Supplementary Material

Population Pharmacokinetics of Brepocitinib in Healthy Adult Volunteers, Patients with Moderate to Severe Plaque Psoriasis, and Patients with Moderate to Severe Alopecia Areata

Running Title: Population Pharmacokinetics of Brepocitinib

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1. Summary of Clinical Studies included in PK Analysis

ClinicalTrials.gov Identifier	Population	Dosing Regimen	Plasma Sampling	Number of Subjects
NCT02310750	HV	1, 3, 10, 30, 100, and 200 mg SD brepocitinib suspension	Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 hours post-dose	41
	HV	10, 30, 100, or 175 mg QD, or 50 mg BID of brepocitinib suspension	Pre-dose on Days 1, 2, 4, 6 and 8. Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, 16 hours post-dose on Day 10	
	HV	100 mg SD of brepocitinib suspension or tablet administered with or without food	Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 hours post-dose	12
	PsO	30, 100 mg QD of brepocitinib suspension or placebo	Pre-dose on Days 1, 7, 14 and 21. Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, 16 hours post-dose on Day 28. Morning samples on Day 29 and 35	21
NCT03236493	HV	100 mg QD brepocitinib tablet	Pre-dose on Days 2, 4, 6, 8, 11, 12 and 13. Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, 16 hours post-dose on Days 1 and 10	6
NCT03656952	HV	200 mg SD brepocitinib tablet	Pre-dose and 0.5, 1, 2, 3, 4, 8, 12, 24, 30, 36, 48 hours post-dose	33
NCT02969018	PsO	30 and 60 mg QD in 4-week induction and 10, 30 mg QD or 100 mg QW in maintenance	Pre-dose on Days 1 and 8. Pre-dose and 0.5 hours post-dose on Days 15, 43, 57 and 71. Pre-dose and 0.5, 1, 2, 4 hours post-dose on Days 29 and 85	189
NCT02974868	AA	60 mg QD in 4-week induction and 30 mg QD in 20-week maintenance or placebo	Pre-dose on Days 1, 15, 43 and 113. Pre-dose and 0.5 hours post-dose on Days 57 and 141. Pre-dose and 0.5, 1 hours post-dose on Day 85. Pre-dose and 0.5, 1, 2, 4 hours post-dose on Days 29 and 169	77

Abbreviations: QD – once daily; SD – single dose; BID – twice daily; HV – healthy volunteers; PsO – plaque psoriasis; AA – alopecia areata

2. Summary of Clinical Study Principal Investigators and Study Sites

ClinicalTrials.gov Identifier	Principal Investigator	Study Site
NCT02310750	Peter J. Winkle	Anaheim Clinical Trails, LLC 1085 N. Harbor Blvd., Anaheim, CA, USA
NCT03236493	Constantino Kantaridis	Pfizer Clinical Research Unit Route de Lennik 808, Brussels, Belgium
NCT03656952	Constantino Kantaridis	Pfizer Clinical Research Unit Route de Lennik 808, Brussels, Belgium
NCT02969018	David M. Pariser	Virginia Clinical Research, Inc. 6160 Kempsville Circle, Norfolk, VA, USA
	Panos Vasiloudes & Matthew Zook	Olympian Clinical Research 2919 Swann Ave., Tampa, FL, USA
	George J Schmieder	Park Avenue Dermatology 906 Park Avenue, Orange Park, FL, USA
	Seth Forman	Forward Clinical Trials, Inc. 4915 Ehrlich Road, Tampa, FL, USA
	Iftikhar Hussain	Vital Prospects Clinical Research Institute, P.C 7307 S. Yale Ave., Tulsa, OK, USA
	Emily M. Becker & John C. Browning	Texas Dermatology and Laser Specialists 3320 Oakwell Ct., San Antonio, TX, USA
	Jerry Bagel	Psoriasis Treatment Center of Central New Jersey 59 One Mile Rd., East Windsor, NJ, USA
	Stacy R. Smith	California Dermatology & Clinical Research Institute 561 Saxony Place, Encinitas, CA, USA
	Richard L. Beasley	Health Concepts 5410 Sheridan Lake Road, Rapid City, SD, USA
	Paul S. Yamauchi	Clinical Science Institute 2001 Santa Monica Blvd., Santa Monica, CA, USA
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ClinicalTrials.gov Identifier	Principal Investigator	Study Site
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	Kim A. Papp	K. Papp Clinical Research Inc. 135 Union Street East, Waterloo, Ontario, Canada
	Anna Olak-Popko	MTZ Clinical Research sp. z o.o. ul. Pawińskiego 5, Warszawa, Poland

