Relative bioavailability of inhaled fluticasone propionate and salmeterol - is population pharmacokinetic modelling a relevant alternative to a non-compartmental approach?

Supplement

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Contents

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1 Abbreviations

CL/F, Apparent clearance from compartment 1 (L/h)
cmt, Compartment
CWRES, Conditional weighted residual
DOSE, Dose or dose increment (µg)
DV, Dependent value, plasma concentration of FP (ng/L)
FP, Fluticasone Propionate
TIME, Independent variable, time after dose (h)
IPRED, Individual model prediction
NONMEM, Non-linear Mixed effect model
PRED, Population model prediction
Q2/F, Distribution clearance to/from compartment 2 (L/h)
Q3/F, Distribution clearance to/from compartment 3 (L/h)
ref, Reference treatment, Advair® Diskus®
SALM, Salmeterol xinafoate
$T_{1/2}$, Post-hoc estimate of terminal half life (h)
test, Test treatment, Wixela® Inhub®
TREA, Treatment alternative, test (TREA=1) and reference (TREA=2) formulation
V1/F, Apparent central (compartment 1) volume of distribution (L)
V2/F, Apparent Peripheral (compartment 2) volume of distribution (L)
V3/F, Apparent Peripheral (compartment 3) volume of distribution (L)

2 Central NONMEM- and R-code elements

Central NONMEM model code elements, essentially with reference to principles outlined by Bauer (2019) [1], and R-code for individual post-hoc estimation of $T_{1/2}$ (denoted thalf_gamma) [2] are depicted in Figure 1.

NONMEM-code applied by study/dose for FP, Models 1-3

```
$SUBROUTINE ADVANS
$MODEL COMP=(DEFOBS1) COMP=(PERIPH1) COMP=(PERIPH2) COMP=(DEPOT1)
$PK
TREA1=0
TREA2=0
IF(TREA.EQ.1)TREA1=1; test
IF(TREA.EQ.2)TREA2=1; reference
MU_1 = THETA(1)
MU_4 = THETA(4)
MU_5 = THETA(5)
MU_6 = THETA(6)
MU_7 = THETA(7)
MU_10= THETA(10)
MU_11= THETA(11)
CL  =EXP(MU_1+ETA(1)); Apparent clearance, CL/F
Q2  =THETA(2)+ETA(2); Apparent distribution clearance, Q2/F
Q3  =THETA(3)+ETA(3); Apparent distribution clearance, Q3/F
S1  =EXP(MU_4+ETA(4)); Apparent central volume of distribution, V1/F
S2  =EXP(MU_5+ETA(5)); Apparent peripheral volume of distribution, V2/F
S3  =EXP(MU_6+ETA(6)); Apparent peripheral volume of distribution, V3/F
K10 =CL/S1; Rate of elimination
K12 =Q2/S1; Rate of distribution to periph comp 2
K21 =Q2/S2; Rate of redistribution
K13 =Q3/S1; Rate of distribution to periph comp 3
K31 =Q3/S3; Rate of redistribution
K41=EXP(TREA1*MU_7+TREA2*MU_10+ETA(7)); monophasic absorption rate constant
F4=EXP(TREA1*(MU_11+ETA(8))+TREA2*0); relative bioavailability, test/ref
------------------------
$ERROR ; proportional and additive
IEPRED=A(1)/S1
LLOQ=1
   PLP  =THETA(8)       ; plasma, proportional
   PLA  =THETA(9)       ; plasma, additive
DEL=1.0E-30
IPRED = ABS(IEPRED)+DEL
W=SQRT((PLP**2*IPRED**2)+PLA**2)
SD = W
IF(COMACT==1) PREDV=IPRED
DUM = (LLOQ - IPRED) / SD
CUMD = PHI(DUM)+DEL
TYPE=1
IF(DV<LLOQ) TYPE=2
IF(MDV==1) TYPE=0
IF(TYPE.EQ.2) DV_LOQ=LLOQ
IF (TYPE .NE. 2.OR.NPDE_MODE==1) THEN
      F_FLAG = 0
      Y = IPRED + SD * ERR(1)
ENDIF
IF (TYPE .EQ. 2.AND.NPDE_MODE==0) THEN
      F_FLAG = 1
      Y = CUMD
      MDVRES=1
ENDIF
```

NONMEM-code applied across studies for SALM, Model 4

```
$LEVEL STUD=(9[1]) ; interstudy variability
$SUBROUTINE ADVANS
$MODEL COMP=(DEFOBS1) COMP=(PERIPH1) COMP=(PERIPH2) COMP=(DEPOT1)
$PK
TREA1=0
TREA2=0
IF(TREA.EQ.1)TREA1=1
IF(TREA.EQ.2)TREA2=1
STUD1=0
STUD2=0
STUD3=0
IF(STUD.EQ.1)STUD1=1
IF(STUD.EQ.2)STUD2=1
IF(STUD.EQ.3)STUD3=1
MU_1 = THETA(1)
MU_2 = THETA(2)
MU_3 = THETA(3)
MU_4 = THETA(4)
MU_5 = THETA(5)
MU_6 = THETA(6)
MU_7 = THETA(7)
MU_10 = THETA(10)
MU_11 = THETA(11)
CL  =EXP(MU_1+ETA(1)); Apparent clearance, CL/F
Q2  =EXP(MU_2+ETA(2)); Apparent distribution clearance Q2/F
Q3  =EXP(MU_3+ETA(3)); Apparent distribution clearance Q3/F
S1  =EXP(MU_4+ETA(4)); Apparent central volume of distribution, V1/F
S2  =EXP(MU_5+ETA(5)); Apparent peripheral volume of distribution, V2/F
S3  =EXP(MU_6+ETA(6)); Apparent peripheral volume of distribution, V3/F
K10 =CL/S1; Rate of elimination
K12 =Q2/S1; Rate of distribution to periph comp 2
K21 =Q2/S2; Rate of redistribution
K13 =Q3/S1; Rate of distribution to periph comp 3
K31 =Q3/S3; Rate of redistribution
K41=EXP(TREA1*MU_7+TREA2*MU_10+ETA(7)) ; monophasic absorption rate constant
F4=EXP(TREA1*(MU_11+ETA(8)+ETA(9))+TREA2*0) ; relative bioavailability, test/ref
------------------------
$ERROR ; proportional and additive
IEPRED=A(1)/S1
LLOQ=1
   PLP  =THETA(8)       ; plasma, proportional
   PLA  =THETA(9)       ; plasma, additive
DEL=1.0E-30
IPRED = ABS(IEPRED)+DEL
W=SQRT((PLP**2*IPRED**2)+PLA**2)
SD = W
IF(COMACT==1) PREDV=IPRED
DUM = (LLOQ - IPRED) / SD
CUMD = PHI(DUM)+DEL
TYPE=1
IF(DV<LLOQ) TYPE=2
IF(MDV==1) TYPE=0
IF(TYPE.EQ.2) DV_LOQ=LLOQ
IF (TYPE .NE. 2.OR.NPDE_MODE==1) THEN
      F_FLAG = 0
      Y = IPRED + SD * ERR(1)
ENDIF
IF (TYPE .EQ. 2.AND.NPDE_MODE==0) THEN
      F_FLAG = 1
      Y = CUMD
      MDVRES=1
ENDIF
```

R-code for post-hoc individual estimation of terminal T½

```
j <- DATA$K12+DATA$K10+DATA$K21+DATA$K31+DATA$K13
k <- DATA$K12*DATA$K31+DATA$K10*DATA$K21+DATA$K10*DATA$K31+
     +DATA$K21*DATA$K31+DATA$K13*DATA$K21
l <- DATA$K10*DATA$K21*DATA$K31

m <- (3*k - j^2)/3
n <- (2*j^3 - 9*j*k + 27*l)/27
Q <- (n^2)/4 + (m^3)/27

alpha <- sqrt(-1*Q)
beta <- -1*n/2
rho <- sqrt(beta^2+alpha^2)
theta <- atan2(alpha,beta)

lambda1 <- j/3 + rho^(1/3)*(cos(theta/3) + sqrt(3)*sin(theta/3))
lambda2 <- j/3 + rho^(1/3)*(cos(theta/3) - sqrt(3)*sin(theta/3))
lambda3 <- j/3 -(2*rho^(1/3)*cos(theta/3))

thalf_alpha <- log(2)/lambda1
thalf_beta <- log(2)/lambda2
thalf_gamma <- log(2)/lambda3
```

Figure 1: Central pharmacokinetic NONMEM-code and post-hoc analysis R-code elements.

3 Model 1: FP 3x100µg, Basic Goodness of Fit

The final FP model, basic goodness of fit are described with and without separation by study/dose and device (TREA) are illustrated in Figures 2 - 5.

