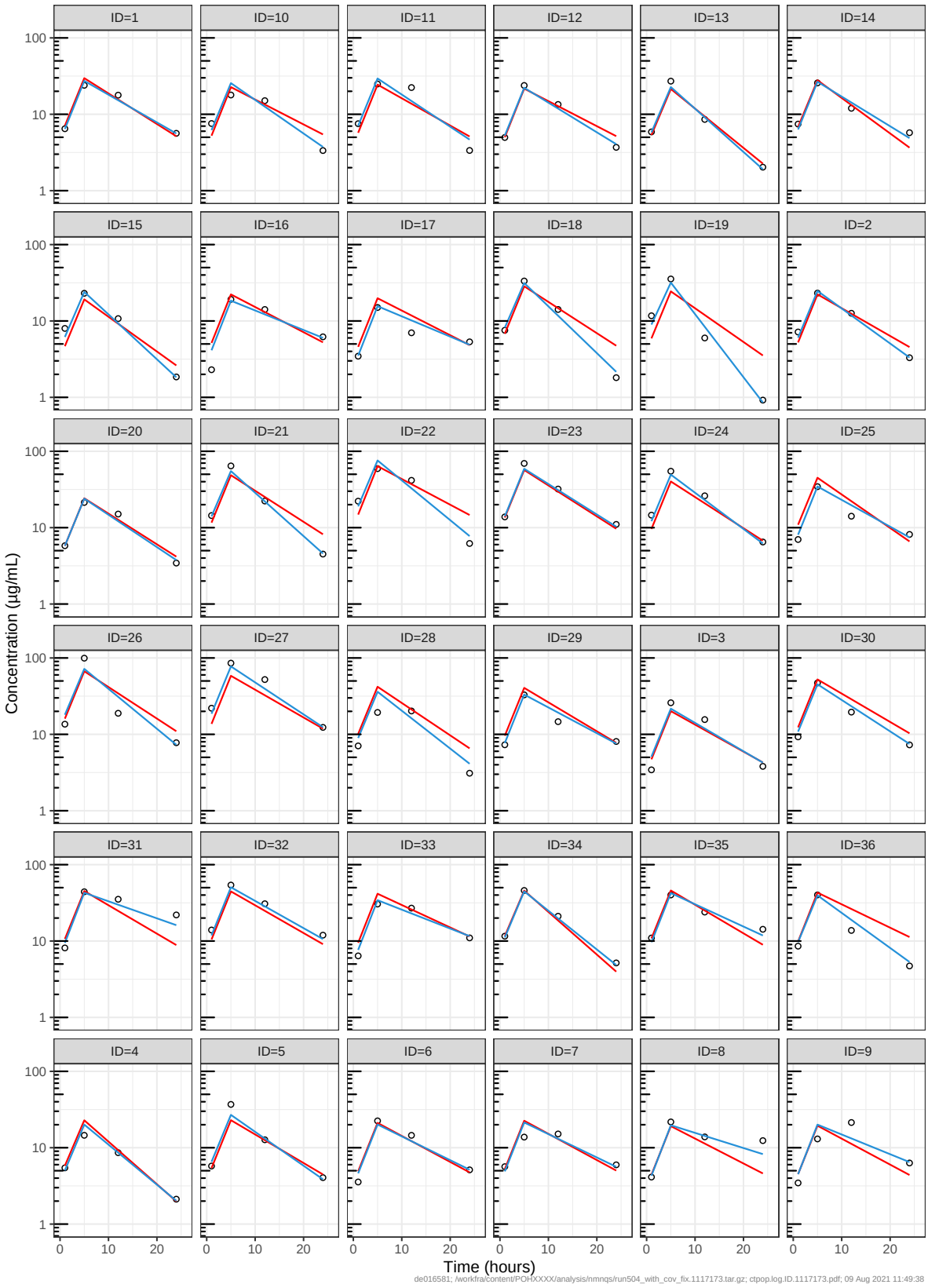
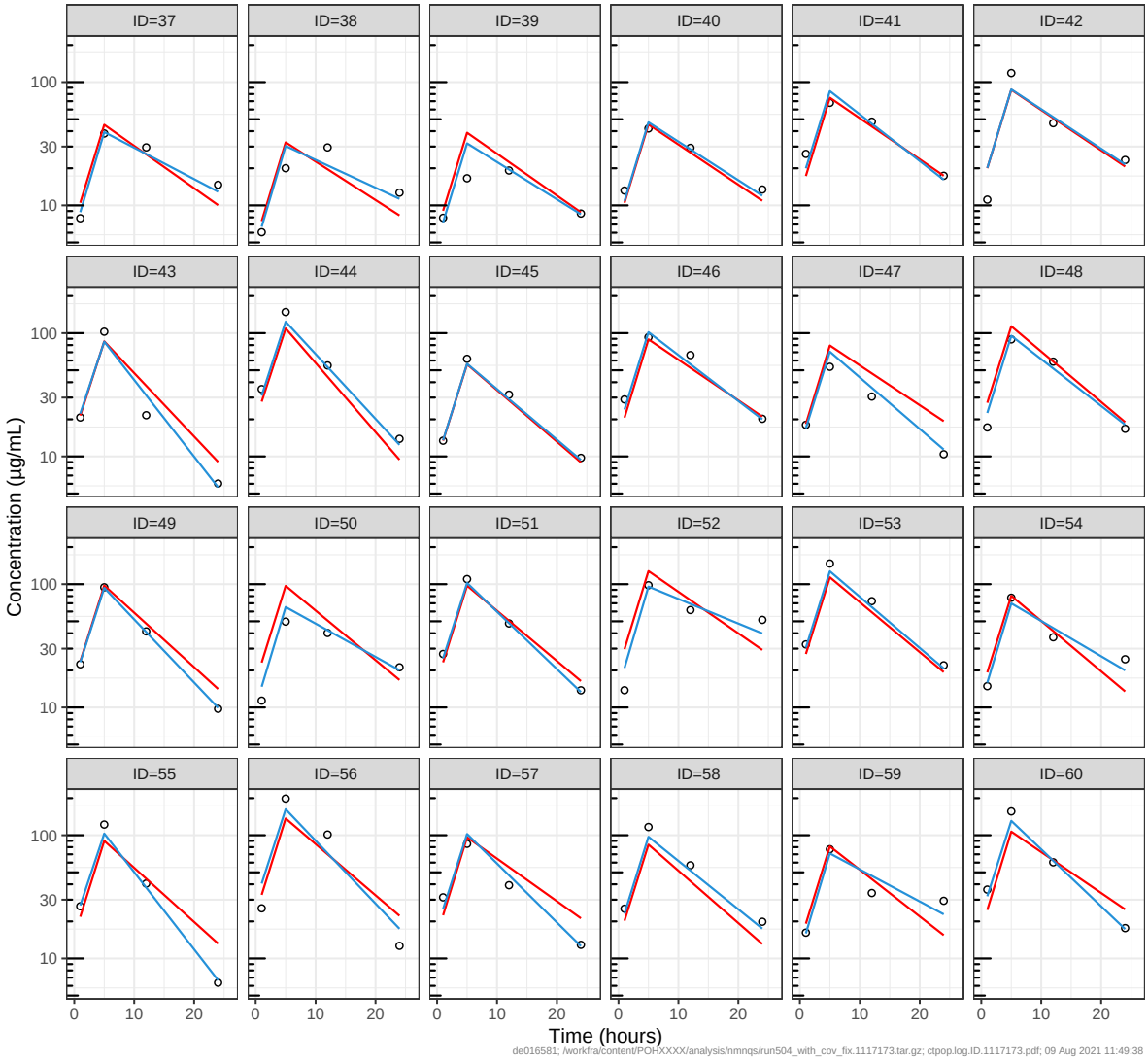


Figure 12: Observed, individual (blue), and population predicted concentrations (red) versus time (model №1117173) (cont'd)



APPENDICES

A POPULATION PHARMACOKINETIC ANALYSIS PLAN

B LISTINGS OF NONMEM CONTROL STREAMS AND REPORT FILES

B.1 Fit № 1117171

```
Mi 14. Apr 14:19:44 CEST 2021
popkin308
;Model Desc: One Compartment Model - IV Dose - (CL/V param.)
;Project Name: library
;Project ID: NO PROJECT DESCRIPTION

$PROB base model
$INPUT ID TIME DV AMT RATE WT AGE SEX EVID MDV
$DATA data_set_504.dat IGNORE=@
$SUBROUTINE ADVAN1 TRANS2
$PK
  TVCL = THETA(1)
  TVV  = THETA(2)
  ETCL = ETA(1)
  ETV  = ETA(2)

  CL = TVCL*EXP(ETA(1))
  V  = TVV*EXP(ETA(2))
  S1 = V

$ERROR
”FIRST
” USE ROCM_REAL,ONLY: THETAF,OMEGAF,SIGMAF

EPSIL  = 1.D-8
QQ = 1
IF (F .LT. EPSIL) THEN
  QQ = 0
ENDIF
IPRED = QQ * F + (1-QQ) * EPSIL


PERR=ERR(1)

Y = IPRED + IPRED*ERR(1)


IF(COMACT.GE.1)THEN
”   STD = SQRT ( SIGMAF(1,1) * IPRED**2 )
ENDIF

IRES   = DV-IPRED
IWRES  = IRES/STD


$THETA
  (0,4) ;[CL]
  (0,30) ;[V]

$OMEGA BLOCK(2)
  0.1 ;[P] INTERINDIVIDUAL VARIABILITY IN CL
  0.001 0.1 ;[P] INTERINDIVIDUAL VARIABILITY IN V
$SIGMA
  0.04 ;[P] PROPORTIONAL COMPONENT OF RESIDUAL VARIABILITY

;$MSFI
$ESTIMATION METHOD=1 INTER PRINT=5 POSTHOC MSF=adv1tr2.MSF
$COV PRINT=E
$TABLE ID TIME AMT EVID MDV IPRED IRES IWRES CWRES RES PRED DV NPDE ESAMPLE=1000 NOAPPEND FILE=sdtab001 NOPRINT ONEHEADER
$TABLE ID CL V ETA1 ETA2 ONEHEADER NOPRINT FILE=patab001
$TABLE ID AGE WT NOPRINT ONEHEADER FILE=cotab001
$TABLE ID SEX NOPRINT ONEHEADER FILE=catab001

NM-TRAN MESSAGES

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1

 (WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

License Registered to: Sanofi
Expiration Date: 14 JAN 2022
Current Date:  14 APR 2021
Days until program expires : 275
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.1
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
 PERFORMED BY NOUS INFOSYSTEMS.