ClinicalTrials.gov Identifier	Principal Investigator	Study Site
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	Małgorzata Płocka	NZOZ Nasz Lekarz – Praktyka Grupowa Lekarzy Rodzinnych z Przychodnią Specjalistyczną ul. Szczytna 20, Toruń, Poland
	Wojciech Baran	WroMedica s.c. ul. Mickiewicza 91, Wroclaw, Poland
	Aleksandra Lesiak	Dermoklinika Centrum Medyczne s.c. ul. Kościuszki 93, Lódź, Poland
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NCT02974868	Brett King	Yale School of Medicine 333 Cedar Street, New Haven, CT, USA
	Panos Vasiloudes & Matthew Zook	Olympian Clinical Research 2919 Swann Ave., Tampa, FL, USA
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	Seth Forman	Forward Clinical Trials, Inc. 4915 Ehrlich Road, Tampa, FL, USA
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ClinicalTrials.gov Identifier	Principal Investigator	Study Site
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	David Rosmarin	Tufts Medical Center 800 Washington St., Boston, MA, USA
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	Lynda J. Spelman	Veracity Clinical Research 250 Ipswich Road, Woolloongabba, Queensland, Australia
	Michael G. Freeman	The Skin Centre 29 Carrara St., Benowa, Queensland, Australia
	Gerald G. Krueger	University of Utah MidValley Dermatology 243 East 6100 South, Murray, UT, USA

ClinicalTrials.gov Identifier	Principal Investigator	Study Site
NCT02974868	Samantha Eisman & Rodney D. Sinclair	Sinclair Dermatology 2 Wellington Parade, East Melbourne, Victoria, Australia
	Stephen P. Shumack	St George Dermatology and Skin Cancer Centre 3/22 Belgrave St., Kogarah, New South Wales, Australia
	Jason Hawkes	Rockefeller University Hospital 1230 York Avenue, New York, NY, USA
	Mary G. Mercurio	University of Rochester Medical Center 601 Elmwood Ave., Rochester, NY, USA
	Afsaneh Alavi	York Dermatology Center 250 Harding Blvd. West, Richmond Hill, Ontario, Canada

3. Base Model Development Key Steps

Run No.	Description	Cond. Number[#]	OFV	AIC	DF	ΔAIC[^]
1	2-compartment model, first-order absorption, random effects on CL/F, Vc/F, and ka, diagonal variance-covariance matrix, exponential error model LTBS, fixed allometric scaling	5.71	3682	3700	-	-
2	Reduce to 1-compartment model due to poor precision of Vp/F (91.3% RSE)	4.51	4335	4349	-2	+649
4	Add absorption lag A_{lag}	4.46	4123	4139	1	-210
6	Remove random effect on k_a due to plausibility of estimating individual k_a values of greater than 3.5 with 105% CV given observed sampling schedule.	5.64	4316	4330	-1	+191
8	Estimate RUV model for each protocol	5.22	3935	3957	4	-373
10	Consolidate RUV model according to Phase 1 and Phase 2 studies	5.06	3943	3959	-3	+2.44
12	Add effect of formulation on A_{lag}	5.16	3878	3894	0	-65.7
18	Fix covariate effect for formulation on A_{lag} to -1, such that there is no absorption lag for this formulation.	5.17	3877	3891	-1	-2.24
22	Add effect of fasting and high-fat meal on k_a	5.57	3806	3824	2	-67.3
24	Remove effect of fasting on k_a	5.13	3811	3827	-1	+3.39
28[*]	Change to full block variance-covariance matrix	15.8	3615	3633	1	-194
29	Assess 2-compartment model again now that structural model is better defined. (VpF: 108% RSE)	9.40	2707	2731	2	-904
28	Change to full block variance-covariance matrix	15.8	3615	3633	-	-
41	Full model estimation – single forward inclusion step	19.6	3515	3563	14	-70
42	Final parsimonious model – single backwards elimination step	16.4	3567	3593	-11	+30

Condition number = square root of the ratio of largest to smallest eigenvalues of correlation matrix. ^AIC and DF are determined based on the current run referenced to the previous run.
*Base model used for full model estimation