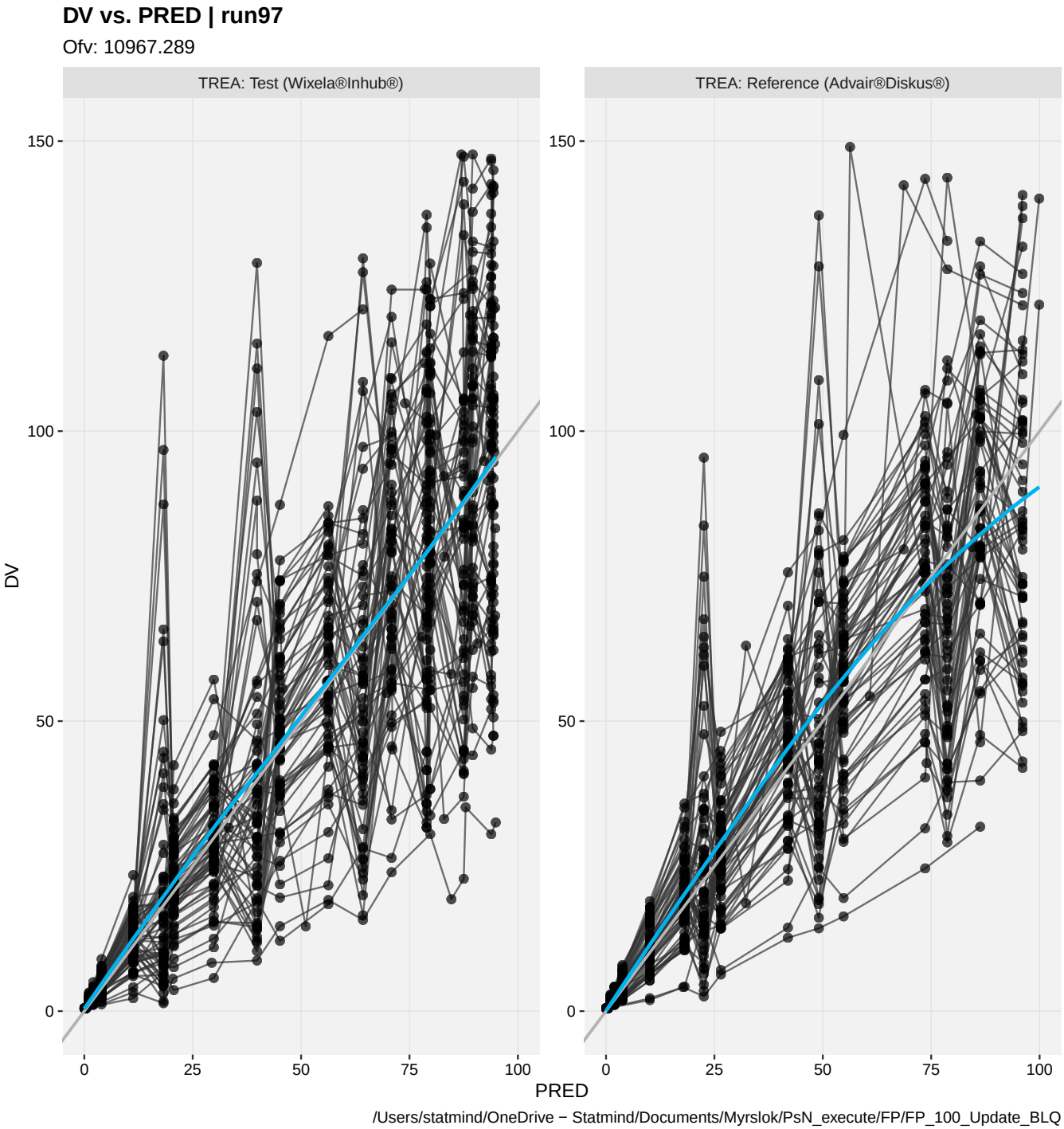

Figure 2: FP 3x100µg, basic goodness of fit, dependent vs typical, predicted concentration

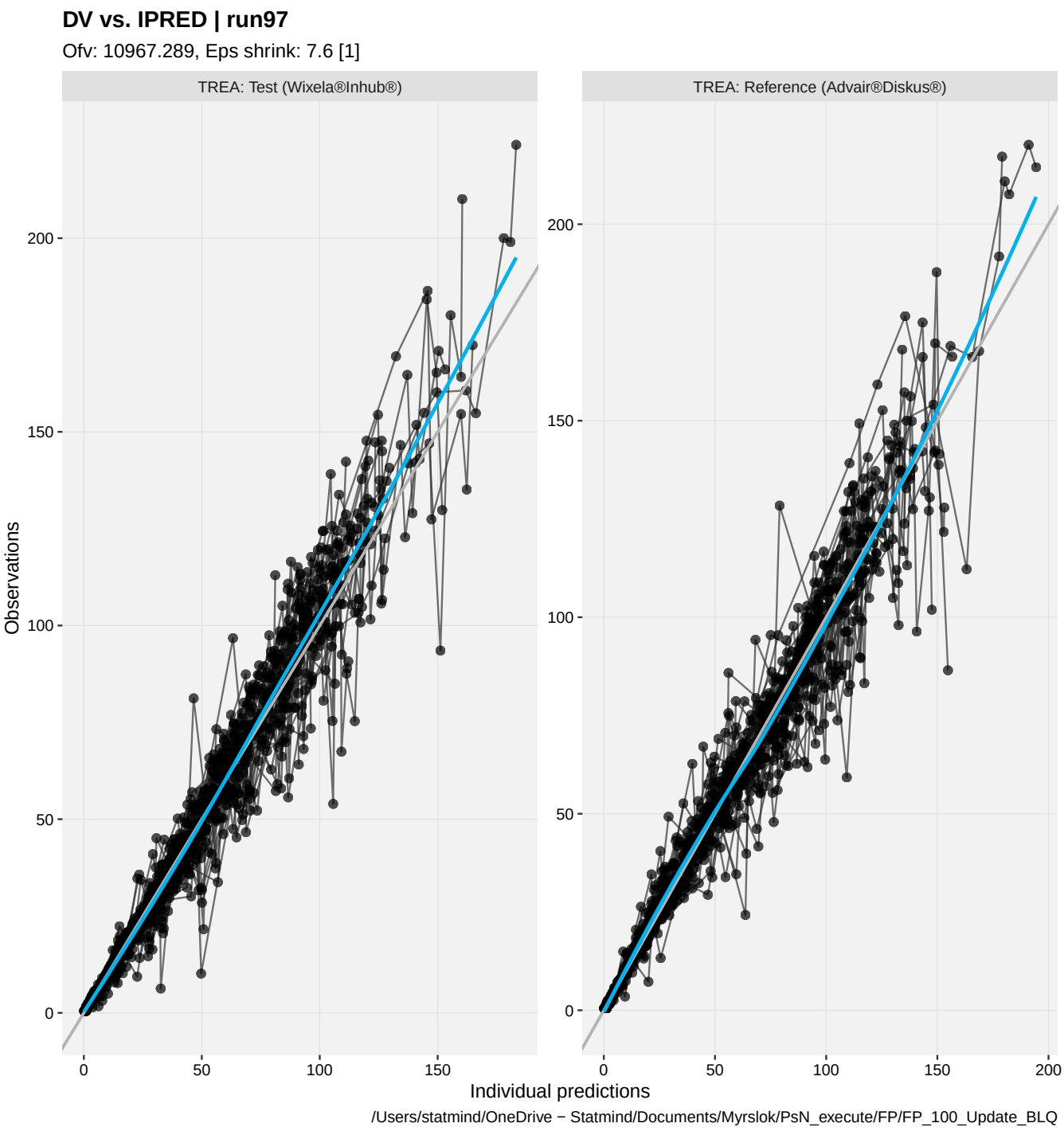

Figure 3: FP 3x100 µg, basic goodness of fit, dependent vs individual, predicted concentration of FP

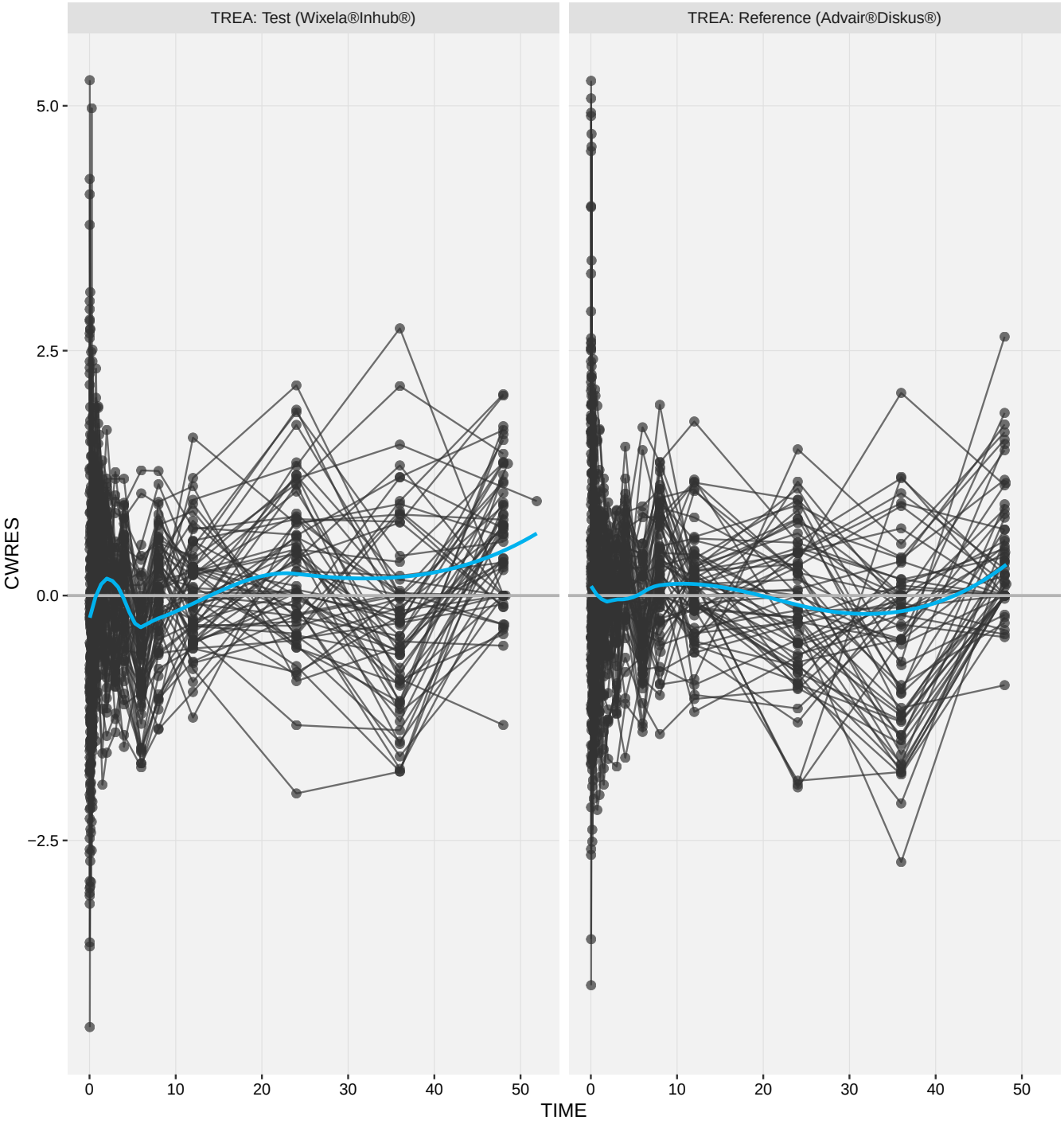

Figure 4: FP 3x100µg, basic goodness of fit, conditional weighted residual vs independent variable (time) (monophasic absorption)