 PROBLEM NO.:    1
 base model
0DATA CHECKOUT RUN:      NO
 DATA SET LOCATED ON UNIT NO.: 2
```

```
 THIS UNIT TO BE REWOUND: NO
 NO. OF DATA RECS IN DATA SET: 300
 NO. OF DATA ITEMS IN DATA SET: 10
 ID DATA ITEM IS DATA ITEM NO.: 1
 DEP VARIABLE IS DATA ITEM NO.: 3
 MDV DATA ITEM IS DATA ITEM NO.: 10
0INDICES PASSED TO SUBROUTINE PRED:
  9  2  4  5  0  0  0  0  0  0  0
0LABELS FOR DATA ITEMS:
 ID TIME DV AMT RATE WT AGE SEX EVID MDV
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
 CL V IPRED IRES IWRES
0FORMAT FOR DATA:
 (10E7.0)

 TOT. NO. OF OBS RECS: 240
 TOT. NO. OF INDIVIDUALS: 60
0LENGTH OF THETA: 2
0DEFAULT THETA BOUNDARY TEST OMITTED: NO
0OMEGA HAS BLOCK FORM:
 1
 1 1
0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO
0INITIAL ESTIMATE OF THETA:
 LOWER BOUND INITIAL EST UPPER BOUND
  0.0000E+00  0.4000E+01  0.1000E+07
  0.0000E+00  0.3000E+02  0.1000E+07
0INITIAL ESTIMATE OF OMEGA:
 BLOCK SET NO. BLOCK                                                    FIXED
      1                                                                  NO
              0.1000E+00
              0.1000E-02 0.1000E+00
0INITIAL ESTIMATE OF SIGMA:
 0.4000E-01
0COVARIANCE STEP OMITTED: NO
 EIGENVLS. PRINTED:     YES
 SPECIAL COMPUTATION:    NO
 COMPRESSED FORMAT:      NO
 GRADIENT METHOD USED: NOSLOW
 SIGDIGITS ETAHAT (SIGLO):       -1
 SIGDIGITS GRADIENTS (SIGL):     -1
 EXCLUDE COV FOR FOCE (NOFCOV):   NO
 TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO
 KNUTHSUMOFF:                     -1
 RESUME COV ANALYSIS (RESUME):    NO
 SIR SAMPLE SIZE (SIRSAMPLE):    -1
 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
 PRECONDTIONING CYCLES (PRECOND): 0
 PRECONDTIONING TYPES (PRECONDS): TOS
 FORCED PRECONDTIONING CYCLES (PFCOND):0
 PRECONDTIONING TYPE (PRETYPE): 0
 FORCED POS. DEFINITE SETTING: (FPOSDEF):0
0TABLES STEP OMITTED: NO
 NO. OF TABLES:     4
 SEED NUMBER (SEED): 11456
 RANMETHOD:       3U
 MC SAMPLES (ESAMPLE): 1000
 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
0-- TABLE 1 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: NO
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID TIME AMT EVID MDV IPRED IRES IWRES CWRES RES PRED DV NPDE
0-- TABLE 2 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID CL V ETA1 ETA2
0-- TABLE 3 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
```

```
0USER-CHOSEN ITEMS:
 ID AGE WT
0-- TABLE 4 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID SEX
1DOUBLE PRECISION PREDPP VERSION 7.4.1

 ONE COMPARTMENT MODEL (ADVAN1)
0MAXIMUM NO. OF BASIC PK PARAMETERS: 2
0BASIC PK PARAMETERS (AFTER TRANSLATION):
  ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1

 TRANSLATOR WILL CONVERT PARAMETERS
 CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)
0COMPARTMENT ATTRIBUTES
 COMPT. NO. FUNCTION INITIAL ON/OFF  DOSE    DEFAULT  DEFAULT
                STATUS  ALLOWED ALLOWED  FOR DOSE FOR OBS.
   1       CENTRAL   ON      NO       YES      YES      YES
   2       OUTPUT    OFF     YES      NO       NO       NO
1
 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
 COMPT. NO.                   INDICES
           SCALE    BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB
                    FRACTION RATE     DURATION LAG
   1         3        *        *        *        *
   2         *        -        -        -        -
          - PARAMETER IS NOT ALLOWED FOR THIS MODEL
          * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
            WILL DEFAULT TO ONE IF APPLICABLE
0DATA ITEM INDICES USED BY PRED ARE:
  EVENT ID DATA ITEM IS DATA ITEM NO.: 9
  TIME DATA ITEM IS DATA ITEM NO.: 2
  DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 4
  DOSE RATE DATA ITEM IS DATA ITEM NO.: 5

0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
1


 #TBLN:   1
 #METH: First Order Conditional Estimation with Interaction

 ESTIMATION STEP OMITTED:       NO
 ANALYSIS TYPE:                 POPULATION
 NUMBER OF SADDLE POINT RESET ITERATIONS: 0
 GRADIENT METHOD USED:      NOSLOW
 CONDITIONAL ESTIMATES USED:    YES
 CENTERED ETA:                  NO
 EPS-ETA INTERACTION:           YES
 LAPLACIAN OBJ. FUNC.:          NO
 NO. OF FUNCT. EVALS. ALLOWED:  224
 NO. OF SIG. FIGURES REQUIRED:  3
 INTERMEDIATE PRINTOUT:         YES
 ESTIMATE OUTPUT TO MSF:        YES
 IND. OBJ. FUNC. VALUES SORTED: NO
 NUMERICAL DERIVATIVE
      FILE REQUEST (NUMDER):      NONE
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
 ETA HESSIAN EVALUATION METHOD (ETADER): 0
 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0
 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100
 GRADIENT SIGDIGITS OF
      FIXED EFFECTS PARAMETERS (SIGL): 100
 NOPRIOR SETTING (NOPRIOR):      OFF
 NOCOV SETTING (NOCOV):          OFF
 DERCONT SETTING (DERCONT):      OFF
 FINAL ETA RE-EVALUATION (FNLETA): ON
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
      IN SHRINKAGE (ETASTYPE):    NO
 NON-INFL. ETA CORRECTION (NONINFETA): OFF
 RAW OUTPUT FILE (FILE): run504_no_cov.ext
 EXCLUDE TITLE (NOTITLE):        NO
 EXCLUDE COLUMN LABELS (NOLABEL): NO
 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5
 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL
 WISHART PRIOR DF INTERPRETATION (WISHTYPE):0
 KNUTHSUMOFF:                    0
 INCLUDE LNTWOPI:                NO
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO
 ADDITIONAL CONVERGENCE TEST (CTYPE=4)?: NO
 EM OR BAYESIAN METHOD USED:      NONE
```

```
 THE FOLLOWING LABELS ARE EQUIVALENT
 PRED=PREDI
 RES=RESI
 WRES=WRESI
 IWRS=IWRESI
 IPRD=IPREDI
 IRS=IRESI

 MONITORING OF SEARCH:


0ITERATION NO.: 0 OBJECTIVE VALUE: 1183.10549448015 NO. OF FUNC. EVALS.: 5
 CUMULATIVE NO. OF FUNC. EVALS.: 5
 NPARAMETR: 4.0000E+00 3.0000E+01 1.0000E-01 1.0000E-03 1.0000E-01 4.0000E-02
 PARAMETER: 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01
 GRADIENT: 3.0692E+02 -1.7250E+02 -4.1113E+01 1.9803E+00 -2.4126E+01 -7.1283E+01

0ITERATION NO.: 5 OBJECTIVE VALUE: 1121.11698234313 NO. OF FUNC. EVALS.: 34
 CUMULATIVE NO. OF FUNC. EVALS.: 39
 NPARAMETR: 3.0876E+00 3.5195E+01 6.3770E-02 1.1428E-03 9.5822E-02 4.8932E-02
 PARAMETER: -1.5890E-01 2.5970E-01 -1.2494E-01 1.4311E-01 7.8605E-02 2.0077E-01
 GRADIENT: 1.0157E+01 4.7850E-01 2.0011E+00 -2.0478E+00 -2.1740E+00 -3.7009E+00

0ITERATION NO.: 10 OBJECTIVE VALUE: 1118.34859503049 NO. OF FUNC. EVALS.: 33
 CUMULATIVE NO. OF FUNC. EVALS.: 72
 NPARAMETR: 3.0850E+00 3.5099E+01 6.3438E-02 2.2243E-02 1.0196E-01 4.9284E-02
 PARAMETER: -1.5973E-01 2.5698E-01 -1.2756E-01 2.7926E+00 6.9971E-02 2.0436E-01
 GRADIENT: 2.9088E-01 -1.1146E-01 7.4480E-02 -5.4869E-03 7.7192E-02 3.2610E-02

0ITERATION NO.: 15 OBJECTIVE VALUE: 1118.34753573063 NO. OF FUNC. EVALS.: 44
 CUMULATIVE NO. OF FUNC. EVALS.: 116
 NPARAMETR: 3.0875E+00 3.5145E+01 6.3387E-02 2.2287E-02 1.0189E-01 4.9336E-02
 PARAMETER: -1.5893E-01 2.5828E-01 -1.2796E-01 2.7993E+00 6.9380E-02 2.0489E-01
 GRADIENT: -3.4560E-04 4.8956E-04 5.3483E-04 1.9612E-05 -3.0228E-04 -7.4252E-04

 #TERM:
0MINIMIZATION SUCCESSFUL
 NO. OF FUNCTION EVALUATIONS USED: 116
 NO. OF SIG. DIGITS IN FINAL EST.: 4.5

 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

 ETABAR:     4.2235E-03 -1.1547E-02
 SE:         2.9195E-02 3.7075E-02
 N:                60       60

 P VAL.:     8.8497E-01 7.5547E-01

 ETASHRINKSD(%) 9.4203E+00 9.2695E+00
 ETASHRINKVR(%) 1.7953E+01 1.7680E+01
 EBVSHRINKSD(%) 9.8896E+00 9.5112E+00
 EBVSHRINKVR(%) 1.8801E+01 1.8118E+01
 EPSSHRINKSD(%) 2.0587E+01
 EPSSHRINKVR(%) 3.6935E+01


 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 240
 N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 441.09049593824290
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1118.3475357306270
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 1559.4380316688698
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

 TOTAL EFFECTIVE ETAS (NIND*NETA):           120

 #TERE:
 Elapsed estimation time in seconds: 0.75
 Elapsed covariance time in seconds: 0.52
 Elapsed postprocess time in seconds: 0.35
1
```

```
 ********************************************************************************************************************************
 ********************                                                  ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
```

```
 #OBJT:**************            MINIMUM VALUE OF OBJECTIVE FUNCTION        ********************
 ********************                                                       ********************
 ************************************************************************************************************************


 #OBJV:****************************************** 1118.348 ************************************************
1
 ************************************************************************************************************************
 ********************                                                       ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************                 FINAL PARAMETER ESTIMATE              ********************
 ********************                                                       ********************
 ************************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

       TH 1    TH 2

       3.09E+00 3.51E+01


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

       ETA1    ETA2

 ETA1
+      6.34E-02

 ETA2
+      2.23E-02 1.02E-01


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

       EPS1

 EPS1
+      4.93E-02

1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******

       ETA1    ETA2

 ETA1
+      2.52E-01

 ETA2
+      2.77E-01 3.19E-01


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***

       EPS1

 EPS1
+      2.22E-01

1
 ************************************************************************************************************************
 ********************                                                       ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************                STANDARD ERROR OF ESTIMATE             ********************
 ********************                                                       ********************
 ************************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

       TH 1    TH 2

       1.14E-01 1.65E+00


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********
```

```
       ETA1    ETA2

 ETA1
+      1.36E-02

 ETA2
+      1.40E-02 1.85E-02


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****


       EPS1

 EPS1
+      7.05E-03

1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******


       ETA1    ETA2

 ETA1
+      2.71E-02

 ETA2
+      1.64E-01 2.90E-02


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***


       EPS1

 EPS1
+      1.59E-02

1
 ********************************************************************************************************************************
 ********************                                                            ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              COVARIANCE MATRIX OF ESTIMATE                 ********************
 ********************                                                            ********************
 ********************************************************************************************************************************


         TH 1    TH 2    OM11    OM12    OM22    SG11

 TH 1
+      1.30E-02

 TH 2
+      4.31E-02 2.72E+00

 OM11
+     -1.14E-04 4.77E-03 1.86E-04

 OM12
+      4.92E-04 -3.05E-03 2.43E-05 1.96E-04

 OM22
+     -2.00E-04 -4.00E-04 2.77E-05 1.09E-04 3.42E-04

 SG11
+      7.94E-05 8.66E-04 -9.83E-06 1.13E-05 1.84E-06 4.97E-05

1
 ********************************************************************************************************************************
 ********************                                                            ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              CORRELATION MATRIX OF ESTIMATE                ********************
 ********************                                                            ********************
 ********************************************************************************************************************************


         TH 1    TH 2    OM11    OM12    OM22    SG11

 TH 1
+      1.14E-01

 TH 2
+      2.29E-01 1.65E+00

 OM11
+     -7.29E-02 2.12E-01 1.36E-02

 OM12
```

```
+      3.08E-01 -1.32E-01 1.28E-01 1.40E-02

 OM22
+     -9.50E-02 -1.31E-02 1.10E-01 4.20E-01 1.85E-02

 SG11
+      9.87E-02 7.45E-02 -1.02E-01 1.14E-01 1.41E-02 7.05E-03

1
 ********************************************************************************************************************************
 ********************                                                        ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************           INVERSE COVARIANCE MATRIX OF ESTIMATE        ********************
 ********************                                                        ********************
 ********************************************************************************************************************************


          TH 1    TH 2    OM11    OM12    OM22    SG11

 TH 1
+      1.05E+02

 TH 2
+     -2.36E+00 4.56E-01

 OM11
+      1.52E+02 -1.53E+01 6.13E+03

 OM12
+     -4.18E+02 1.87E+01 -1.50E+03 8.25E+03

 OM22
+      1.79E+02 -5.48E+00 4.26E+01 -2.71E+03 3.88E+03

 SG11
+     -7.58E+00 -1.12E+01 1.57E+03 -1.73E+03 2.90E+02 2.10E+04

1
```

```
 ********************************************************************************************************************************
 ********************                                                        ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************           EIGENVALUES OF COR MATRIX OF ESTIMATE        ********************
 ********************                                                        ********************
 ********************************************************************************************************************************


           1       2       3       4       5       6

       3.34E-01 7.19E-01 9.24E-01 1.20E+00 1.29E+00 1.53E+00

 Elapsed finaloutput time in seconds: 0.04
 #CPUT: Total CPU Time in Seconds, 1.686
Stop Time:
Mi 14. Apr 14:19:48 CEST 2021
```

B.2 Fit № 1117172

```
Mi 14. Apr 14:20:00 CEST 2021
popkin306
;Model Desc: One Compartment Model - IV Dose - (CL/V param.)