4. Final Model Diagnostic Plots

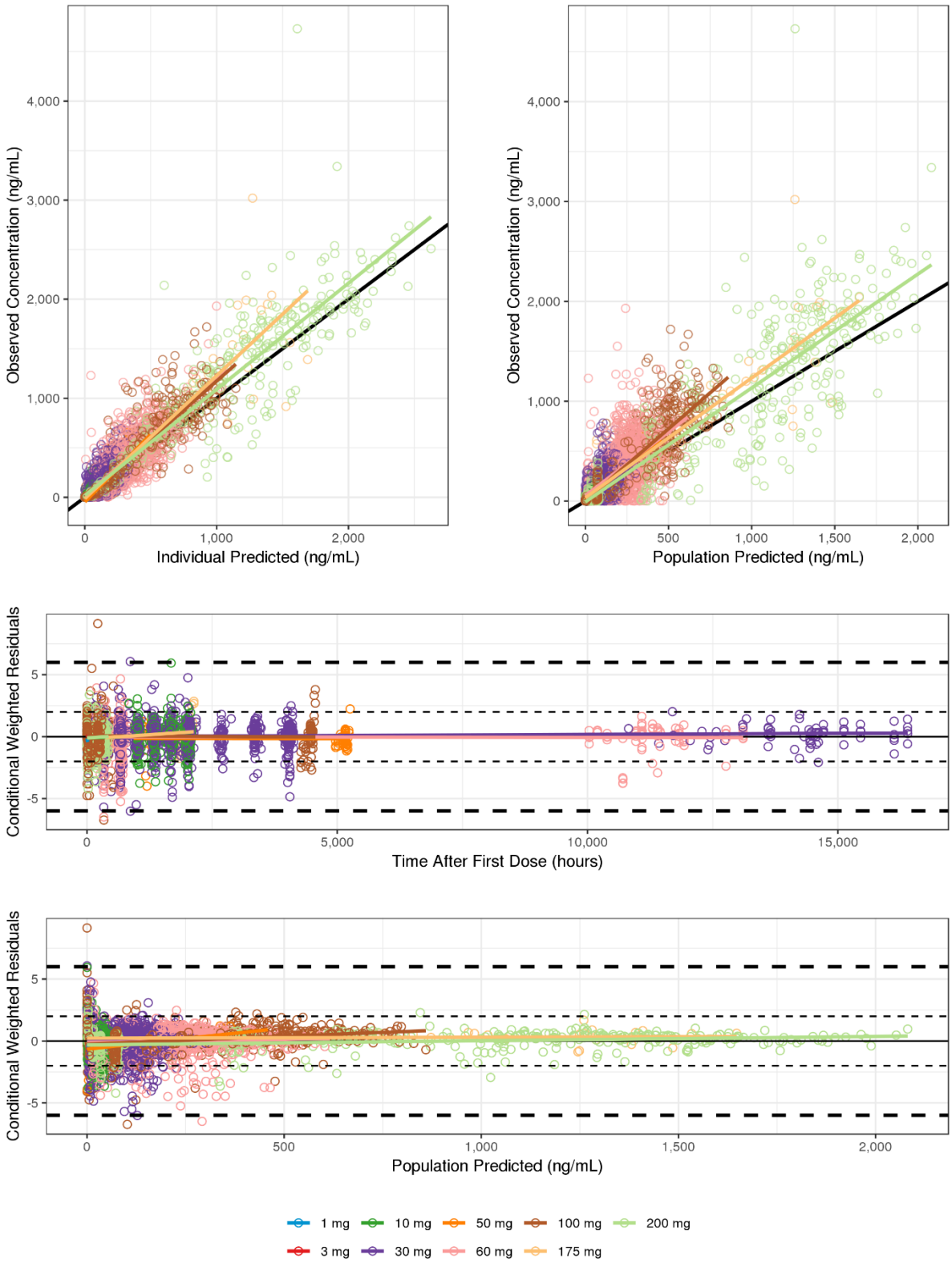


Figure S1: *Top left:* Observed versus individual predicted concentrations. *Top right:* Observed versus population predicted concentrations. *Middle:* Conditional weighted residuals versus time after first dose. *Bottom:* Conditional weighted residuals versus population predicted concentrations. The black line is the line of identity, colored lines are linear regressions stratified by dose. Black dashed horizontal lines represent conditional weighted residuals that are ± 2 (fine) and ± 6 (bold) standard deviations from the mean.