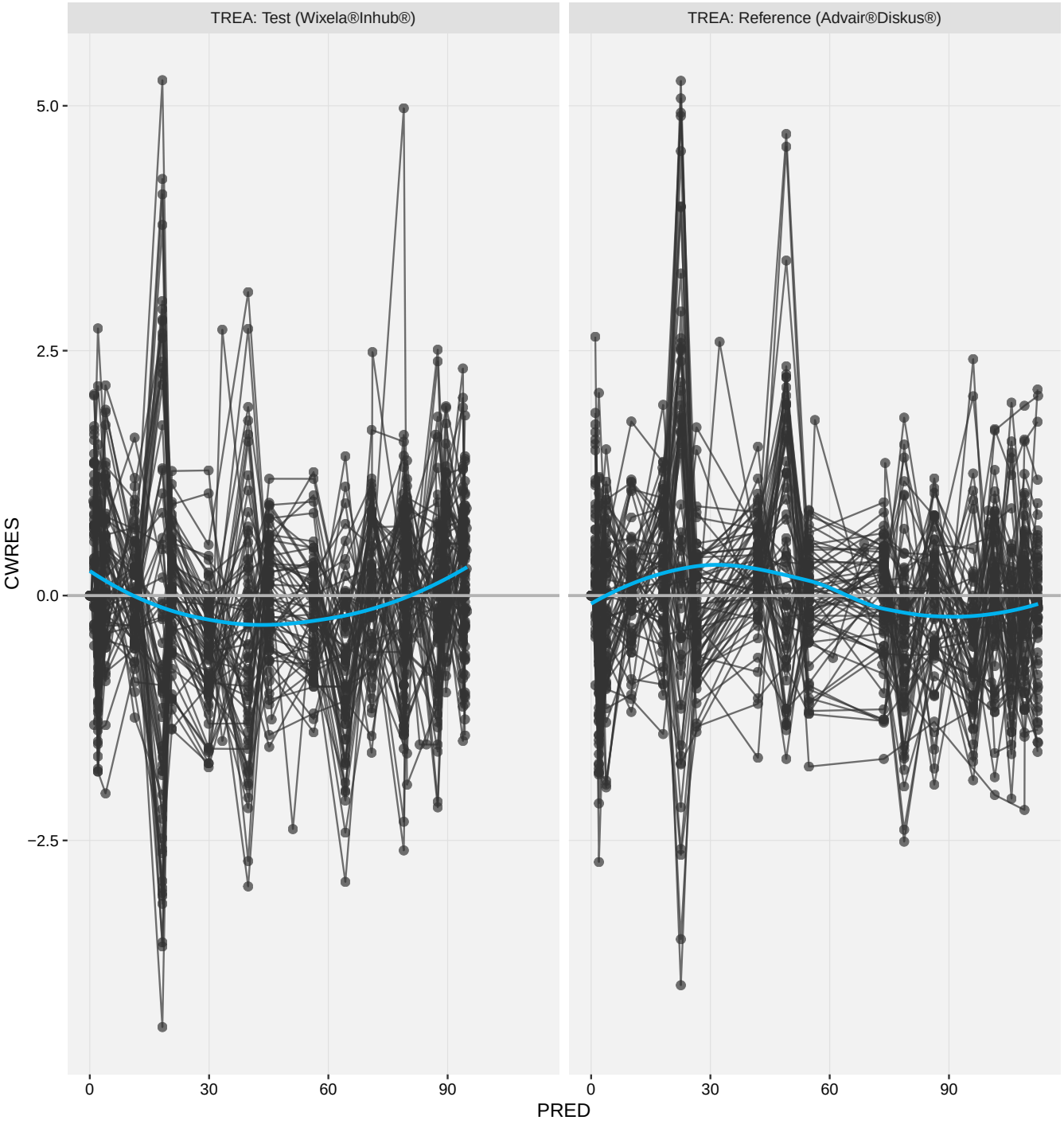

Figure 5: FP 3x100µg, basic goodness of fit, conditional weighted residual vs typical, predicted concentration of FP (monophasic absorption)

4 Model 2: FP 3x250µg, Basic Goodness of Fit

The final FP 3x250µg model, basic goodness of fit are described with and without separation by study/dose and device (TREA) are illustrated in Figures 6 - 9.

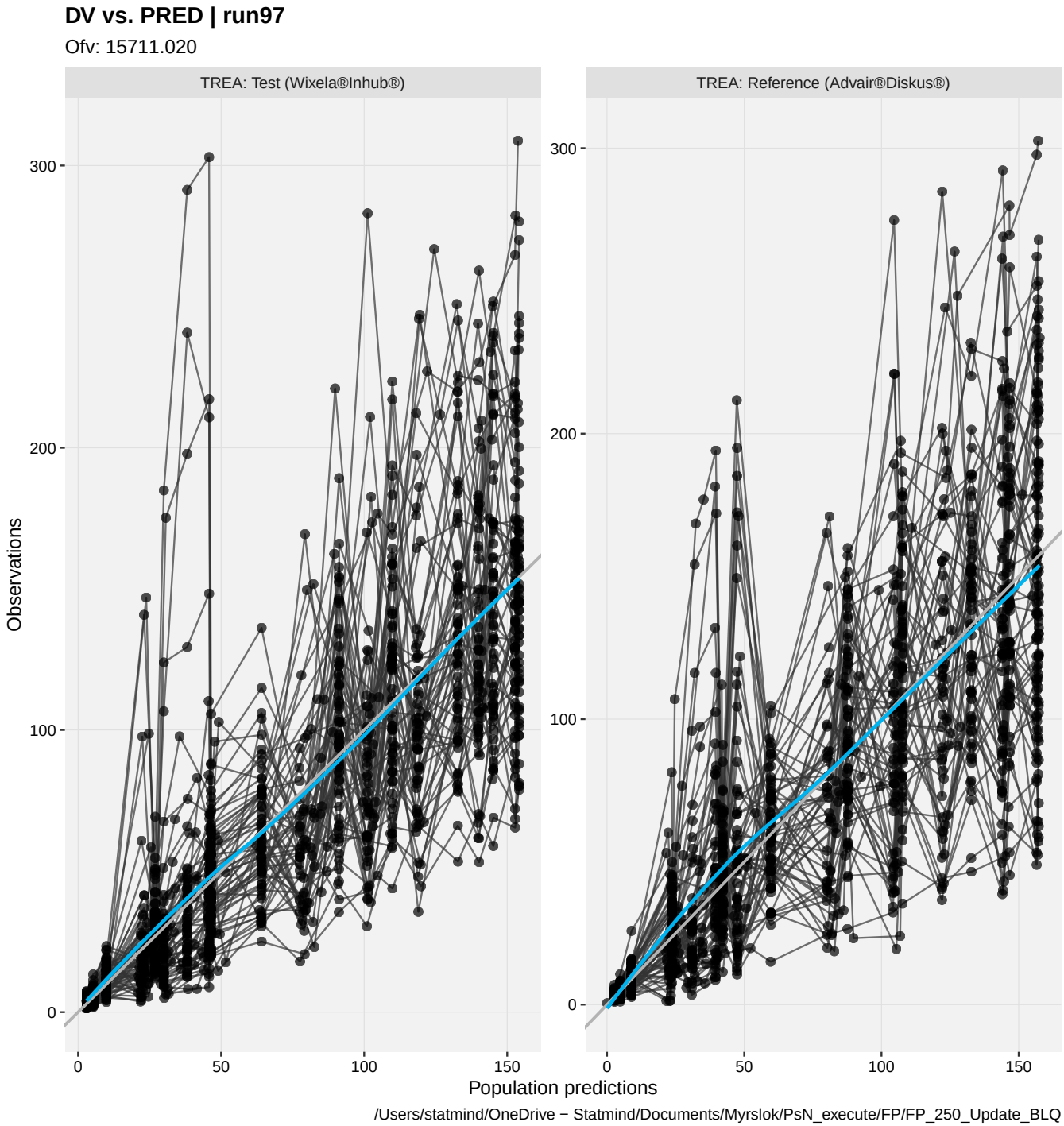

Figure 6: FP 3x250µg, basic goodness of fit, dependent vs typical, predicted concentration

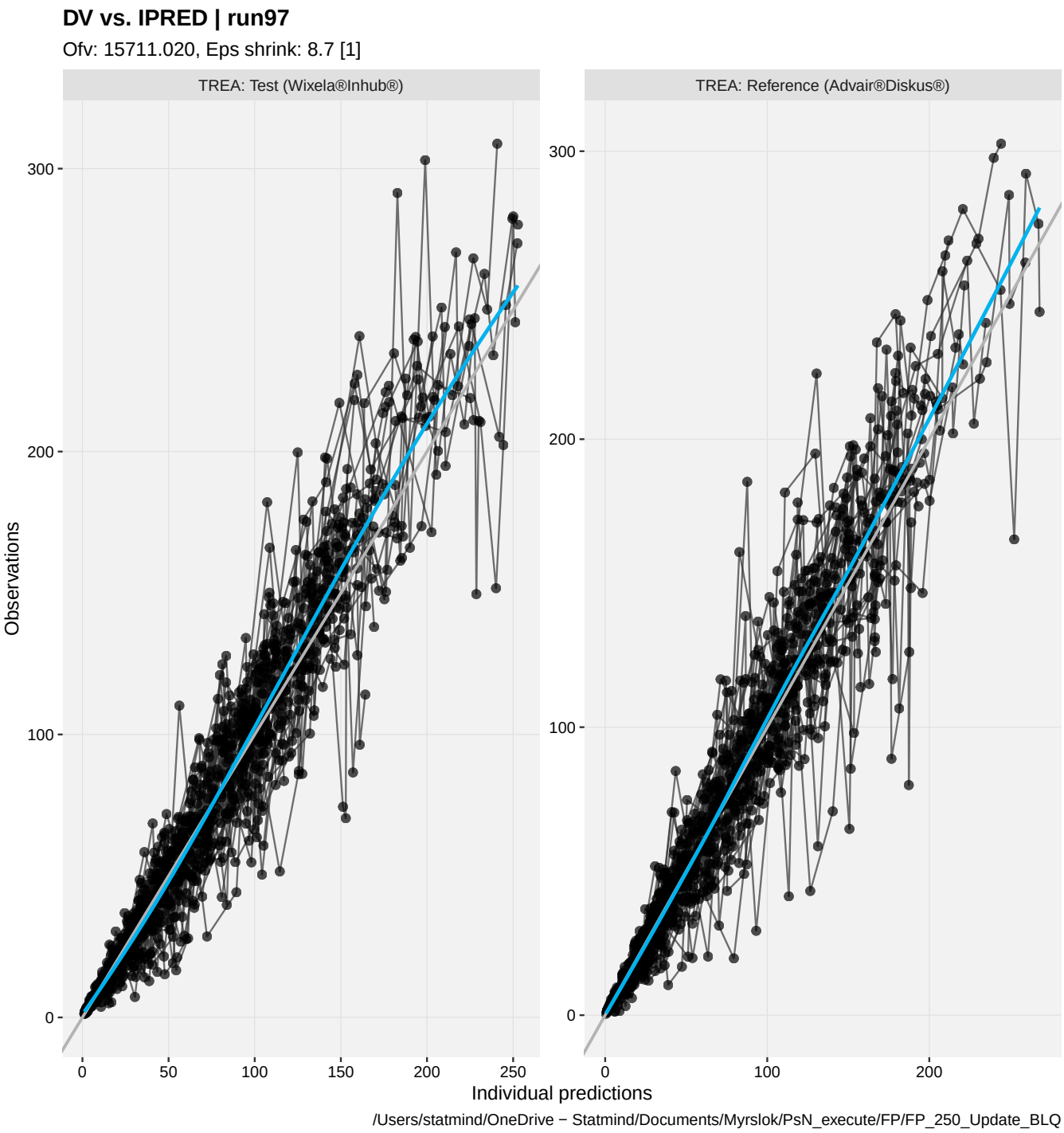

Figure 7: FP 3x250 µg, basic goodness of fit, dependent vs individual, predicted concentration of FP