;Project Name: library
;Project ID: NO PROJECT DESCRIPTION

$PROB all covariates estimated
$INPUT ID TIME DV AMT RATE WT AGE SEX EVID MDV
$DATA data_set_504.dat IGNORE=@; Ignore records beginning with letter C
$SUBROUTINE ADVAN1 TRANS2
$PK
  TVCL   = THETA(1)
  TVV    = THETA(2)
  WTCLEXP = THETA(3)
  WTVEXP = THETA(4)
  AGECLEXP = THETA(5)
  AGEVEXP = THETA(6)
  SEXCLEXP = THETA(7)
  SEXVEXP = THETA(8)

  ETCL = ETA(1)
  ETV = ETA(2)

  CL  = TVCL*EXP(ETA(1))*(WT/70)**THETA(3)*(AGE/50)**THETA(5)*THETA(7)**SEX
  V   = TVV*EXP(ETA(2))*(WT/70)**THETA(4)*(AGE/50)**THETA(6)*THETA(8)**SEX
  S1  = V

$ERROR
"FIRST
" USE ROCM_REAL,ONLY: THETAF,OMEGAF,SIGMAF

EPSIL = 1.D-8
QQ = 1
IF (F .LT. EPSIL) THEN
  QQ = 0
ENDIF
IPRED = QQ * F + (1-QQ) * EPSIL


PERR=ERR(1)

Y = IPRED + IPRED*ERR(1)


IF(COMACT.GE.1)THEN
"   STD = SQRT ( SIGMAF(1,1) * IPRED**2 )
ENDIF

IRES   = DV-IPRED
IWRES  = IRES/STD


$THETA
  (0,4) ;[CL]
  (0,30) ;[V]
  0.8   ;[CL~WT]
  0.8   ;[V~WT]
  -0.1  ;[CL~AGE]
  0.1   ;[V~AGE]
  0.7   ;[CL~SEX]
  0.7   ;[V~SEX]

$OMEGA BLOCK(2)
  0.1 ;[P] INTERINDIVIDUAL VARIABILITY IN CL
  0.001 0.1 ;[P] INTERINDIVIDUAL VARIABILITY IN V
$SIGMA
  0.04 ;[P] PROPORTIONAL COMPONENT OF RESIDUAL VARIABILITY

;$MSFI
$ESTIMATION METHOD=COND INTERACTION MAXEVAL=9999 PRINT=5 NOABORT
$COV UNCONDITIONAL MATRIX=R PRINT=E
$TABLE ID TIME AMT EVID MDV IPRED IRES IWRES CWRES NPDE ESAMPLE=1000 FILE=sdtab001 NOPRINT ONEHEADER
$TABLE ID CL V ETA1 ETA2 ONEHEADER NOPRINT FILE=patab001
$TABLE ID AGE WT NOPRINT ONEHEADER FILE=cotab001
$TABLE ID SEX NOPRINT ONEHEADER FILE=catab001

NM-TRAN MESSAGES

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1

 (WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

License Registered to: Sanofi
Expiration Date: 14 JAN 2022
Current Date:  14 APR 2021
Days until program expires : 275
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.1
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
 PERFORMED BY NOUS INFOSYSTEMS.
```

```
 PROBLEM NO.:    1
 all covariates estimated
0DATA CHECKOUT RUN:      NO
 DATA SET LOCATED ON UNIT NO.: 2
 THIS UNIT TO BE REWOUND: NO
 NO. OF DATA RECS IN DATA SET: 300
 NO. OF DATA ITEMS IN DATA SET: 10
 ID DATA ITEM IS DATA ITEM NO.: 1
 DEP VARIABLE IS DATA ITEM NO.: 3
 MDV DATA ITEM IS DATA ITEM NO.: 10
0INDICES PASSED TO SUBROUTINE PRED:
   9  2  4  5  0  0  0  0  0  0  0
0LABELS FOR DATA ITEMS:
 ID TIME DV AMT RATE WT AGE SEX EVID MDV
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
 CL V IPRED IRES IWRES
0FORMAT FOR DATA:
 (10E7.0)

 TOT. NO. OF OBS RECS: 240
 TOT. NO. OF INDIVIDUALS: 60
0LENGTH OF THETA: 8
0DEFAULT THETA BOUNDARY TEST OMITTED: NO
0OMEGA HAS BLOCK FORM:
  1
  1  1
0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO
0INITIAL ESTIMATE OF THETA:
 LOWER BOUND INITIAL EST UPPER BOUND
  0.0000E+00  0.4000E+01  0.1000E+07
  0.0000E+00  0.3000E+02  0.1000E+07
 -0.1000E+07  0.8000E+00  0.1000E+07
 -0.1000E+07  0.8000E+00  0.1000E+07
 -0.1000E+07 -0.1000E+00  0.1000E+07
 -0.1000E+07  0.1000E+00  0.1000E+07
 -0.1000E+07  0.7000E+00  0.1000E+07
 -0.1000E+07  0.7000E+00  0.1000E+07
0INITIAL ESTIMATE OF OMEGA:
 BLOCK SET NO. BLOCK                                                FIXED
       1                                                             NO
              0.1000E+00
              0.1000E-02 0.1000E+00
0INITIAL ESTIMATE OF SIGMA:
 0.4000E-01
0COVARIANCE STEP OMITTED: NO
 R MATRIX SUBSTITUTED:  YES
 S MATRIX SUBSTITUTED:   NO
 EIGENVLS. PRINTED:     YES
 COMPRESSED FORMAT:      NO
 GRADIENT METHOD USED: NOSLOW
 SIGDIGITS ETAHAT (SIGLO):       -1
 SIGDIGITS GRADIENTS (SIGL):     -1
 EXCLUDE COV FOR FOCE (NOFCOV):   NO
 TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO
 KNUTHSUMOFF:                     -1
 RESUME COV ANALYSIS (RESUME):    NO
 SIR SAMPLE SIZE (SIRSAMPLE):    -1
 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
 PRECONDTIONING CYCLES (PRECOND): 0
 PRECONDTIONING TYPES (PRECONDS): TOS
 FORCED PRECONDTIONING CYCLES (PFCOND):0
 PRECONDTIONING TYPE (PRETYPE): 0
 FORCED POS. DEFINITE SETTING: (FPOSDEF):0
0TABLES STEP OMITTED: NO
 NO. OF TABLES:     4
 SEED NUMBER (SEED): 11456
 RANMETHOD:       3U
 MC SAMPLES (ESAMPLE): 1000
 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
0-- TABLE 1 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID TIME AMT EVID MDV IPRED IRES IWRES CWRES NPDE
0-- TABLE 2 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
```

```
0USER-CHOSEN ITEMS:
 ID CL V ETA1 ETA2
0-- TABLE 3 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID AGE WT
0-- TABLE 4 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID SEX
1DOUBLE PRECISION PREDPP VERSION 7.4.1

 ONE COMPARTMENT MODEL (ADVAN1)
0MAXIMUM NO. OF BASIC PK PARAMETERS: 2
0BASIC PK PARAMETERS (AFTER TRANSLATION):
  ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1

 TRANSLATOR WILL CONVERT PARAMETERS
 CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)
0COMPARTMENT ATTRIBUTES
 COMPT. NO. FUNCTION INITIAL ON/OFF DOSE    DEFAULT DEFAULT
                  STATUS  ALLOWED ALLOWED FOR DOSE FOR OBS.