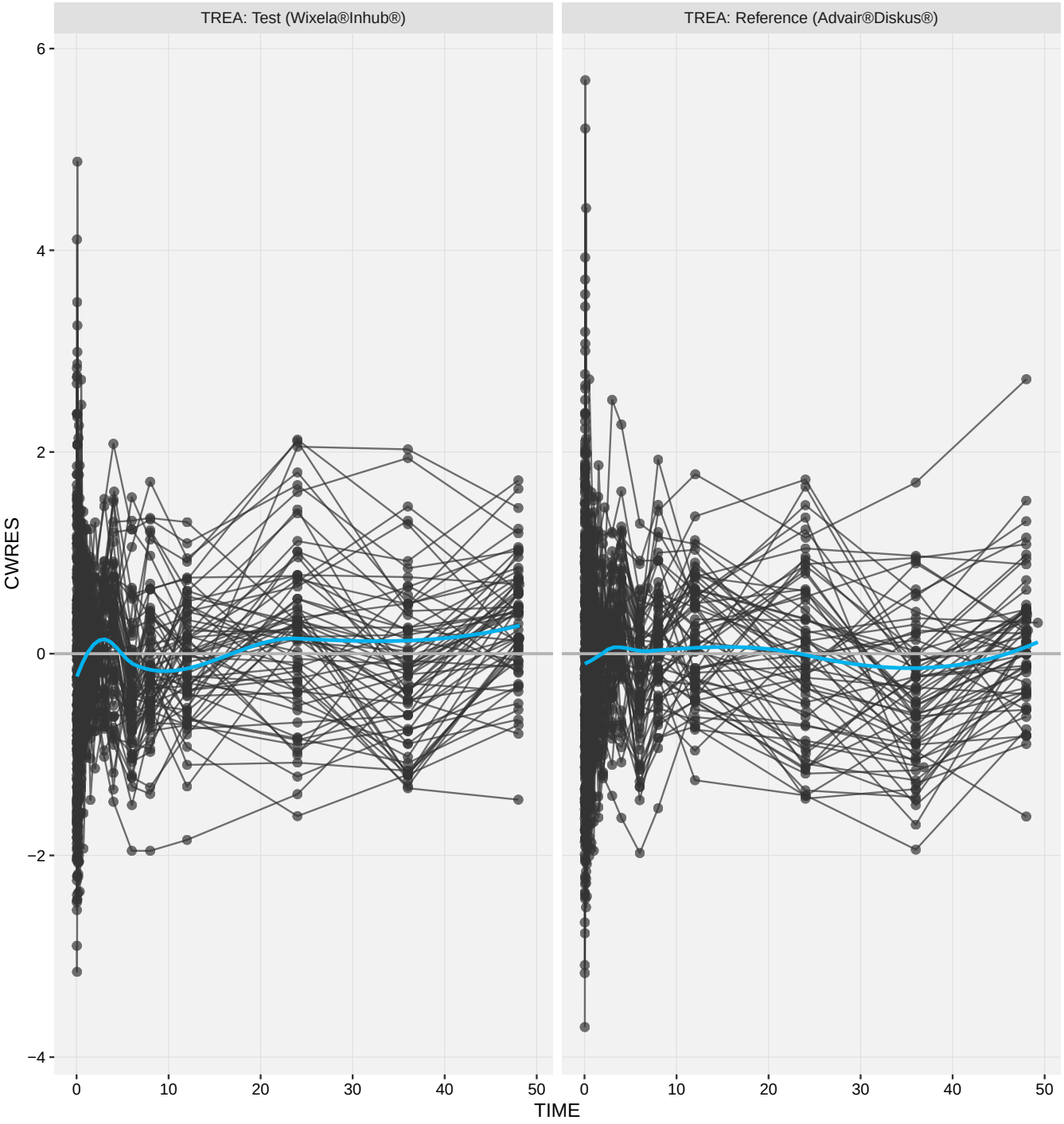

Figure 8: FP 3x250µg, basic goodness of fit, conditional weighted residual vs independent variable (time) (monophasic absorption)

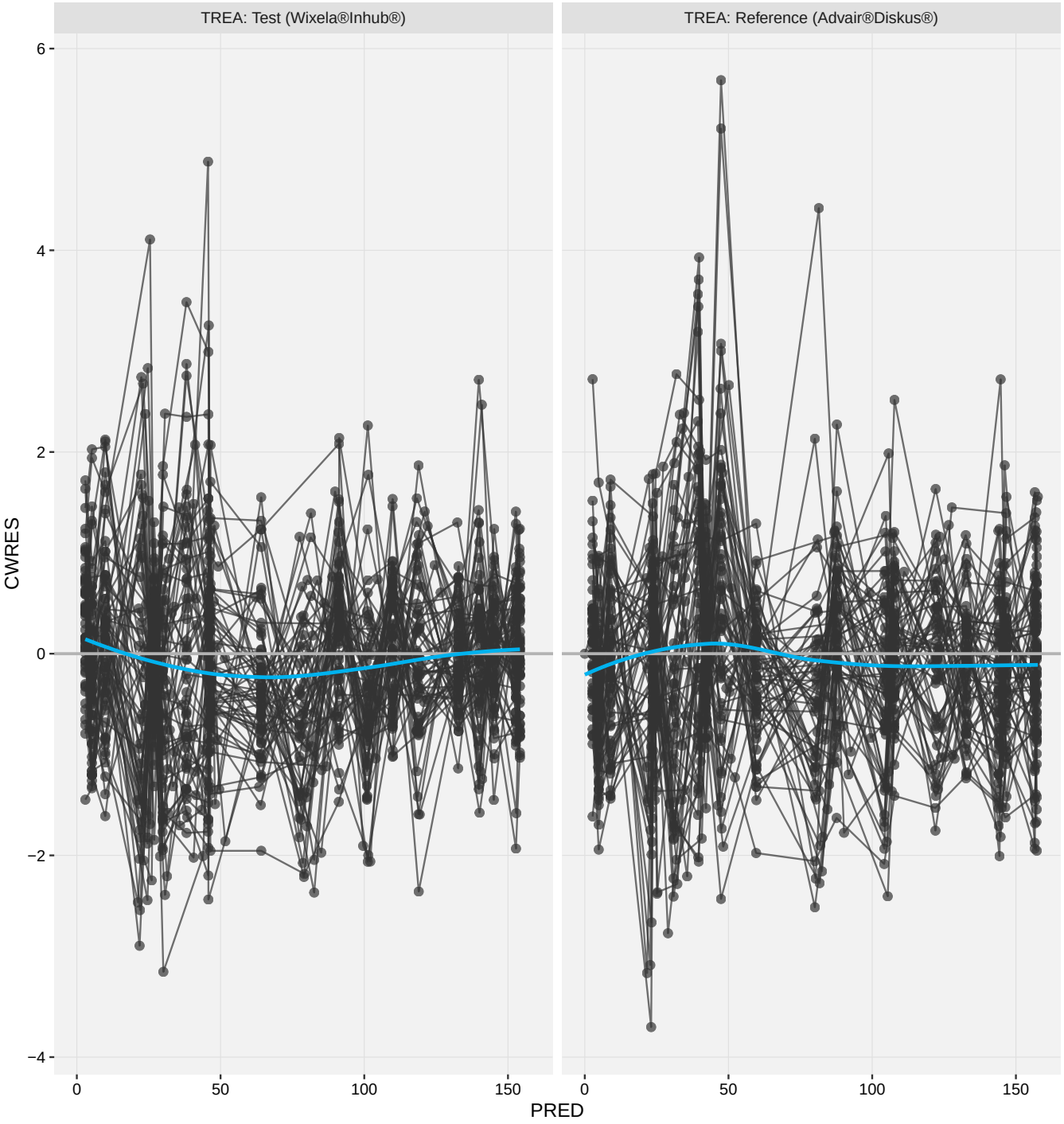

Figure 9: FP 3x250µg, basic goodness of fit, conditional weighted residual vs typical, predicted concentration of FP (monophasic absorption)

5 Model 3: FP 3x500µg, Basic Goodness of Fit

The final FP 3x500µg model, basic goodness of fit are described with and without separation by study/dose and device (TREA) are illustrated in Figures 10 - 13.

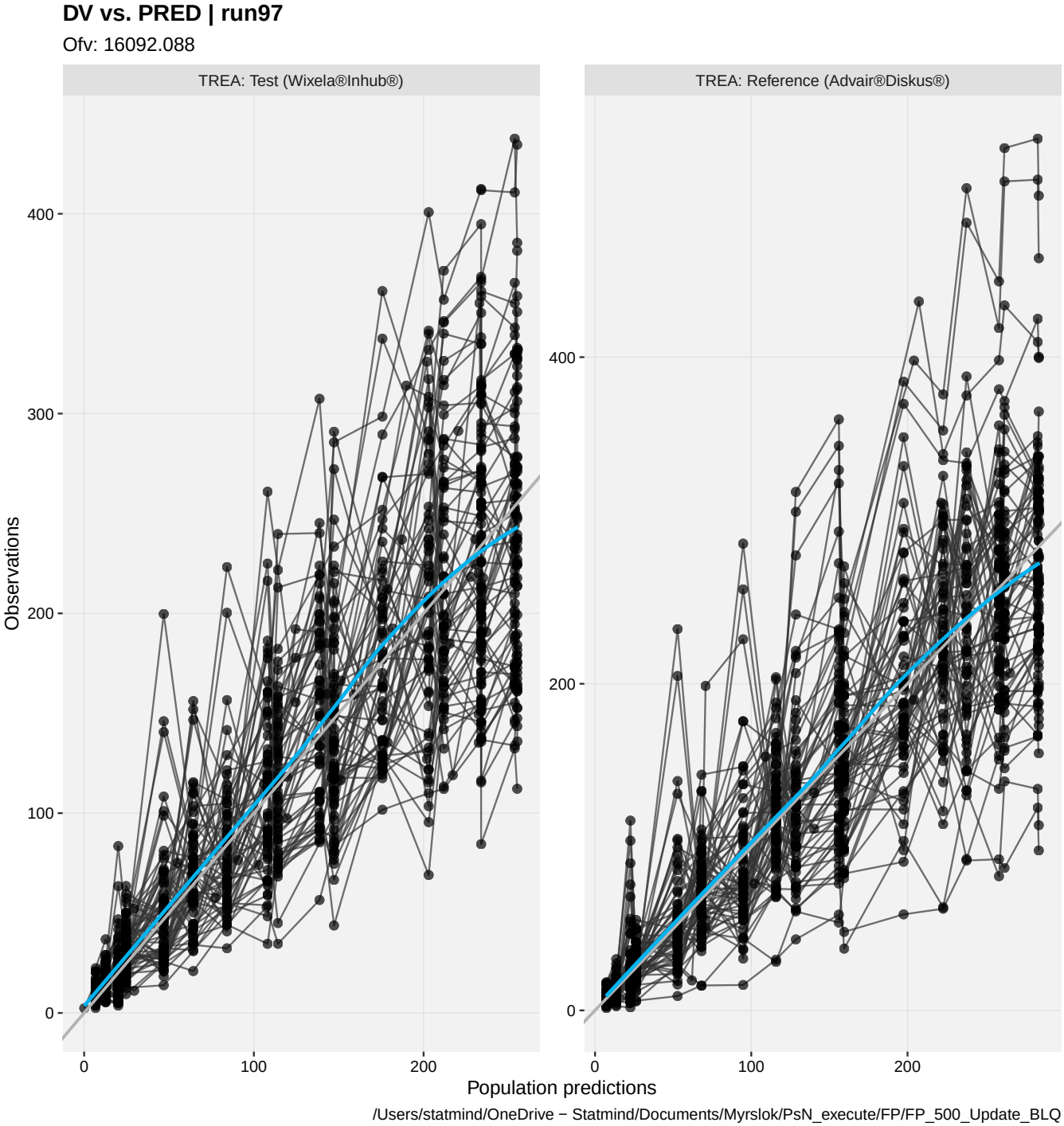

Figure 10: FP 3x100µg, basic goodness of fit, dependent vs typical, predicted concentration

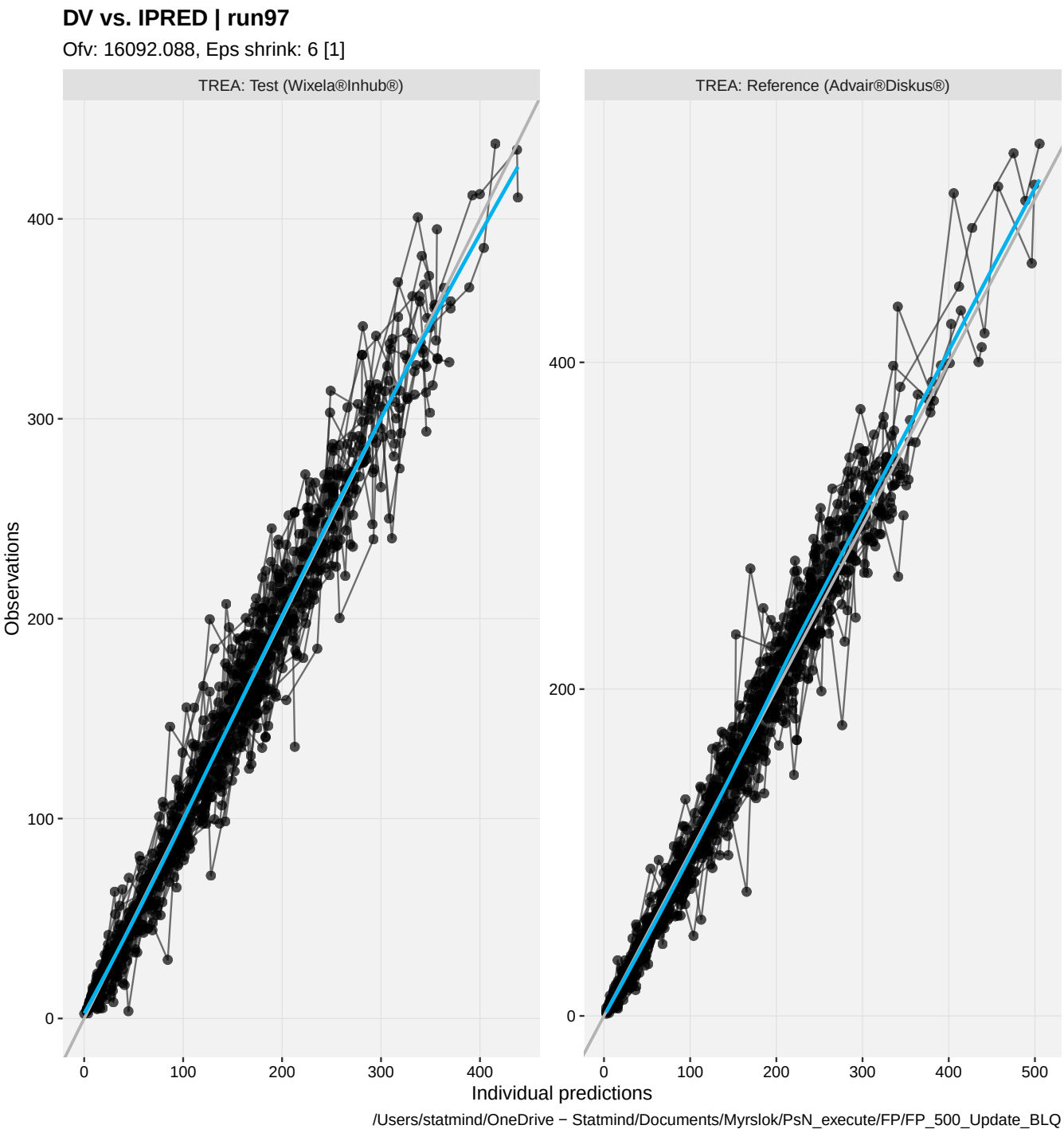

Figure 11: FP 3x500 µg, basic goodness of fit, dependent vs individual, predicted concentration of FP

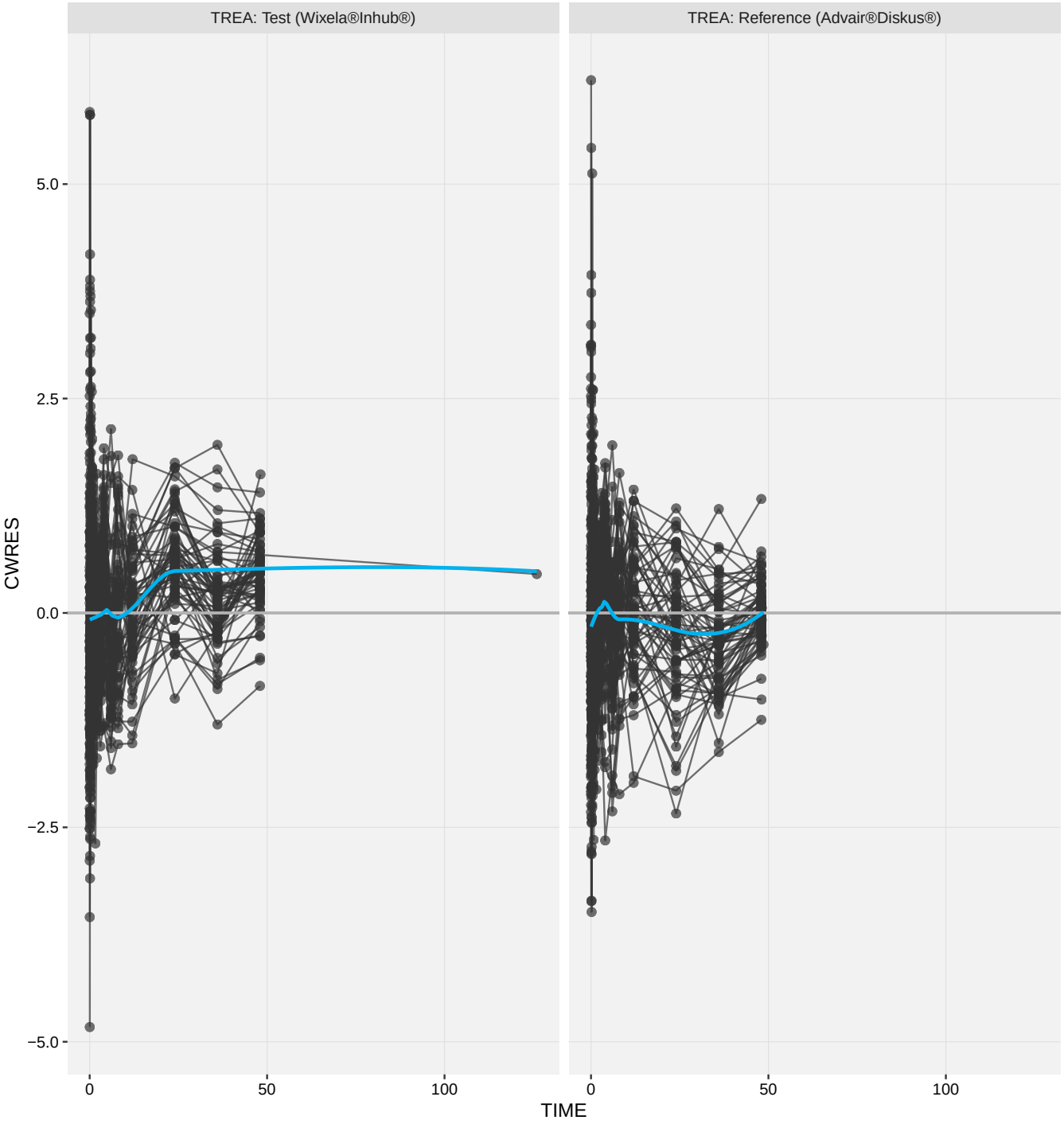

Figure 12: FP 3x500µg, basic goodness of fit, conditional weighted residual vs independent variable (time) (monophasic absorption)