   1       CENTRAL   ON      NO      YES     YES     YES
   2       OUTPUT    OFF     YES     NO      NO      NO
1
 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
 COMPT. NO.                   INDICES
           SCALE   BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB
                   FRACTION RATE     DURATION LAG
   1         3        *        *        *        *
   2         *        -        -        -        -
          - PARAMETER IS NOT ALLOWED FOR THIS MODEL
          * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
            WILL DEFAULT TO ONE IF APPLICABLE
0DATA ITEM INDICES USED BY PRED ARE:
  EVENT ID DATA ITEM IS DATA ITEM NO.: 9
  TIME DATA ITEM IS DATA ITEM NO.: 2
  DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 4
  DOSE RATE DATA ITEM IS DATA ITEM NO.: 5

0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
1


 #TBLN:   1
 #METH: First Order Conditional Estimation with Interaction

 ESTIMATION STEP OMITTED:       NO
 ANALYSIS TYPE:                 POPULATION
 NUMBER OF SADDLE POINT RESET ITERATIONS: 0
 GRADIENT METHOD USED:      NOSLOW
 CONDITIONAL ESTIMATES USED:    YES
 CENTERED ETA:                  NO
 EPS-ETA INTERACTION:           YES
 LAPLACIAN OBJ. FUNC.:          NO
 NO. OF FUNCT. EVALS. ALLOWED:  9999
 NO. OF SIG. FIGURES REQUIRED:  3
 INTERMEDIATE PRINTOUT:         YES
 ESTIMATE OUTPUT TO MSF:        NO
 ABORT WITH PRED EXIT CODE 1:   NO
 IND. OBJ. FUNC. VALUES SORTED: NO
 NUMERICAL DERIVATIVE
     FILE REQUEST (NUMDER):      NONE
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
 ETA HESSIAN EVALUATION METHOD (ETADER): 0
 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0
 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100
 GRADIENT SIGDIGITS OF
     FIXED EFFECTS PARAMETERS (SIGL): 100
 NOPRIOR SETTING (NOPRIOR):      OFF
 NOCOV SETTING (NOCOV):          OFF
 DERCONT SETTING (DERCONT):      OFF
 FINAL ETA RE-EVALUATION (FNLETA): ON
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
     IN SHRINKAGE (ETASTYPE):    NO
 NON-INFL. ETA CORRECTION (NONINFETA): OFF
```

```
 RAW OUTPUT FILE (FILE): run504_full_cov.ext
 EXCLUDE TITLE (NOTITLE):        NO
 EXCLUDE COLUMN LABELS (NOLABEL): NO
 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5
 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL
 WISHART PRIOR DF INTERPRETATION (WISHTYPE):0
 KNUTHSUMOFF:                    0
 INCLUDE LNTWOPI:                NO
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO
 ADDITIONAL CONVERGENCE TEST (CTYPE=4)?: NO
 EM OR BAYESIAN METHOD USED:      NONE


 THE FOLLOWING LABELS ARE EQUIVALENT
 PRED=PREDI
 RES=RESI
 WRES=WRESI
 IWRS=IWRESI
 IPRD=IPREDI
 IRS=IRESI

 MONITORING OF SEARCH:


0ITERATION NO.: 0 OBJECTIVE VALUE: 1173.07762337495 NO. OF FUNC. EVALS.: 11
 CUMULATIVE NO. OF FUNC. EVALS.: 11
 NPARAMETR: 4.0000E+00 3.0000E+01 8.0000E-01 8.0000E-01 -1.0000E-01 1.0000E-01 7.0000E-01 7.0000E-01 1.0000E-01 1.0000E-03
          1.0000E-01 4.0000E-02
 PARAMETER: 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 -1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01
          1.0000E-01 1.0000E-01
 GRADIENT: 2.0435E+02 -2.7205E+02 1.4229E+02 -3.4476E+02 3.1911E+01 7.0862E+00 3.2563E+02 -2.0425E+03 2.2631E+00 2.2510E+00
         -4.7241E+01 -5.5370E+01

0ITERATION NO.: 5 OBJECTIVE VALUE: 1085.35374344000 NO. OF FUNC. EVALS.: 63
 CUMULATIVE NO. OF FUNC. EVALS.: 74
 NPARAMETR: 3.0253E+00 3.2901E+01 5.1192E-01 1.4497E+00 -1.7324E-01 9.8036E-02 9.2245E-01 9.7236E-01 9.3091E-02 9.5206E-04
          8.7163E-02 4.7461E-02
 PARAMETER: -1.7929E-01 1.9231E-01 6.3989E-02 1.8122E-01 -1.7324E-01 9.8036E-02 1.3178E-01 1.3891E-01 6.4206E-02 9.8676E-02
          3.1300E-02 1.8552E-01
 GRADIENT: -3.5179E+00 3.0903E+01 -2.3627E+01 5.7794E+01 3.0120E+01 4.3508E-01 -1.4327E+01 2.0089E+02 4.5204E+01 -4.3976E-01
          3.0766E+01 5.0787E+00

0ITERATION NO.: 10 OBJECTIVE VALUE: 1065.48099762496 NO. OF FUNC. EVALS.: 64
 CUMULATIVE NO. OF FUNC. EVALS.: 138
 NPARAMETR: 2.8813E+00 3.3234E+01 5.1186E-01 1.5571E+00 -5.7113E-01 5.9889E-02 9.5825E-01 9.2575E-01 4.8053E-02 6.3051E-04
          5.1234E-02 5.0602E-02
 PARAMETER: -2.2806E-01 2.0238E-01 6.3983E-02 1.9464E-01 -5.7113E-01 5.9889E-02 1.3689E-01 1.3225E-01 -2.6643E-01 9.0955E-02
         -2.3441E-01 2.1755E-01
 GRADIENT: -6.2542E+01 4.9387E+01 -9.2499E+01 1.1855E+02 -4.5593E+00 1.7155E+00 -2.2909E+01 1.5766E+02 1.8164E+01 2.0717E-01
         -3.3438E-01 1.3817E+01

0ITERATION NO.: 15 OBJECTIVE VALUE: 1058.33809122106 NO. OF FUNC. EVALS.: 64
 CUMULATIVE NO. OF FUNC. EVALS.: 202
 NPARAMETR: 3.0353E+00 3.2405E+01 6.6843E-01 1.3186E+00 -5.3638E-01 5.1553E-02 9.0060E-01 9.4181E-01 3.1067E-02 6.5672E-04
          4.5717E-02 5.0472E-02
 PARAMETER: -1.7598E-01 1.7711E-01 8.3554E-02 1.6482E-01 -5.3638E-01 5.1553E-02 1.2866E-01 1.3454E-01 -4.8452E-01 1.1782E-01
         -2.9145E-01 2.1627E-01
 GRADIENT: 2.5638E+00 -2.9444E+00 6.4505E+00 -4.0433E+00 -1.0457E-01 9.1730E-02 1.3945E+01 -1.6930E+01 9.0060E-01 -1.6250E
       -01
          -5.2134E-01 1.2478E+00

0ITERATION NO.: 20 OBJECTIVE VALUE: 1058.30560317531 NO. OF FUNC. EVALS.: 94
 CUMULATIVE NO. OF FUNC. EVALS.: 296
 NPARAMETR: 3.0329E+00 3.2408E+01 6.6074E-01 1.3214E+00 -5.3543E-01 5.1948E-02 9.0222E-01 9.4487E-01 3.0706E-02 1.4979E-03
          4.6623E-02 5.0237E-02
 PARAMETER: -1.7676E-01 1.7721E-01 8.2592E-02 1.6517E-01 -5.3543E-01 5.1948E-02 1.2889E-01 1.3498E-01 -4.9036E-01 2.7031E-01
         -2.8227E-01 2.1394E-01
 GRADIENT: -4.7532E-01 -2.9986E-01 -3.7410E-01 -8.1016E-01 -1.9892E-01 9.9097E-03 -9.3734E+00 -6.5398E+00 -2.7172E-02 4.2305
       E-03
          -2.2940E-02 -4.7244E-02

0ITERATION NO.: 23 OBJECTIVE VALUE: 1058.30371059334 NO. OF FUNC. EVALS.: 74
 CUMULATIVE NO. OF FUNC. EVALS.: 370
 NPARAMETR: 3.0313E+00 3.2384E+01 6.5978E-01 1.3215E+00 -5.3407E-01 5.2296E-02 9.0388E-01 9.4676E-01 3.0720E-02 1.4790E-03
          4.6609E-02 5.0258E-02
 PARAMETER: -1.7729E-01 1.7645E-01 8.2473E-02 1.6519E-01 -5.3407E-01 5.2296E-02 1.2913E-01 1.3525E-01 -4.9012E-01 2.6684E-01
         -2.8240E-01 2.1414E-01
 GRADIENT: 1.7079E-02 1.3051E-03 2.9960E-02 2.9268E-03 -3.6916E-03 -1.0592E-03 8.6663E-02 4.7356E-03 -2.9742E-03 4.7080E-05
          3.6857E-05 -2.8823E-03

 #TERM:
0MINIMIZATION SUCCESSFUL
 NO. OF FUNCTION EVALUATIONS USED: 370
 NO. OF SIG. DIGITS IN FINAL EST.: 3.6

 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

 ETABAR:     4.1114E-03 -9.3810E-03
 SE:         1.8817E-02 2.2907E-02
 N:                60       60

 P VAL.:     8.2704E-01 6.8215E-01
```

```
 ETASHRINKSD(%) 1.6139E+01 1.7119E+01
 ETASHRINKVR(%) 2.9673E+01 3.1307E+01
 EBVSHRINKSD(%) 1.7124E+01 1.7497E+01
 EBVSHRINKVR(%) 3.1316E+01 3.1933E+01
 EPSSHRINKSD(%) 1.7012E+01
 EPSSHRINKVR(%) 3.1130E+01


 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 240
 N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 441.09049593824290
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1058.3037105933363
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 1499.3942065315791
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

 TOTAL EFFECTIVE ETAS (NIND*NETA):           120

 #TERE:
 Elapsed estimation time in seconds: 2.10
 Elapsed covariance time in seconds: 2.85
 Elapsed postprocess time in seconds: 0.46
1
```

```
 ********************************************************************************************************************************
 ********************                                                        ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 #OBJT:***************            MINIMUM VALUE OF OBJECTIVE FUNCTION         ********************
 ********************                                                        ********************
 ********************************************************************************************************************************
```

```
 #OBJV:***************************************** 1058.304 **********************************************
1
 ********************************************************************************************************************************
 ********************                                                        ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************                 FINAL PARAMETER ESTIMATE               ********************
 ********************                                                        ********************
 ********************************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

       TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8

       3.03E+00 3.24E+01 6.60E-01 1.32E+00 -5.34E-01 5.23E-02 9.04E-01 9.47E-01


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

       ETA1    ETA2

 ETA1
+      3.07E-02

 ETA2
+      1.48E-03 4.66E-02


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

       EPS1

 EPS1
+      5.03E-02
```

```