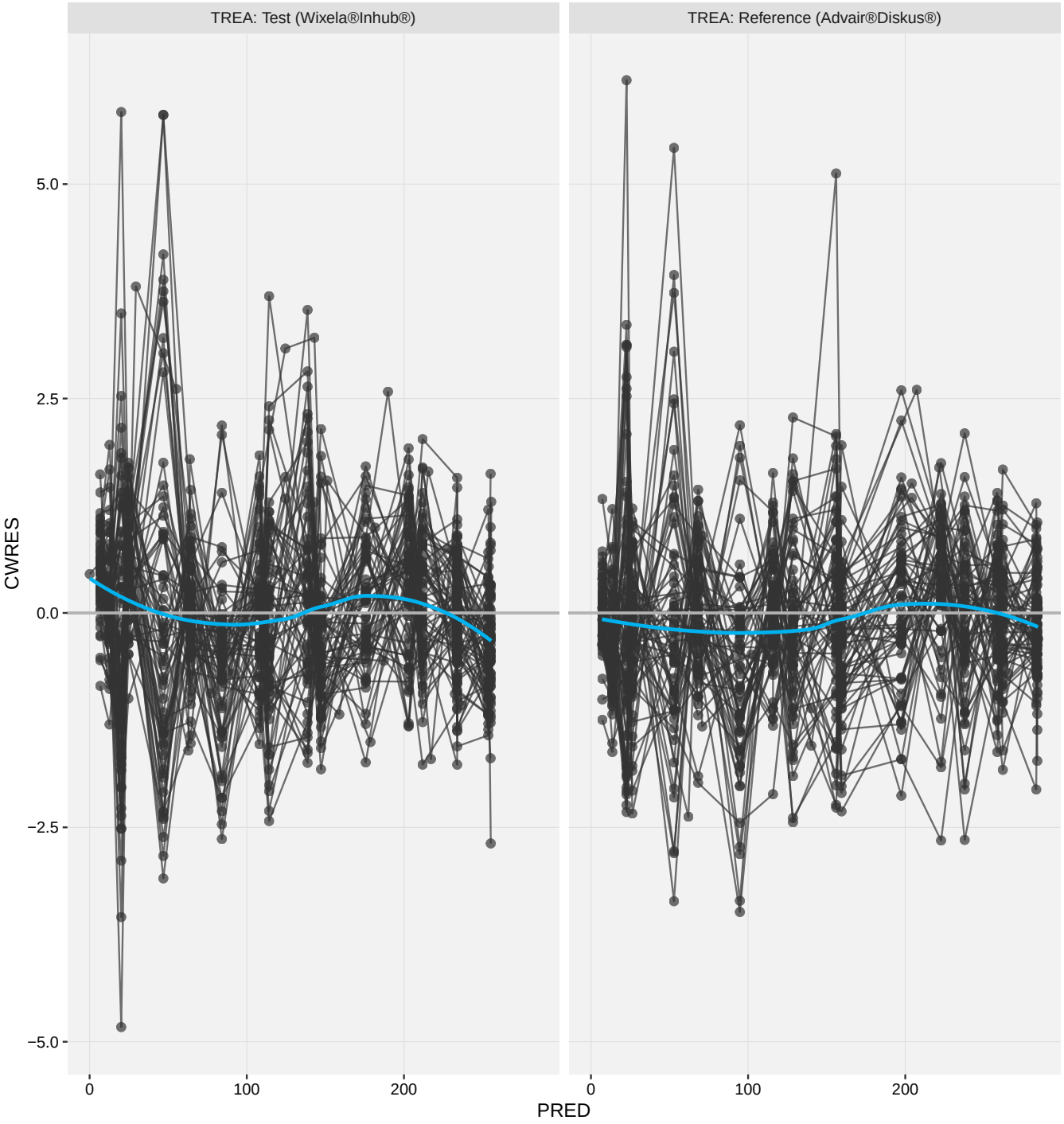

Figure 13: FP 3x500µg, basic goodness of fit, conditional weighted residual vs typical, predicted concentration of FP (monophasic absorption)

6 Model 4: SALM 3x50µg, Basic Goodness of Fit

The final SALM model 16 basic goodness of fit are desbribed - with and without separation by dose and device (TREA) - are illustrated in Figures 14 - **??**, .

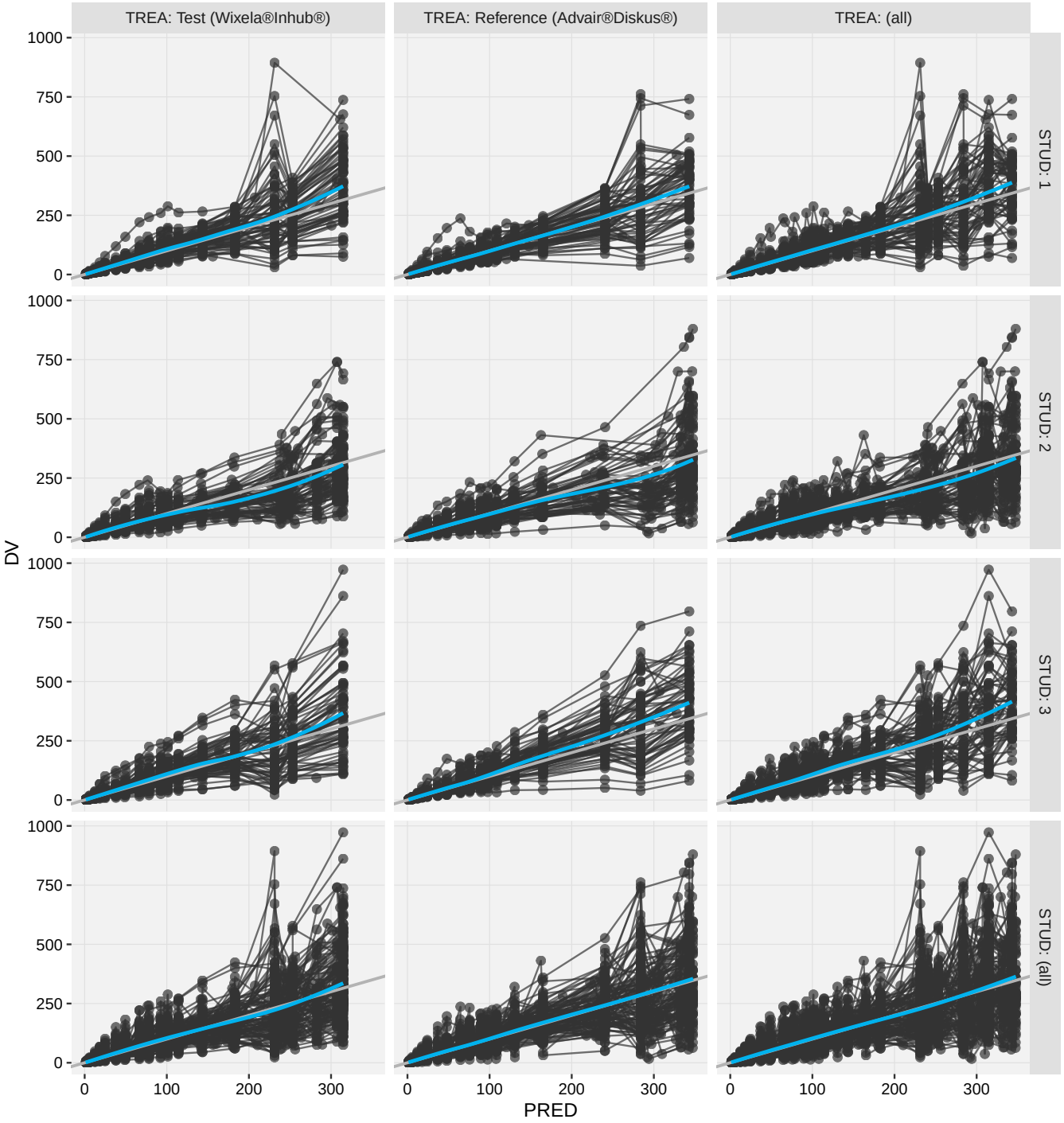

Figure 14: SALM, basic goodness of fit, dependent vs typical, predicted concentration of FP

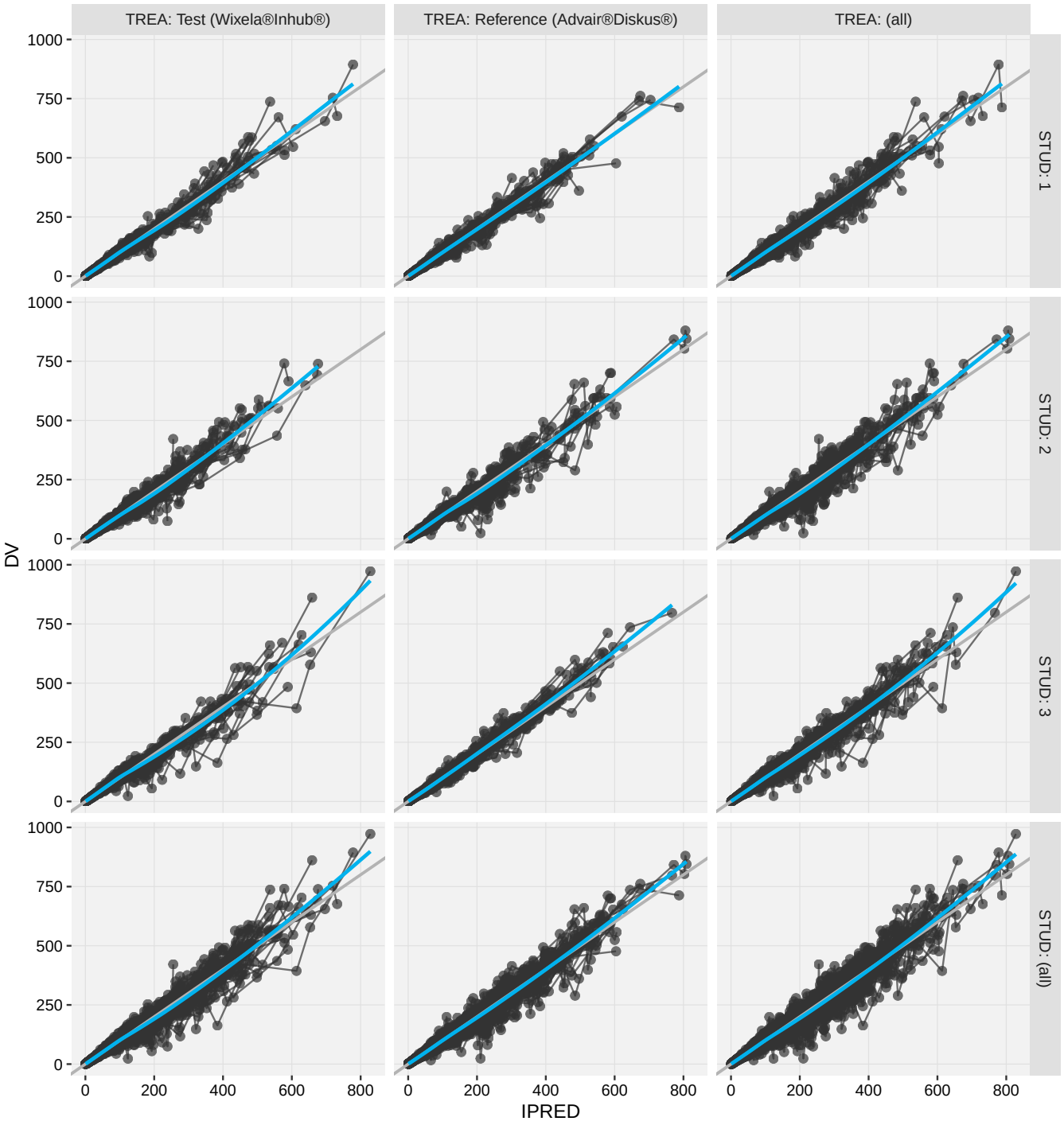

Figure 15: SALM, basic goodness of fit, dependent vs individual, predicted concentration of FP

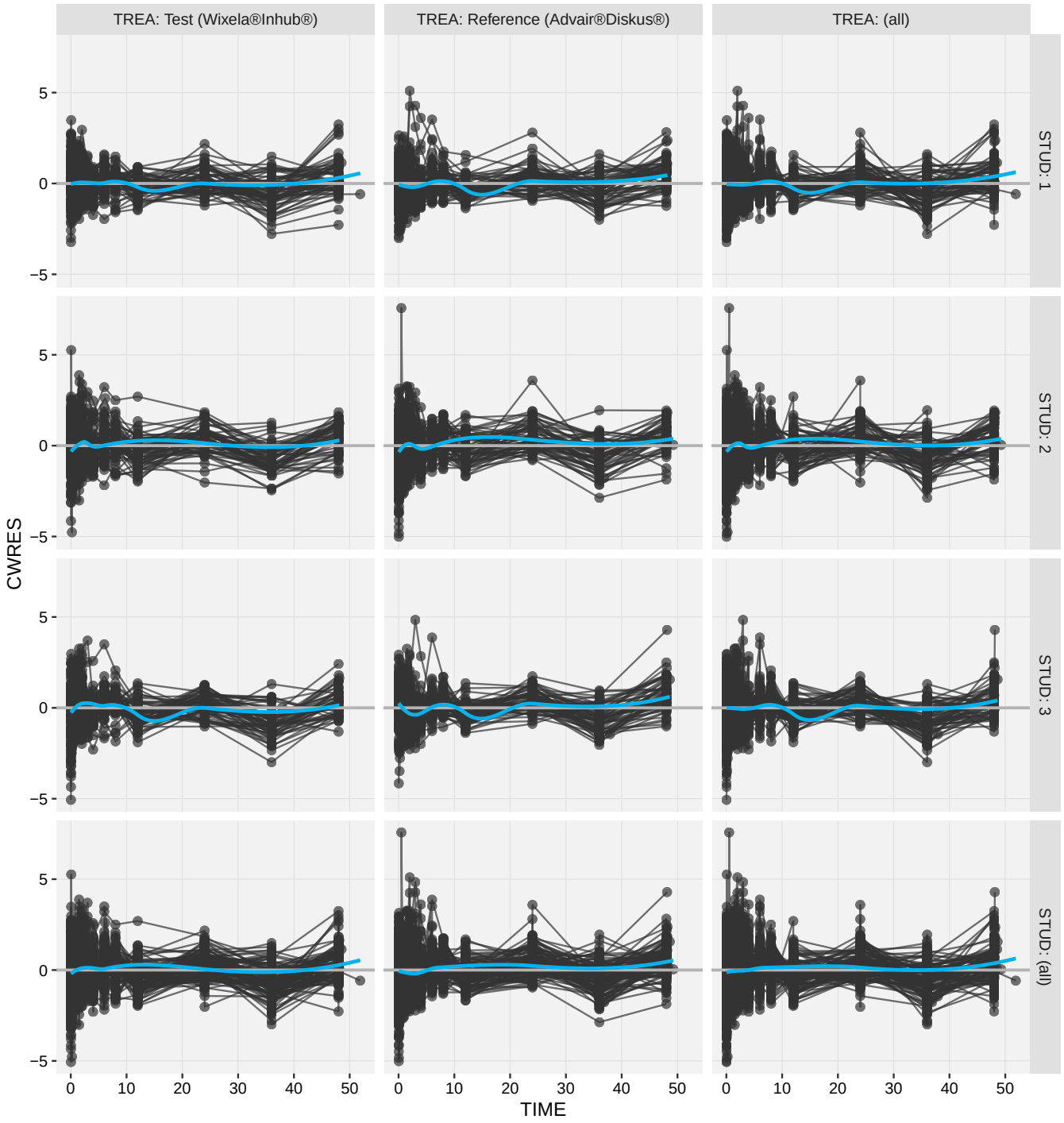

Figure 16: SALM, basic goodness of fit, conditional weighted residual vs independent variable (time)

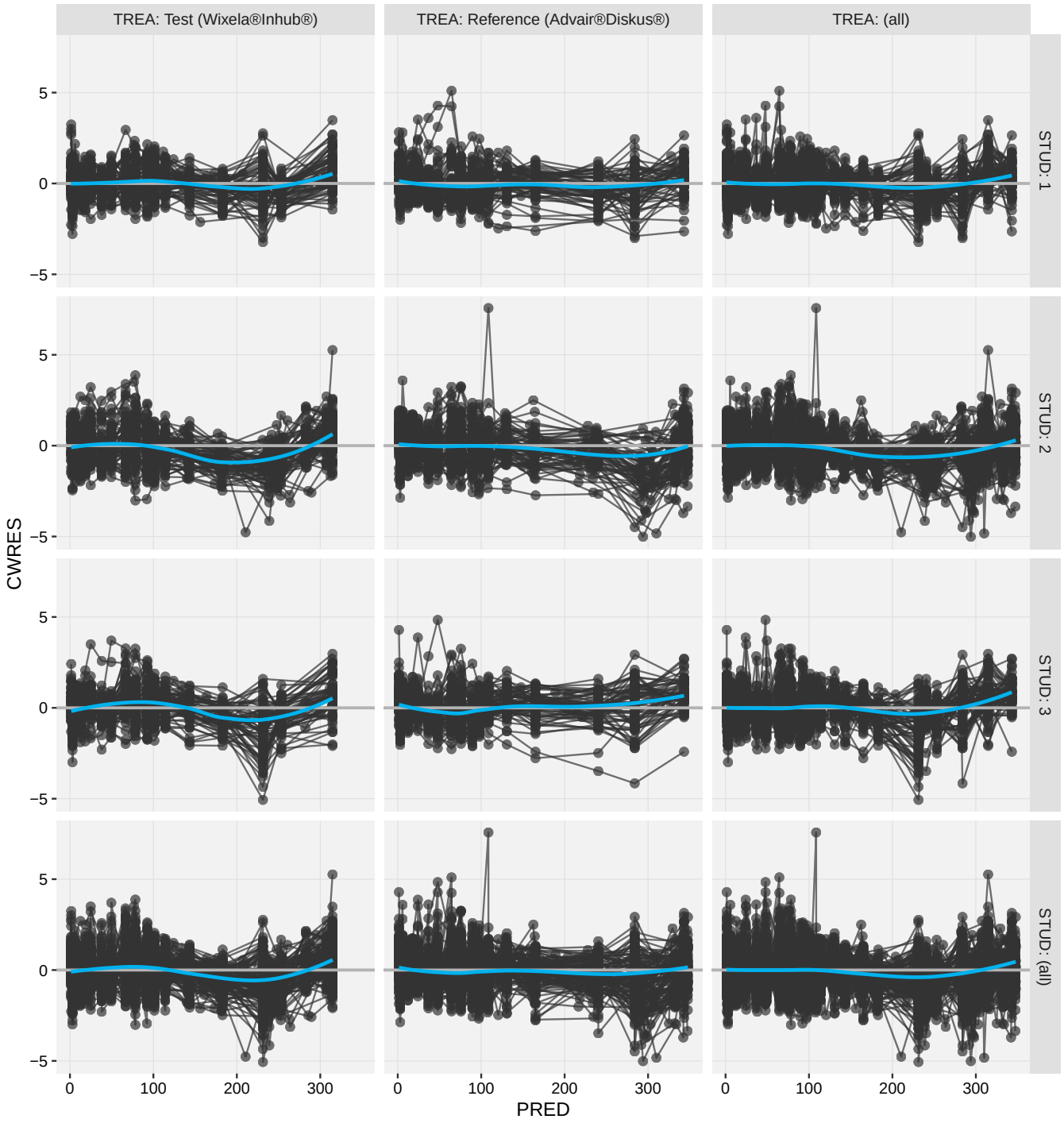

Figure 17: SALM, basic goodness of fit, conditional weighted residual vs typical, predicted concentration of FP

7 Model validation - critical deviations from a rule of thumb

There is general scientific consensus that even a small difference in the Akaike's information criterion (AIC) between alternative statistical models should be regarded significant. At the same time, it is important not to focus solely on the AIC value (or OFV if you like in the NONMEM context) but also consider complexity and generalizability of the model. Here we would like to present rationales for why we considered it relevant to deviate from the general principle at two turning points of the analysis of FP, the description of pulmonary absorption and the appropriate choice of parametrization to explore relative extent of bioavailability as basis for the comparison with NCA.

7.1 Preliminary modeling attempt: monophasic vs biphasic absorption of FP

An early attempt across studies was performed with FP to contrast fitting a full model implying biphasic compared with a reduced model implying monophasic absorption and provisionally with F4_rel fixed to 1, the outcomes of which are detailed in Table 1. Using the drop in Akaike's information criterion, AIC (OFV + 2 x number of parameters)[3], indicated that absorption of inhaled FP could be better described using a biphasic rather than a monophasic approach; AICfull model - AICreduced model = -75.614 (due to the drop in OFV, considerably lower than the 2 x increase in the number of parameters). However, biphasic parametrization of absorption was rejected and so was analysis of FP across studies/doses, in summary because of i) the estimated absorption rate constants differed marginally with the full model suggesting overparametrization, ii) F4_rel - a central parameter to be estimated with our final modeling approach - was fixed to 1, iii) the simultaneous fit across studies revealed with the present data set indistinguishable pre- and post absorption nonlinear pharmacokinetic elements of FP (cf. Figure 18 and Table 1), and iv) technically suboptimal minimization routines; in contrast to the early attempts, final analyses considered the benefit of model fitting to exponentiated rather than log-transformed data, and the use of a combined proportional and additive rather than a sole proportional residual error model - two necessary measures for adequate post-hoc assessment of terminal half life.