1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******


       ETA1    ETA2

 ETA1
+      1.75E-01

 ETA2
+      3.91E-02 2.16E-01


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***


       EPS1

 EPS1
+      2.24E-01

1
 ************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************               STANDARD ERROR OF ESTIMATE           ********************
 ********************                                                    ********************
 ************************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********


       TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8

       1.16E-01 1.58E+00 1.60E-01 2.02E-01 1.03E-01 1.29E-01 5.14E-02 6.75E-02


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********


       ETA1    ETA2

 ETA1
+      9.15E-03

 ETA2
+      7.58E-03 1.38E-02


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****


       EPS1

 EPS1
+      6.75E-03

1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******


       ETA1    ETA2

 ETA1
+      2.61E-02

 ETA2
+      1.98E-01 3.20E-02


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***


       EPS1

 EPS1
+      1.51E-02

1
 ************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              COVARIANCE MATRIX OF ESTIMATE         ********************
```

```
 ********************                                                                    ********************
 ************************************************************************************************************************


         TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8    OM11    OM12    OM22    SG11


 TH 1
+      1.35E-02

 TH 2
+      2.92E-02 2.49E+00

 TH 3
+     -2.77E-03 -1.14E-02 2.56E-02

 TH 4
+     -1.03E-03 -5.59E-02 4.27E-03 4.06E-02

 TH 5
+      3.39E-04 -2.39E-03 -1.27E-03 -3.35E-04 1.06E-02

 TH 6
+     -1.52E-04 3.39E-03 -3.11E-04 -2.51E-03 2.27E-03 1.67E-02

 TH 7
+     -3.62E-03 -7.02E-03 -1.83E-03 -3.53E-04 6.25E-04 -1.08E-04 2.64E-03

 TH 8
+     -6.33E-04 -6.55E-02 -3.61E-04 -3.06E-03 -1.02E-04 8.81E-04 4.51E-04 4.56E-03

 OM11
+     -2.62E-05 4.83E-04 9.86E-06 4.23E-05 2.81E-05 -1.56E-05 9.14E-06 -1.56E-05 8.38E-05

 OM12
+      6.76E-05 2.23E-04 3.33E-05 2.90E-05 7.44E-06 -2.58E-05 -1.01E-05 -5.10E-06 9.66E-06 5.75E-05

 OM22
+     -7.16E-05 2.20E-03 -1.00E-05 2.69E-05 -3.96E-05 -4.29E-05 5.11E-06 -6.36E-05 1.37E-05 2.38E-05 1.91E-04

 SG11
+      1.20E-04 5.36E-04 -4.47E-06 -1.75E-05 -6.65E-06 1.78E-05 -7.00E-06 2.05E-05 -1.71E-05 -2.23E-06 -2.32E-05 4.56E-05

1
 ************************************************************************************************************************
 ********************                                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              CORRELATION MATRIX OF ESTIMATE                        ********************
 ********************                                                                    ********************
 ************************************************************************************************************************


         TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8    OM11    OM12    OM22    SG11


 TH 1
+      1.16E-01

 TH 2
+      1.59E-01 1.58E+00

 TH 3
+     -1.49E-01 -4.49E-02 1.60E-01

 TH 4
+     -4.41E-02 -1.76E-01 1.32E-01 2.02E-01

 TH 5
+      2.83E-02 -1.47E-02 -7.69E-02 -1.61E-02 1.03E-01

 TH 6
+     -1.01E-02 1.66E-02 -1.50E-02 -9.63E-02 1.70E-01 1.29E-01

 TH 7
+     -6.07E-01 -8.65E-02 -2.22E-01 -3.41E-02 1.18E-01 -1.63E-02 5.14E-02

 TH 8
+     -8.07E-02 -6.14E-01 -3.34E-02 -2.25E-01 -1.46E-02 1.01E-01 1.30E-01 6.75E-02

 OM11
+     -2.46E-02 3.34E-02 6.73E-03 2.29E-02 2.97E-02 -1.32E-02 1.94E-02 -2.53E-02 9.15E-03

 OM12
+      7.67E-02 1.86E-02 2.74E-02 1.90E-02 9.52E-03 -2.63E-02 -2.59E-02 -9.96E-03 1.39E-01 7.58E-03

 OM22
+     -4.45E-02 1.01E-01 -4.53E-03 9.64E-03 -2.77E-02 -2.40E-02 7.19E-03 -6.81E-02 1.09E-01 2.27E-01 1.38E-02

 SG11
+      1.53E-01 5.03E-02 -4.13E-03 -1.29E-02 -9.55E-03 2.04E-02 -2.02E-02 4.49E-02 -2.77E-01 -4.36E-02 -2.48E-01 6.75E-03

1
 ************************************************************************************************************************
 ********************                                                                    ********************
```

```
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************           INVERSE COVARIANCE MATRIX OF ESTIMATE      ********************
 ********************                                                      ********************
 ************************************************************************************************************************


         TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8    OM11    OM12    OM22    SG11


 TH 1
+      1.48E+02

 TH 2
+     -1.52E+00 8.18E-01

 TH 3
+      3.07E+01 -8.97E-02 4.84E+01

 TH 4
+     -9.70E-01 2.04E+00 -3.92E+00 3.17E+01

 TH 5
+     -1.63E+01 6.59E-01 1.45E-03 1.38E+00 1.01E+02

 TH 6
+      7.07E+00 -6.79E-01 1.27E+00 1.39E+00 -1.51E+01 6.36E+01

 TH 7
+      2.26E+02 -2.14E+00 7.52E+01 -3.27E+00 -4.79E+01 1.89E+01 7.58E+02

 TH 8
+     -2.19E+01 1.32E+01 -3.13E+00 5.02E+01 1.80E+01 -2.20E+01 -7.32E+01 4.52E+02

 OM11
+     -2.43E+01 -6.24E+00 -1.12E+01 -2.51E+01 -3.17E+01 9.19E+00 -7.84E+01 -8.56E+01 1.32E+04

 OM12
+     -1.68E+02 1.60E+00 -5.42E+01 -7.92E+00 -1.20E+01 1.90E+01 -1.77E+02 -1.22E+01 -1.94E+03 1.89E+04

 OM22
+      4.27E+01 -7.64E+00 1.25E+01 -1.44E+01 1.93E+01 8.76E+00 3.66E+01 -5.00E+01 -7.12E+01 -2.37E+03 5.97E+03

 SG11
+     -3.25E+02 -1.69E+01 -6.49E+01 -5.01E+01 3.83E+01 -1.55E+01 -4.50E+02 -3.40E+02 4.98E+03 -6.23E+02 2.89E+03 2.64E+04

1
```

```
 ************************************************************************************************************************
 ********************                                                      ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************           EIGENVALUES OF COR MATRIX OF ESTIMATE      ********************
 ********************                                                      ********************
 ************************************************************************************************************************


          1       2       3       4       5       6       7       8       9      10      11      12


       2.36E-01 2.95E-01 6.20E-01 7.70E-01 8.48E-01 9.78E-01 1.00E+00 1.09E+00 1.31E+00 1.37E+00 1.61E+00 1.86E+00

 Elapsed finaloutput time in seconds: 0.04
 #CPUT: Total CPU Time in Seconds, 5.413
Stop Time:
Mi 14. Apr 14:20:09 CEST 2021
```

B.3 Fit № 1117173

```
Mi 14. Apr 14:20:09 CEST 2021
popkin308
;Model Desc: One Compartment Model - IV Dose - (CL/V param.)
;Project Name: library
;Project ID: NO PROJECT DESCRIPTION

$PROB fixed covariates
$INPUT ID TIME DV AMT RATE WT AGE SEX EVID MDV
$DATA data_set_504.dat IGNORE=@
$SUBROUTINE ADVAN1 TRANS2
$PK
  TVCL   = THETA(1)
  TVV    = THETA(2)
  WTCLEXP = THETA(3)
  WTVEXP = THETA(4)
  AGECLEXP = THETA(5)
  AGEVEXP = THETA(6)
  SEXCLEXP = THETA(7)
  SEXVEXP = THETA(8)

  ETCL = ETA(1)
  ETV = ETA(2)

  CL  = TVCL*EXP(ETA(1))*(WT/70)**THETA(3)*(AGE/50)**THETA(5)*THETA(7)**SEX
  V   = TVV*EXP(ETA(2))*(WT/70)**THETA(4)*(AGE/50)**THETA(6)*THETA(8)**SEX
  S1  = V

$ERROR
"FIRST
" USE ROCM_REAL,ONLY: THETAF,OMEGAF,SIGMAF

EPSIL  = 1.D-8
QQ = 1
IF (F .LT. EPSIL) THEN
  QQ = 0
ENDIF
IPRED = QQ * F + (1-QQ) * EPSIL


PERR=ERR(1)

Y = IPRED + IPRED*ERR(1)


IF(COMACT.GE.1)THEN
"   STD = SQRT ( SIGMAF(1,1) * IPRED**2 )
ENDIF

IRES   = DV-IPRED
IWRES  = IRES/STD


$THETA
  (0.0,4)        ;[CL]
  (0.0,30)        ;[V]
  (0.75 FIXED) ;[CL~WT]
  (1.0 FIXED) ;[V~WT]
  -0.1        ;[CL~AGE]
  (0.0 FIXED) ;[V~AGE]
  (1.0 FIXED) ;[CL~SEX]
  (1.0 FIXED) ;[V~SEX]

$OMEGA BLOCK(2)
  0.1 ;[P] INTERINDIVIDUAL VARIABILITY IN CL
  0.001 0.1 ;[P] INTERINDIVIDUAL VARIABILITY IN V
$SIGMA
  0.04 ;[P] PROPORTIONAL COMPONENT OF RESIDUAL VARIABILITY

;$MSFI
$ESTIMATION METHOD=1 INTER PRINT=5 POSTHOC MSF=adv1tr2.MSF
$COV PRINT=E
$TABLE ID TIME AMT EVID MDV IPRED IRES IWRES CWRES RES PRED DV NPDE ESAMPLE=1000 NOAPPEND FILE=sdtab001 NOPRINT ONEHEADER
$TABLE ID CL V ETA1 ETA2 ONEHEADER NOPRINT FILE=patab001
;$TABLE ID NOPRINT CL V ONEHEADER FILE=patab001
$TABLE ID AGE WT NOPRINT ONEHEADER FILE=cotab001
$TABLE ID SEX NOPRINT ONEHEADER FILE=catab001
;$TABLE ID TIME IPRED NOPRINT ONEHEADER FILE=sdtab00

NM-TRAN MESSAGES

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1

 (WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

License Registered to: Sanofi
Expiration Date: 14 JAN 2022
Current Date:  14 APR 2021
Days until program expires : 275
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.1
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
```

```
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
 PERFORMED BY NOUS INFOSYSTEMS.

 PROBLEM NO.:    1
 fixed covariates
0DATA CHECKOUT RUN:      NO
 DATA SET LOCATED ON UNIT NO.: 2
 THIS UNIT TO BE REWOUND: NO
 NO. OF DATA RECS IN DATA SET: 300
 NO. OF DATA ITEMS IN DATA SET: 10
 ID DATA ITEM IS DATA ITEM NO.: 1
 DEP VARIABLE IS DATA ITEM NO.: 3
 MDV DATA ITEM IS DATA ITEM NO.: 10
0INDICES PASSED TO SUBROUTINE PRED:
  9  2  4  5  0  0  0  0  0  0  0
0LABELS FOR DATA ITEMS:
 ID TIME DV AMT RATE WT AGE SEX EVID MDV
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
 CL V IPRED IRES IWRES
0FORMAT FOR DATA:
 (10E7.0)

 TOT. NO. OF OBS RECS: 240
 TOT. NO. OF INDIVIDUALS: 60
0LENGTH OF THETA: 8
0DEFAULT THETA BOUNDARY TEST OMITTED: NO
0OMEGA HAS BLOCK FORM:
  1
  1  1
0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO
0INITIAL ESTIMATE OF THETA:
 LOWER BOUND INITIAL EST UPPER BOUND
  0.0000E+00  0.4000E+01  0.1000E+07
  0.0000E+00  0.3000E+02  0.1000E+07
  0.7500E+00  0.7500E+00  0.7500E+00
  0.1000E+01  0.1000E+01  0.1000E+01
 -0.1000E+07 -0.1000E+00  0.1000E+07
  0.0000E+00  0.0000E+00  0.0000E+00
  0.1000E+01  0.1000E+01  0.1000E+01
  0.1000E+01  0.1000E+01  0.1000E+01
0INITIAL ESTIMATE OF OMEGA:
 BLOCK SET NO. BLOCK                                                FIXED
       1                                                             NO
              0.1000E+00
              0.1000E-02 0.1000E+00
0INITIAL ESTIMATE OF SIGMA:
 0.4000E-01
0COVARIANCE STEP OMITTED: NO
 EIGENVLS. PRINTED:     YES
 SPECIAL COMPUTATION:    NO
 COMPRESSED FORMAT:      NO
 GRADIENT METHOD USED: NOSLOW
 SIGDIGITS ETAHAT (SIGLO):       -1
 SIGDIGITS GRADIENTS (SIGL):     -1
 EXCLUDE COV FOR FOCE (NOFCOV):   NO
 TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO
 KNUTHSUMOFF:                    -1
 RESUME COV ANALYSIS (RESUME):    NO
 SIR SAMPLE SIZE (SIRSAMPLE):    -1
 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
 PRECONDTIONING CYCLES (PRECOND): 0
 PRECONDTIONING TYPES (PRECONDS): TOS
 FORCED PRECONDTIONING CYCLES (PFCOND):0
 PRECONDTIONING TYPE (PRETYPE): 0
 FORCED POS. DEFINITE SETTING: (FPOSDEF):0
0TABLES STEP OMITTED: NO
 NO. OF TABLES:     4
 SEED NUMBER (SEED): 11456
 RANMETHOD:        3U
 MC SAMPLES (ESAMPLE): 1000
 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
0-- TABLE 1 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: NO
 PRINTED:           NO
 HEADER:            YES
 FILE TO BE FORWARDED: NO
 FORMAT:            S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID TIME AMT EVID MDV IPRED IRES IWRES CWRES RES PRED DV NPDE
0-- TABLE 2 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:           NO
 HEADER:            YES
 FILE TO BE FORWARDED: NO
 FORMAT:            S1PE11.4
 LFORMAT:
 RFORMAT:
```

```
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID CL V ETA1 ETA2
0-- TABLE 3 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID AGE WT
0-- TABLE 4 --
0RECORDS ONLY: ALL
04 COLUMNS APPENDED: YES
 PRINTED:          NO
 HEADER:           YES
 FILE TO BE FORWARDED: NO
 FORMAT:           S1PE11.4
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID SEX
1DOUBLE PRECISION PREDPP VERSION 7.4.1

 ONE COMPARTMENT MODEL (ADVAN1)
0MAXIMUM NO. OF BASIC PK PARAMETERS: 2
0BASIC PK PARAMETERS (AFTER TRANSLATION):
  ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1

 TRANSLATOR WILL CONVERT PARAMETERS
 CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)
0COMPARTMENT ATTRIBUTES
 COMPT. NO. FUNCTION INITIAL ON/OFF DOSE    DEFAULT DEFAULT
                  STATUS  ALLOWED ALLOWED FOR DOSE FOR OBS.
   1       CENTRAL   ON      NO      YES     YES     YES
   2       OUTPUT    OFF     YES     NO      NO      NO
1
 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
 COMPT. NO.                    INDICES
           SCALE    BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB
                    FRACTION RATE     DURATION LAG
   1         3        *        *        *        *
   2         *        -        -        -        -
          - PARAMETER IS NOT ALLOWED FOR THIS MODEL
          * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
            WILL DEFAULT TO ONE IF APPLICABLE
0DATA ITEM INDICES USED BY PRED ARE:
  EVENT ID DATA ITEM IS DATA ITEM NO.: 9
  TIME DATA ITEM IS DATA ITEM NO.: 2
  DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 4
  DOSE RATE DATA ITEM IS DATA ITEM NO.: 5

0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
1


 #TBLN:   1
 #METH: First Order Conditional Estimation with Interaction

 ESTIMATION STEP OMITTED:       NO
 ANALYSIS TYPE:                 POPULATION
 NUMBER OF SADDLE POINT RESET ITERATIONS: 0
 GRADIENT METHOD USED:      NOSLOW
 CONDITIONAL ESTIMATES USED:    YES
 CENTERED ETA:                  NO
 EPS-ETA INTERACTION:           YES
 LAPLACIAN OBJ. FUNC.:          NO
 NO. OF FUNCT. EVALS. ALLOWED:  728
 NO. OF SIG. FIGURES REQUIRED:  3
 INTERMEDIATE PRINTOUT:         YES
 ESTIMATE OUTPUT TO MSF:        YES
 IND. OBJ. FUNC. VALUES SORTED: NO
 NUMERICAL DERIVATIVE
     FILE REQUEST (NUMDER):     NONE
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
 ETA HESSIAN EVALUATION METHOD (ETADER): 0
 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0
 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100
 GRADIENT SIGDIGITS OF
     FIXED EFFECTS PARAMETERS (SIGL): 100
 NOPRIOR SETTING (NOPRIOR):     OFF
 NOCOV SETTING (NOCOV):         OFF
 DERCONT SETTING (DERCONT):     OFF
 FINAL ETA RE-EVALUATION (FNLETA): ON
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
     IN SHRINKAGE (ETASTYPE):   NO
 NON-INFL. ETA CORRECTION (NONINFETA): OFF
```

```
 RAW OUTPUT FILE (FILE): run504_with_cov_fix.ext
 EXCLUDE TITLE (NOTITLE):        NO
 EXCLUDE COLUMN LABELS (NOLABEL): NO
 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5
 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL
 WISHART PRIOR DF INTERPRETATION (WISHTYPE):0
 KNUTHSUMOFF:                    0
 INCLUDE LNTWOPI:                NO
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO
 ADDITIONAL CONVERGENCE TEST (CTYPE=4)?: NO
 EM OR BAYESIAN METHOD USED:      NONE


 THE FOLLOWING LABELS ARE EQUIVALENT
 PRED=PREDI
 RES=RESI
 WRES=WRESI
 IWRS=IWRESI
 IPRD=IPREDI
 IRS=IRESI

 MONITORING OF SEARCH:


0ITERATION NO.: 0 OBJECTIVE VALUE: 1161.60514749014 NO. OF FUNC. EVALS.: 6
 CUMULATIVE NO. OF FUNC. EVALS.: 6
 NPARAMETR: 4.0000E+00 3.0000E+01 -1.0000E-01 1.0000E-01 1.0000E-03 1.0000E-01 4.0000E-02
 PARAMETER: 1.0000E-01 1.0000E-01 -1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01
 GRADIENT: 3.6866E+02 -9.7362E+01 2.6628E+01 -6.4106E+01 2.3816E+00 3.1189E+01 -7.3257E+01

0ITERATION NO.: 5 OBJECTIVE VALUE: 1074.60533449796 NO. OF FUNC. EVALS.: 39
 CUMULATIVE NO. OF FUNC. EVALS.: 45
 NPARAMETR: 2.6544E+00 3.2730E+01 -5.6648E-01 5.5442E-02 6.6512E-04 4.6351E-02 5.0224E-02
 PARAMETER: -3.1009E-01 1.8709E-01 -5.6648E-01 -1.9492E-01 8.9326E-02 -2.8450E-01 2.1381E-01
 GRADIENT: -1.3584E+02 2.6955E+01 3.0517E-01 1.7719E+01 3.3738E-01 -7.3568E+00 1.6102E+01

0ITERATION NO.: 10 OBJECTIVE VALUE: 1065.36549483411 NO. OF FUNC. EVALS.: 40
 CUMULATIVE NO. OF FUNC. EVALS.: 85
 NPARAMETR: 2.8738E+00 3.2328E+01 -5.3143E-01 3.4024E-02 1.1002E-03 5.0656E-02 4.9839E-02
 PARAMETER: -2.3066E-01 1.7475E-01 -5.3143E-01 -4.3905E-01 1.8862E-01 -2.4036E-01 2.0995E-01
 GRADIENT: -1.8051E+00 8.6704E-01 6.7803E-02 -2.2649E-01 -2.1390E-03 6.4816E-02 -2.6550E-01

0ITERATION NO.: 15 OBJECTIVE VALUE: 1065.36236757899 NO. OF FUNC. EVALS.: 56
 CUMULATIVE NO. OF FUNC. EVALS.: 141
 NPARAMETR: 2.8781E+00 3.2332E+01 -5.2947E-01 3.4119E-02 1.1427E-03 5.0512E-02 4.9965E-02
 PARAMETER: -2.2917E-01 1.7485E-01 -5.2947E-01 -4.3766E-01 1.9562E-01 -2.4180E-01 2.1122E-01
 GRADIENT: 1.7725E-03 -1.4003E-02 1.2636E-03 -1.6091E-03 -8.5481E-04 4.5606E-03 5.8223E-03

0ITERATION NO.: 17 OBJECTIVE VALUE: 1065.36236710184 NO. OF FUNC. EVALS.: 21
 CUMULATIVE NO. OF FUNC. EVALS.: 162
 NPARAMETR: 2.8781E+00 3.2332E+01 -5.2947E-01 3.4120E-02 1.1465E-03 5.0511E-02 4.9964E-02
 PARAMETER: -2.2917E-01 1.7486E-01 -5.2947E-01 -4.3764E-01 1.9627E-01 -2.4182E-01 2.1121E-01
 GRADIENT: -6.4983E-05 -2.8571E-03 1.2341E-03 -6.1348E-04 -1.4661E-04 6.5106E-04 1.2468E-03

 #TERM:
0MINIMIZATION SUCCESSFUL
 NO. OF FUNCTION EVALUATIONS USED: 162
 NO. OF SIG. DIGITS IN FINAL EST.: 3.1

 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

 ETABAR:     4.2047E-03 -9.8313E-03
 SE:         2.0094E-02 2.4121E-02
 N:                60       60

 P VAL.:     8.3425E-01 6.8358E-01

 ETASHRINKSD(%) 1.5028E+01 1.6163E+01
 ETASHRINKVR(%) 2.7797E+01 2.9714E+01
 EBVSHRINKSD(%) 1.5715E+01 1.6432E+01
 EBVSHRINKVR(%) 2.8960E+01 3.0165E+01
 EPSSHRINKSD(%) 1.7460E+01
 EPSSHRINKVR(%) 3.1872E+01


 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 240
 N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 441.09049593824290
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1065.36236710184
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 1506.4528630400782
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

 TOTAL EFFECTIVE ETAS (NIND*NETA):           120

 #TERE:
 Elapsed estimation time in seconds: 1.21
 Elapsed covariance time in seconds: 0.93
 Elapsed postprocess time in seconds: 0.48
1
```

```
********************************************************************************************************************************
********************                                                              ********************
********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
#OBJT:***************            MINIMUM VALUE OF OBJECTIVE FUNCTION       ********************
********************                                                              ********************
********************************************************************************************************************************




#OBJV:***************************************** 1065.362 **************************************************
1
********************************************************************************************************************************
********************                                                              ********************
********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
********************                 FINAL PARAMETER ESTIMATE                 ********************
********************                                                              ********************
********************************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

       TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8

       2.88E+00 3.23E+01 7.50E-01 1.00E+00 -5.29E-01 0.00E+00 1.00E+00 1.00E+00


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

       ETA1    ETA2

 ETA1
+      3.41E-02

 ETA2
+      1.15E-03 5.05E-02


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

       EPS1

 EPS1
+      5.00E-02

1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******

       ETA1    ETA2

 ETA1
+      1.85E-01

 ETA2
+      2.76E-02 2.25E-01


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***

       EPS1

 EPS1
+      2.24E-01

1
```

```
 ********************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              STANDARD ERROR OF ESTIMATE            ********************
 ********************                                                    ********************
 ********************************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********

       TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8

       8.92E-02 1.22E+00 ......... ......... 9.54E-02 ......... ......... .........