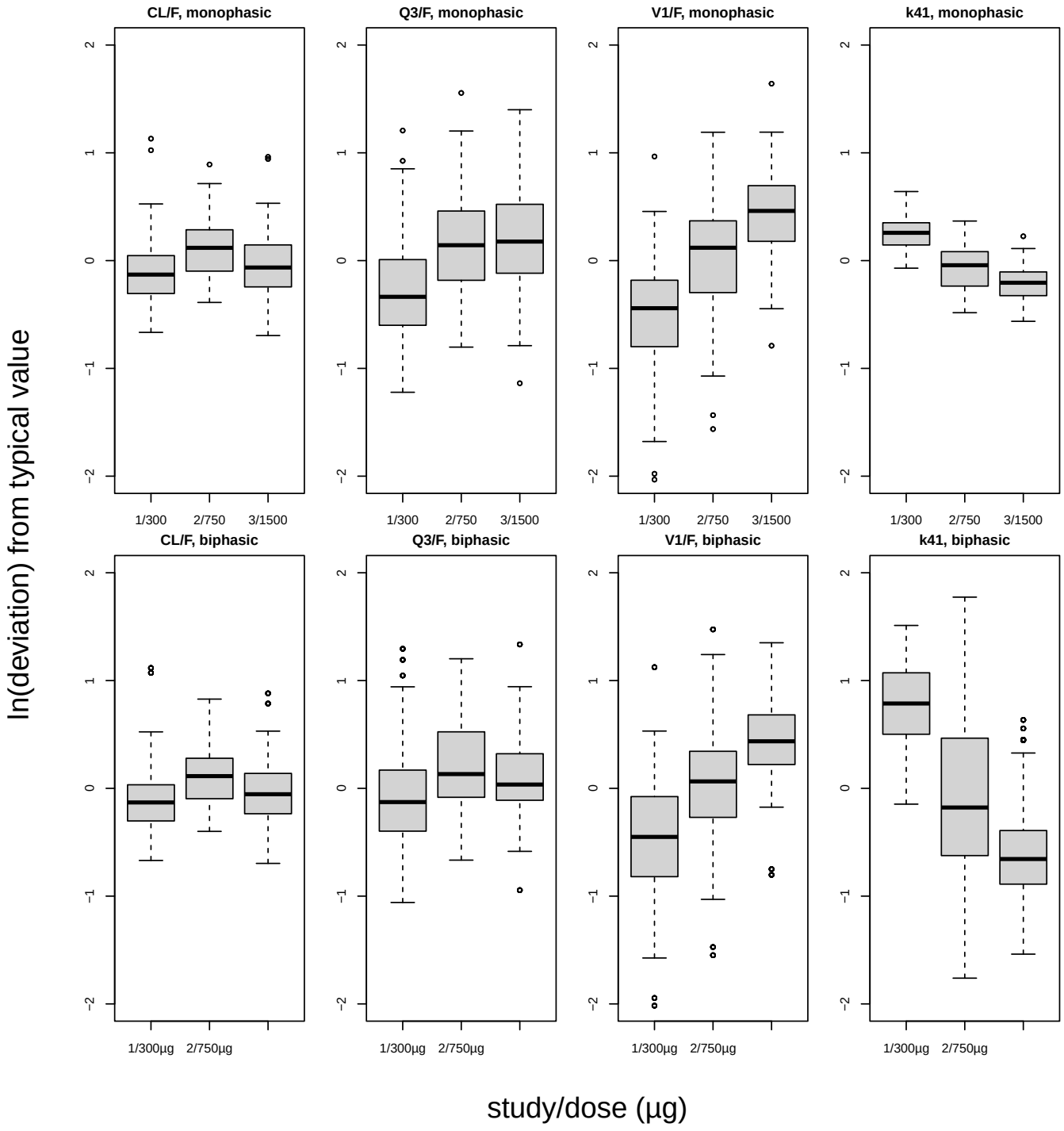

Figure 18: Preliminary analysis of considered between subject variability, deviation from the typical value from typical values across studies/dose of FP applying models fitted to log transformed data using, sole proportional error model.

Table 1: Typical empirical population pharmacokinetic parameter estimates (relative standard error) obtained with preliminary model attempts, simultaneously applied to all data of FP across studies: monophasic (Model 7) and biphasic (Model 8) absorption, accounting for values below the lower limit of quantification.

Item_Model	Unit	Model 7 (RSE)	Model 8 (RSE)
Minimization	-	SAEM_I-IMP*_I	SAEM_I-IMP*_I
ofv	-	-13240.92	-13322.53
CL/F	L/h	492.7 (0.02613)	502.5 (0.02562)
Q2/F	L/h	285.4 (0.03913)	197.2 (0.05071)
Q3/F	L/h	125.7 (0.04778)	95.62 (0.07783)
V1/F	L	325.5 (0.06113)	296.3 (0.05979)
V2/F	L	2137 (0.02301)	1849 (0.04673)
V3/F	L	6937 (0.07156)	5564 (0.08169)
k41	1/h	0.2711 (0.02948)	0.2066 (0.07289)
k51	1/h	NA	0.1849 (0.009137)
F4	-	NA	0.2379 (0.03071)
CP_PROP	-	0.1854 (0.009279)	0.3844 (0.04322)
CL/F_OMEGA	-	0.3408 (0.4559)	0.3333 (0.0911)
Q3/F_OMEGA	-	0.5984 (0.6573)	0.5618 (0.07893)
V1/F_OMEGA	-	0.7246 (0.07911)	0.7121 (0.08272)
k41_OMEGA	-	0.2756 (0.1547)	0.865 (0.08839)
CL/F_IOV	-	0.1317 (0.06646)	0.1367 (0.07718)
V1/F_IOV	-	0.4291 (0.06418)	0.4255 (0.05738)

7.2 Final modeling: alternative approaches to address relative bioavailability of FP

Alternative model strategies were explored to assess relative rate and extent of systemic relative bioavailability of FP. Treatment was used as categorical covariate of the relative rate (Cmax[test]/Cmax[ref]), and the relative extent was either addressed by i) introducing F4_rel as a population model parameter or ii) by applying treatment-differentiated apparent elimination clearance (CL/F) with F4_rel = 1/(CL/F[test]/CL/F[ref]). The latter treatment-differentiation was also applied for apparent central volume of distribution (V1/F) in order to further increase the degree of freedom for apparent rate of elimination - k10 = CL/F/V1/F. Final population parameter estimates, post-hoc estimates of T½ and Cmax, and bioequivalence tests with alternative i) are presented in the body of the manuscript. Corresponding outcomes of model alternative ii) reflected alternative i) well as far as FP 3x100 µg and FP 3x250 µg were concerned (Tables 2-4) and thus can be regarded a sensitivity test of the basic jointly applied pharmacokinetic model, namely alternative i). The difference in the Akaike's information criteria (cf. above) - -77.18 and -390.1 in favor of the model using treatment-differentiated assessment of apparent elimination clearance may indeed indicate that approach could be a relevant alternative to using relative bioavailability as parameter in a population pharmacokinetic analysis of bioequivalence.

Indeed, good agreement between between the two approaches to handle relative extent of bioavailability was interpreted as a good indication of a robust pharmacokinetic basic model (linear first order absorption and disposition). However, considering our particular objective, to compare a model-based approach with conventional NCA, we mean that the model approach should parametrically have a relative extent of bioavailability as parameter and outcome variable in the bioequivalnce test rather than treatment-forced differentiation of apparent elimination clearance. Moreover, the minimization process in NONMENM with alternativ ii) did not converge with data after 3 x 500 µg of FP, which finally concluded the decision to use relative bioavailability as model parameter.

Table 2: Typical empirical population pharmacokinetic parameter estimates (relative standard error) obtained with alternative model addressing relative bioavailability of FP between test and reference, separately applied to studies of F 3 x 100 µg (Model 101) and F 3 x 250 µg (Model 102), accounting for values below the lower limit of quantification. The model did not converge with F 3 x 500 µg.

Item_Model	Unit	Model 101 (RSE)	Model 102 (RSE)
Minimization	-	SAEM_I-IMP*_I	SAEM_I-IMP*_I
ofv	-	10886.10	15316.89
CL/F_test	L/h	481.5 (0.04556)	580 (0.03744)
Q2/F	L/h	410.9 (0.09922)	1311 (0.1053)
Q3/F	L/h	199.5 (0.06062)	353.4 (0.04249)
V1/F_test	L	243.5 (0.1045)	285 (0.1052)
V2/F	L	1085 (0.1028)	16.48 (0.5061)
V3/F	L	2441 (0.03987)	4613 (0.05264)
k41_test	1/h	0.4405 (0.04984)	0.2373 (0.06466)
CP_PROP	-	0.1425 (0.01834)	0.1955 (0.02274)
CP_ADD	-	0.2852 (0.1277)	0.3211 (0.2985)
CL/F_ref	L/h	513.8 (0.03446)	606.5 (0.06447)
V1/F_ref	L	231.9 (0.02465)	284 (0.03148)
k41_ref	1/h	0.4913 (0.02693)	0.2513 (0.05243)
CL/F_OMEGA_test	-	0.3641 (0.03172)	0.2955 (0.1177)
V1/F_OMEGA_test	-	0.7442 (0.06806)	0.7589 (0.7927)
V2/F_OMEGA	-	0.5105 (0.07515)	2.063 (0.2279)
V3/F_OMEGA	-	0.2164 (0.182)	0.3113 (0.4547)
k41_OMEGA	-	0.1734 (0.1041)	0.242 (0.2102)
CL/F_OMEGA_ref	-	0.3411 (0.04353)	0.3162 (0.05333)
V1/F_OMEGA_ref	-	0.7233 (0.04136)	0.7795 (0.1407)

Table 3: Descriptive statistics of post-hoc individual estimates of T½ and - within the framework of sampling occasions - individually predicted Cmax with alternative parametrization.

Substance	STUD	DOSE	TREA	Parameter	Unit	n	mean	sd
FP	1	3 x 100	Test	T½	h	65	14.35	2.529
FP	1	3 x 100	Reference	T½	h	65	12.84	2.171
FP	2	3 x 250	Test	T½	h	65	15.38	3.307
FP	2	3 x 250	Reference	T½	h	64	14.43	3.268
FP	1	3 x 100	Test	Cmax	ng/L	65	101.5	30.05
FP	1	3 x 100	Reference	Cmax	ng/L	66	109.5	27.67
FP	2	3 x 250	Test	Cmax	ng/L	65	153.2	44.69
FP	2	3 x 250	Reference	Cmax	ng/L	64	154.8	47.80

Table 4: Bioequivalence of test vs reference based on individual post-hoc inverted apparent clerance and overted Cmax ratios with alternative parametrization.

Substance	Study	Dose_µg	Parameter	estimate	lower.ci	upper.ci	conf.level
FP	1	3x100	CL_F_ratio	1.043	1.009	1.079	0.9
FP	2	3x250	CL_F_ratio	1.072	1.023	1.122	0.9
FP	1	3x100	Cmax_ratio	0.915	0.894	0.937	0.9
FP	2	3x250	Cmax_ratio	0.999	0.962	1.039	0.9

8 References

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