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

       ETA1    ETA2

 ETA1
+      1.13E-02

 ETA2
+      7.27E-03 1.50E-02


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

       EPS1

 EPS1
+      7.40E-03

1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******

       ETA1    ETA2

 ETA1
+      3.05E-02

 ETA2
+      1.74E-01 3.33E-02


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***

       EPS1

 EPS1
+      1.66E-02

1
 ********************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              COVARIANCE MATRIX OF ESTIMATE         ********************
 ********************                                                    ********************
 ********************************************************************************************************************************


         TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8    OM11    OM12    OM22    SG11


 TH 1
+      7.97E-03

 TH 2
+      7.37E-03 1.49E+00

 TH 3
+     ......... ......... .........

 TH 4
+     ......... ......... ......... .........

 TH 5
+      3.35E-03 -2.42E-02 ......... ......... 9.09E-03

 TH 6
+     ......... ......... ......... ......... ......... .........

 TH 7
```

```
+     ......... ......... ......... ......... ......... ......... .........

 TH 8
+     ......... ......... ......... ......... ......... ......... ......... .........

 OM11
+     -1.75E-04 3.34E-03 ......... ......... 2.38E-05 ......... ......... ......... 1.27E-04

 OM12
+      2.39E-04 1.30E-03 ......... ......... 1.01E-04 ......... ......... ......... 2.08E-06 5.28E-05

 OM22
+     -5.50E-05 5.45E-03 ......... ......... -1.88E-04 ......... ......... ......... 8.08E-06 2.55E-05 2.24E-04

 SG11
+      1.33E-04 2.67E-04 ......... ......... -1.16E-04 ......... ......... ......... -1.79E-05 -9.17E-06 -4.45E-05 5.48E-05

1
 ************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************              CORRELATION MATRIX OF ESTIMATE        ********************
 ********************                                                    ********************
 ************************************************************************************************************************


          TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8    OM11    OM12    OM22    SG11


 TH 1
+      8.92E-02

 TH 2
+      6.76E-02 1.22E+00

 TH 3
+     ......... ......... .........

 TH 4
+     ......... ......... ......... .........

 TH 5
+      3.94E-01 -2.08E-01 ......... ......... 9.54E-02

 TH 6
+     ......... ......... ......... ......... ......... .........

 TH 7
+     ......... ......... ......... ......... ......... ......... .........

 TH 8
+     ......... ......... ......... ......... ......... ......... ......... .........

 OM11
+     -1.74E-01 2.43E-01 ......... ......... 2.22E-02 ......... ......... ......... 1.13E-02

 OM12
+      3.68E-01 1.47E-01 ......... ......... 1.46E-01 ......... ......... ......... 2.55E-02 7.27E-03

 OM22
+     -4.11E-02 2.98E-01 ......... ......... -1.31E-01 ......... ......... ......... 4.80E-02 2.34E-01 1.50E-02

 SG11
+      2.01E-01 2.95E-02 ......... ......... -1.64E-01 ......... ......... ......... -2.15E-01 -1.70E-01 -4.02E-01 7.40E-03

1
 ************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************           INVERSE COVARIANCE MATRIX OF ESTIMATE    ********************
 ********************                                                    ********************
 ************************************************************************************************************************


          TH 1    TH 2    TH 3    TH 4    TH 5    TH 6    TH 7    TH 8    OM11    OM12    OM22    SG11


 TH 1
+      2.05E+02

 TH 2
+     -1.94E+00 8.76E-01

 TH 3
+     ......... ......... .........

 TH 4
+     ......... ......... ......... .........

 TH 5
+     -8.24E+01 2.48E+00 ......... ......... 1.59E+02

 TH 6
+     ......... ......... ......... ......... ......... .........
```

```
 TH 7
+     ......... ......... ......... ......... ......... ......... .........

 TH 8
+     ......... ......... ......... ......... ......... ......... ......... .........

 OM11
+      2.60E+02 -2.80E+01 ......... ......... -1.32E+02 ......... ......... ......... 9.38E+03

 OM12
+     -8.47E+02 -9.73E+00 ......... ......... 3.62E+01 ......... ......... ......... -5.49E+02 2.46E+04

 OM22
+     -3.24E+01 -2.22E+01 ......... ......... 1.78E+02 ......... ......... ......... 9.47E+02 -1.80E+03 6.47E+03

 SG11
+     -7.46E+02 -2.31E+01 ......... ......... 6.31E+02 ......... ......... ......... 2.97E+03 4.66E+03 5.82E+03 2.80E+04

1
```

```
 ************************************************************************************************************************
 ********************                                                    ********************
 ********************      FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ********************
 ********************           EIGENVALUES OF COR MATRIX OF ESTIMATE      ********************
 ********************                                                    ********************
 ************************************************************************************************************************


          1       2       3       4       5       6       7

       3.40E-01 4.25E-01 6.40E-01 1.01E+00 1.22E+00 1.63E+00 1.73E+00

 Elapsed finaloutput time in seconds: 0.05
 #CPUT: Total CPU Time in Seconds, 2.678
Stop Time:
Mi 14. Apr 14:20:14 CEST 2021
```

C LISTINGS OF SOURCE FILES

C.1 R Scripts

C.1.1 Exploratory analysis

```
##****************************************************************
## Study R-script name : exploratory .R
## Description : data overview of NONMEM input dataset
## Platform : openSUSE Linux, version 15.1
## Original programmer : TF
## Current programmer / Modified by :TF
## Compound number :
## Study code :
## Date completed : Apr 2021
## Outputs created : figures , tables
## R version : R version 3.6.1
## NONMEM version : 7.4.1
##****************************************************************

rm(list=ls())

# additional packages ----------------------------------------
library(plyr)
library(dplyr)
library(papeR)
library(reshape)
library(ggplot2)

# set working directory --------------------------------------------------
wd <- "/workfra/content/POHXXXX/analysis/"
setwd(wd)

# additional functions ---------------------------------------
source("./R/datalist.R")
source("./R/dataoverview.R")
source("./R/getN.R")
source("./R/ckeckdat.R")
source("./R/carryfwd.R")
source("./R/plotlist.R")
source("./R/appendList.R")
source("./R/makeFootnote.R")

PKdat <- getN("data_set_504.dat") # import NONMEM analysis dataset
PKdat<-PKdat%>%
  dplyr::mutate(DOSE=case_when(AMT==1000 ~ 1, AMT==2000 ~ 2, AMT==4000 ~ 4), DOSE=carryfwd(DOSE), SEX= recode_factor
      (SEX, '0' = "female", '1' = "male"))

class_sum1<- PKdat%>%
  dplyr::select(ID, DV, EVID, MDV)

# dplyr::summarise(n = n()) %>%
# dplyr::mutate(rel.freq = round(100 * n/sum(n), 1))

dataoverview(class_sum1, filename = "OverviewPKSamples", variables = 'DV',group="MDV", caption= "Overview of PK samples (
    statistics in \\textmu g/mL)", label ="tab:SumPKsamples")


dataoverview(PKdat[!duplicated(PKdat$ID),], filename = "SummaryContCovariates", variables = c('AGE','WT'), variable.labels =
    c('Age (years)','Weight (kg)'), caption= "Summary statistics of continuous covariates", label ="tab:SumContCov")

PKdat2<-PKdat%>%
  dplyr::select(ID, SEX,WT, AGE)%>%
  dplyr::filter(!duplicated(ID))

df<-melt(PKdat2, id.vars=c("ID","SEX"), measure.vars=c("WT", "AGE"), variable_name = " covariate ")
```

```
class_sum3<-df%>%
  dplyr::group_by(covariate, SEX)%>%
  dplyr::mutate(covariate=recode_factor(covariate, 'AGE'="Age(y)", 'WT'="Weight (kg)"))%>%
  dplyr::summarise(n=n(), mean=mean(value), sd=sd(value), min=min(value), q1=quantile(value, probs=0.25), median=median(value), q3=quantile(value, probs=0.75), max=max(value))

datalist(class_sum3,filename="SummaryContCovariatesSEX", digits=1, variablelabels=c("Covariate", "Sex","N","Mean",'SD', "Min","Q1", 'Median',"Q3", "Max"), caption="Summary statistics of continuous covariates by sex", label="tab:SumContCovSEX")

dataoverview(PKdat[!duplicated(PKdat$ID),], filename="SummaryCatCovariates", variables='SEX',type="factor", caption="Number and percentage of subjects by sex", label="tab:SumCatCov")

class_sum4<-PKdat%>%
 dplyr::filter(EVID==0)%>%
  dplyr::group_by(DOSE, TIME)%>%
  dplyr::summarise(n=n(), q25=quantile(DV, probs=0.025, na.rm=T), median=median(DV, na.rm=T), q975=quantile(DV, probs=0.975, na.rm=T))%>%
  dplyr::rename(DV=median)%>%
  dplyr::mutate(ID=1, WT=1)

p1<-ggplot(data=PKdat[PKdat$EVID==0,], aes(TIME, DV, group=ID, colour=WT))+geom_line()+geom_line(data=class_sum4, colour="black", size=1)+scale_x_continuous(name="Time (hours)")+scale_y_continuous(name="Concentration µ(g/mL)")+facet_wrap(~case_when(DOSE==1~"1 mg", DOSE==2~"2  mg",DOSE==4~"4 mg"))+scale_colour_gradient(low="salmon", high="#56B1F7", na.value=NA, name="Weight (kg)")+theme_bw(12);p1
 plotlist(list(p1), file="ctplotallone.lin.DOSE", width=8.5, height=5., subdir="plots")

p2<-ggplot(data=PKdat[PKdat$EVID==0,], aes(TIME, DV, group=ID, colour=WT))+geom_line()+geom_line(data=class_sum4, colour="black", size=1)+scale_x_continuous(name="Time (hours)")+scale_y_log10(name="Concentration µ(g/mL)")+annotation_logticks(sides="l")+facet_wrap(~case_when(DOSE==1~"1 mg", DOSE==2~"2  mg",DOSE==4~"4 mg"))+scale_colour_gradient(low="salmon", high="#56B1F7", na.value=NA, name="Weight (kg)")+theme_bw(12);p2
 plotlist(list(p2), file="ctplotallone.log.DOSE", width=8.5, height=5., subdir="plots")

# save R workspace------------------------------------------------------------
#save.image("exploratory.RData")
```

C.1.2 Post-processing of NONMEM runs

```
##***************************************************************
## Study R-script name : postprocessing.R
## Description : post-processing of NONMEM runs
## Platform : openSUSE Linux, version 15.1
## Original programmer : TF
## Current programmer / Modified by : SG
## Compound number :
## Study code :
## Date completed : Apr 2021
## Outputs created : figures, tables
## R version : R version 3.6.1
## NONMEM version : 7.4.1
##***************************************************************

rm(list=ls())

# additional packages ----------------------------------

library(plyr)
library(dplyr)
library(papeR)
library(reshape)
library(ggplot2)

# set working directory ----------------------------------------------------
wd <- "/workfra/content/POHXXXX/analysis/"
setwd(wd)

# additional functions ----------------------------------

source("standard.plots.R")
source("./R/unziparch.R")
source("./R/ziparch.R")
source("./R/getnmr7.R")
source("./R/createXposeClassesSanofi.R")
source("./R/getnmr7.esti.R")
source("./R/printnmr7.R")
source("./R/npdeplot.R")
source("./R/contcorr.R")
source("./R/datalist.R")
source("./R/dataoverview.R")
source("./R/paramsum.R")
source("./R/gofplots.R")
source("./R/ctpop.R")
source("./R/getN.R")
source("./R/ckeckdat.R")
source("./R/carryfwd.R")
source("./R/plotlist.R")
source("./R/printSessionInfo.R")
source("./R/extractdata.R")
source("./R/makeFootnote.R")
source("./R/compnmr7.R")
source("./R/unpaste.R")
source("./R/check.factor.R")
source("./R/appendList.R")

##create symbolic links in a separate folder only for model comparison
basemodel<-"run504_no_cov.1117171.tar.gz"
fullcovmod<-"run504_full_cov.1117172.tar.gz"
finalmodel <-"run504_with_cov_fix.1117173.tar.gz"

system(paste("ln␣-s␣",wd,"nmnqs/",basemodel,"␣",wd,"comparison/nmnqs/",basemodel, sep=""))
system(paste("ln␣-s␣",wd,"nmnqs/",fullcovmod,"␣",wd,"comparison/nmnqs/",fullcovmod, sep=""))
system(paste("ln␣-s␣",wd,"nmnqs/",finalmodel,"␣",wd,"comparison/nmnqs/",finalmodel, sep=""))

## base model
standard.plots(
```

```
  path=wd,
  num=1117171,
  subdir="comparison",
  base_model = T

)
## full covariates
standard.plots(
  path=wd,
  num=1117172,
  subdir="comparison",
  base_model = F

)
## fixing some covariates
standard.plots(
  path=wd,
  num=1117173,
  subdir="comparison",
  base_model = F

)
## extract files from archive for inclusion in the report
system(paste("tar -xvzf ",wd,"nmnqs/",basemodel," tables/paramsum1117171.tex -C tables", sep="")) # parameter summary
system(paste("tar -xvzf ",wd,"nmnqs/",basemodel," plots -C plots", sep="")) # GOF plots
system(paste("tar -xvzf ",wd,"nmnqs/",basemodel," -C tables/ run504_no_cov1117171.rep", sep="")) # NONMEM control stream
    and report file

system(paste("tar -xvzf ",wd,"nmnqs/",fullcovmod,"tables/paramsum1117172.tex -C tables", sep=""))
system(paste("tar -xvzf ",wd,"nmnqs/",fullcovmod,"plots -C plots", sep=""))
system(paste("tar -xvzf ",wd,"nmnqs/",fullcovmod,"-C tables/ run504_full_cov1117172.rep", sep="")) # NONMEM control stream
    and report file
system(paste("tar -xvzf ",wd,"nmnqs/",finalmodel,"tables/paramsum1117173.tex -C tables", sep=""))
system(paste("tar -xvzf ",wd,"nmnqs/",finalmodel,"plots -C plots", sep=""))
system(paste("tar -xvzf ",wd,"nmnqs/",finalmodel,"-C tables/ run504_with_cov_fix1117173.rep", sep="")) # NONMEM control
    stream and report file


# ------------------------------------------
# R version and packages
#------------------------------------------

 printSessionInfo (subdir="tables")

# save R workspace------------------------------------------------------------

#save.image("postprocessing.RData")
```

C.1.3 Goodness-of-fit plots and parameter summary

```
##*************************************************************
## Study R-script name : standard.plots.R
## Description : Creates GoF plots and summary tables for NONMEM runs
##  the tar.gz file containing NONMEM results is extracted in a
##  temporary directory, plots and tables are created and added
##  to the tar.gz file
## Platform : openSUSE Linux, version 15.1
## Original programmer : AS
## Current programmer / Modified by : TF,SG
## Date completed : Apr 2021
## R version : R version 3.6.1
## NONMEM version : 7.4.1
##*************************************************************

standard.plots <- function(num, path, del=T, subdir, base_model=F
                           #, digits=2, ym=0.45, xm=1.8,
                           #nofactor = c("ID", "DV", "TIME", "TVCL", "TVV", "CL", "V"), cor.lowETA=F, cor.lowCOV=T,
                           #thetaVariableNames=c("TVCL (mL/h)", "TVV (L)", "CLBWT", "VBWT")
                           ) {


wd <- path
  setwd(wd) ## set working directory, nmanalysis folder where NM runs were performed from
num=num
#unzip file
unziparch(num) #unzip archive into a tmp folder, create subfolders, save all plots in tmp folder


getnmr7(num, xposeread=T, data=F, RM=T, check=T, shrinkage = T) ## input run number from archive (Xpose step)
 extractdata(num)

## use temporary data object
mydat = paste("dat",num,sep='')
cmd = mydat
tmp<-eval(parse(text=cmd))

# create table with model outputs
printnmr7(eval(parse(text=paste('fit',num,sep=''))), digits=2, formatted=F, path=paste(wd,"nmntmp", num,"/tables",sep = "")
       )

# parameter summary table
paramsum(eval(parse(text=paste('fit',num,sep=''))), path=paste(wd,"nmntmp", num,"/tables",sep = ""), table.placement = "!
      htpb", label = paste("tab:paramsum",num, sep=""))#, thetaVariableNames=thetaVariableNames)

#  gofplots A (DV vs IPRED and PRED) and B (CWRES)
 gofplots(tmp,num=num,conc="DV",time="TIME", timelabel="time (hours)", logdata=F, cmt=1, label = " concentration μ(g/mL)",
            lloq=0, show.dv = 2, smooth=T, addname=NULL,subdir= paste("nmntmp", num,"/plots",sep = ""), theme_set = theme_bw()
                +
              theme(legend.position = "bottom", legend.box = "horizontal", strip.background = element_rect(fill = "#e6ffe6",
                    linetype = "dashed"), strip.text = element_text(size = 12), text = element_text(size = 12), plot.caption =
                    element_text(size = 10, colour = "darkgrey")), alpha.bw = 0.5)

# individual plots of observations, together with individual, and population predictions
ctpop(tmp,num=num, conc="DV", idv="TIME", xlabel="Time (hours)", ylabel="Concentration μ(g/mL)", profile=c('ID'), logdata=F,
        addname=NULL, theme_set = theme_bw(10),subdir= paste("nmntmp", num,"/plots",sep = ""))


# npde plots
npdeplot(tmp, num=num,addname=NULL, time="TIME", timelabel = "time (hours)", predlabel="population predicted concentration
      μ(g/mL)",log=F, alpha.bw=0.5, npde=5,ym = 0.45, theme_set = theme_bw(12), subdir=paste("nmntmp", num,"/plots",sep = ""
      ))


# plot correlation on eta vs covariates and eta vs eta

contcorr(tmp, num=num, cov = c("ETA1","ETA2", "WT","SEX","AGE"), covlabels = c("ETA CL", "ETA V","WT","SEX","AGE"),
      addname = 'ETA', alpha.bw = 0.5, theme_set = theme_bw(10),subdir = paste("nmntmp", num,"/plots",sep = ""))
```

```
59
61  ziparch(num, del=T) #zip tmp folder

63  ## for base model we want a comparison with other relevant models from an extra comparison folder
    if(base_model==T){
65  wd_comp<-paste(".",subdir,sep="/")
    setwd(wd_comp)
67  comparison<<-compnmr7(merging=T, OBJref=num) # run comparison

69  baseModelsubset<-subset(comparison, select=c("ARCHIVE","PROBLEM","nPSE","OBJ", "OBJdiff", "ETCL:ETCL", "ETV:ETV"))
        %>%
      dplyr::rename(ETCL="ETCL:ETCL", ETV = "ETV:ETV")%>%
71    dplyr::mutate(ETCL=sqrt(ETCL), ETV=sqrt(ETV))
    write.csv(baseModelsubset, file="modelcomp.csv")
73  datalist(baseModelsubset, filename="modelcomp", subdir=subdir, path=path, caption="Comparison of models", label="tab:
        comparison", digits=c(0,0,0,1,1,1, 3, 3))
    setwd(wd)}
75  }
```

C.2 R Settings

```
R session information:
-----------------------------------------------------------------
R version 3.6.1 (2019-07-05)
Platform: x86_64-suse-linux-gnu (64-bit)
Running under: openSUSE Leap 15.1

Matrix products: default
BLAS: /usr/lib64/R/lib/libRblas.so
LAPACK: /usr/lib64/R/lib/libRlapack.so

Random number generation:
 RNG:   Inversion
 Normal: Mersenne-Twister
 Sample: Rejection

locale:
 [1] LC_CTYPE=de_DE.UTF-8 LC_NUMERIC=C
 [3] LC_TIME=de_DE.UTF-8 LC_COLLATE=de_DE.UTF-8
 [5] LC_MONETARY=de_DE.UTF-8 LC_MESSAGES=de_DE.UTF-8
 [7] LC_PAPER=de_DE.UTF-8 LC_NAME=C
 [9] LC_ADDRESS=C       LC_TELEPHONE=C
[11] LC_MEASUREMENT=de_DE.UTF-8 LC_IDENTIFICATION=C

attached base packages:
 [1] base  datasets graphics grDevices grid methods parallel
 [8] splines stats utils

other attached packages:
 [1] Biobase_2.44.0 BiocGenerics_0.30.0 car_3.0-4
 [4] carData_3.0-2 dplyr_1.0.0    foreach_1.4.7
 [7] gam_1.16.1    ggplot2_3.3.1  lattice_0.20-38
[10] mclust_5.4.5  npde_2.0       papeR_1.0-4
[13] plyr_1.8.6    reshape_0.8.8  xpose4_4.5.3
[16] xtable_1.8-4

loaded via a namespace (and not attached):
 [1] abind_1.4-5   acepack_1.4.1  assertthat_0.2.1
 [4] backports_1.1.5 base64enc_0.1-3 cellranger_1.1.0
 [7] checkmate_1.9.4 cluster_2.1.0 codetools_0.2-16
[10] colorspace_1.4-1 compiler_3.6.1 crayon_1.3.4
[13] curl_4.2      data.table_1.12.6 digest_0.6.22
[16] ellipsis_0.3.0 farver_2.0.3  forcats_0.4.0
[19] foreign_0.8-72 Formula_1.2-3 gdata_2.17.0
[22] generics_0.0.2 GGally_2.0.0  glue_1.4.1
[25] gmodels_2.18.1 gridExtra_2.3 gtable_0.3.0
[28] gtools_3.8.1  haven_2.2.0    Hmisc_4.3-0
[31] hms_0.5.3     htmlTable_1.13.2 htmltools_0.4.0
[34] htmlwidgets_1.5.1 iterators_1.0.12 knitr_1.28
[37] labeling_0.3  latticeExtra_0.6-28 lifecycle_0.2.0
[40] magrittr_1.5  MASS_7.3-51.4  Matrix_1.2-17
[43] mgcv_1.8-31   munsell_0.5.0  nlme_3.1-142
[46] nnet_7.3-12   openxlsx_4.1.3 pillar_1.4.4
[49] pkgconfig_2.0.3 prettyunits_1.0.2 progress_1.2.2
[52] purrr_0.3.4   R6_2.4.1       RColorBrewer_1.1-2
[55] Rcpp_1.0.3    readxl_1.3.1   rio_0.5.16
[58] rlang_0.4.6   rpart_4.1-15   rstudioapi_0.10
[61] scales_1.1.1  stringi_1.4.6  stringr_1.4.0
[64] survival_2.44-1.1 tibble_3.0.1 tidyselect_1.1.0
[67] tools_3.6.1   vctrs_0.3.1    withr_2.1.2
[70] xfun_0.10     zip_2.1.1
```