5. NONMEM Model File

```
; B793 TYK2/JAK1 Population PK model
; -------------------------------------------------------------
; PK concentrations (ng/mL)
; AMT in mg
; Time = Time after first dose (TAFD)
; id = STID
$PROBLEM run1.mod
; 1-compartment model
; First-order absorption
; Absorption lag for tablet formulation
; Random effects on CL and VD
; Full block variance-covariance matrix
; Log-transformed Both Sides
; Exponential error model for each Phase
; Fixed allometric scaling
; Food effect on absorption constant + relative bioavailability
; Dose (>= 175 mg) effect on relative bioavailability
; Race (asian) effect on clearance

$INPUT
C, ; Comment flag
PROT, ; Study protocol (1001 – Phase I study, 1004 – Phase II study)
STID=ID, ; Unique subject identifier
AMT, ; Dose record
DOSE, ; Administered dose (mg)
FORM, ; Formulation (1 – suspension; 2 – tablet)
FOOD, ; Fed status (0 – fasting/no regard to food; 1 – high-fat meal)
TAFD=TIME, ; Formulation Effect - ALAG1
RACE, ; Race (1 – non-Asian race; 3 – Asian race)
BWT, ; Baseline body weight (kg)
MDV, ; Missing dependent variable flag
EVID, ; Event ID flag
CMT, ; Compartment number
DV  ; Dependent variable – Brepocitinib concentrations (ng/mL)
$DATA B793Combined_POPPK_FOABS_05FEB2020.csv IGNORE = C

$SUBROUTINE ADVAN2 TRANS2

$PK
; Structural Covariates
; Fixed Allometric Scaling - CL, VD
  ALLMCL = (BWT/70)**THETA(7)
  ALLMVD = (BWT/70)**THETA(8)
```

```
; Formulation Effect - ALAG1
; Tablet (FORM.EQ.2) as the reference population
  FORMLAG = 1
  IF(FORM.NE.2) FORMLAG = 1 + THETA(9)

; Food Effect - KA
; Dose not given with high-fat meal as the reference population
; 1 - Fed High-fat Meal
  FOODKA = 1
  IF(FOOD.EQ.1) FOODKA = 1 + THETA(10)

; Final Model Covariates
; Dose Effect - FREL
; Patients on less than 175 mg as reference population
  DOSEFREL = 1
  IF (DOSE.GE.175) DOSEFREL = 1 + THETA(11)

; Race Effect - CL
; Races other than Asian as reference population
; 3 – Asian
  RACECL = 1
  IF (RACE.EQ.3) RACECL = 1 + THETA(12)

; Food Effect - FREL
; Dose not given with high-fat meal as the reference population
; 1 - Fed High-fat Meal
  FOODFREL = 1
  IF (FOOD.EQ.1) FOODFREL = 1 + THETA(13)

; Population PK Parameters
  POPFREL = 1*FOODFREL*DOSEFREL
  POPKA = THETA(1)*FOODKA
  POPCL = THETA(2)*ALLMCL*RACECL
  POPV2 = THETA(3)*ALLMVD
  POPLAG = THETA(4)*FORMLAG

; Individual PK Parameters
  F1 = POPFREL
  KA = POPKA
  CL = POPCL*EXP(ETA(1))
  V = POPV2*EXP(ETA(2))
  ALAG1 = POPLAG

; Residual Unexplained Variability
; Phase 1 - 1001, 1009, 1019; Phase 2 - 1004, 1005
```

```
  POPRUVEXP = THETA(5)
  IF (PROT.EQ.1004.OR.PROT.EQ.1005) POPRUVEXP = THETA(6)

; Micro-rate Constants
  K = CL/V

; Scaling - AMT in mg, Concentrations in ng/mL
  S2 = V/1000

$ERROR
; Individual Prediction (LTBS)
  IPRED = LOG(0.2)
  IF(F.GT.0) IPRED = LOG(F)

; Standard Deviation
  RUVEXP = POPRUVEXP
  W = SQRT(RUVEXP*RUVEXP)

; Objective Function
  Y = IPRED+W*EPS(1)

$THETA
  (0.001,2) ; TVKA
  (0.001,20) ; TVCL
  (0.001,100) ; TVV2
  (0.001,0.35) ; TVALAG1
  (0.001,0.75) ; TVPHASE1RUVEXP
  (0.001,0.75) ; TVPHASE2RUVEXP
  0.75 FIX ; TVALLMCL
  1.00 FIX ; TVALLMVD
  -1 FIX ; TVFORMLAG
  (-0.999,0.001) ; TVFOODKA
  (-0.999,-0.001) ; TVDOSE175FREL
  (-0.999,-0.001) ; TVRACE3CL
  (-0.999,-0.001) ; TVFOODFEDF1

$OMEGA BLOCK (2)
  0.3 ; PPVCL
  0.1 0.3 ; PPVV2

$SIGMA
  1 FIX ; ERRRES

$ESTIMATION PRINT=5 MAXEVAL=9999 METHOD=1 INTER FILE=run1.ext

$COVARIANCE PRINT=E UNCONDITIONAL
```

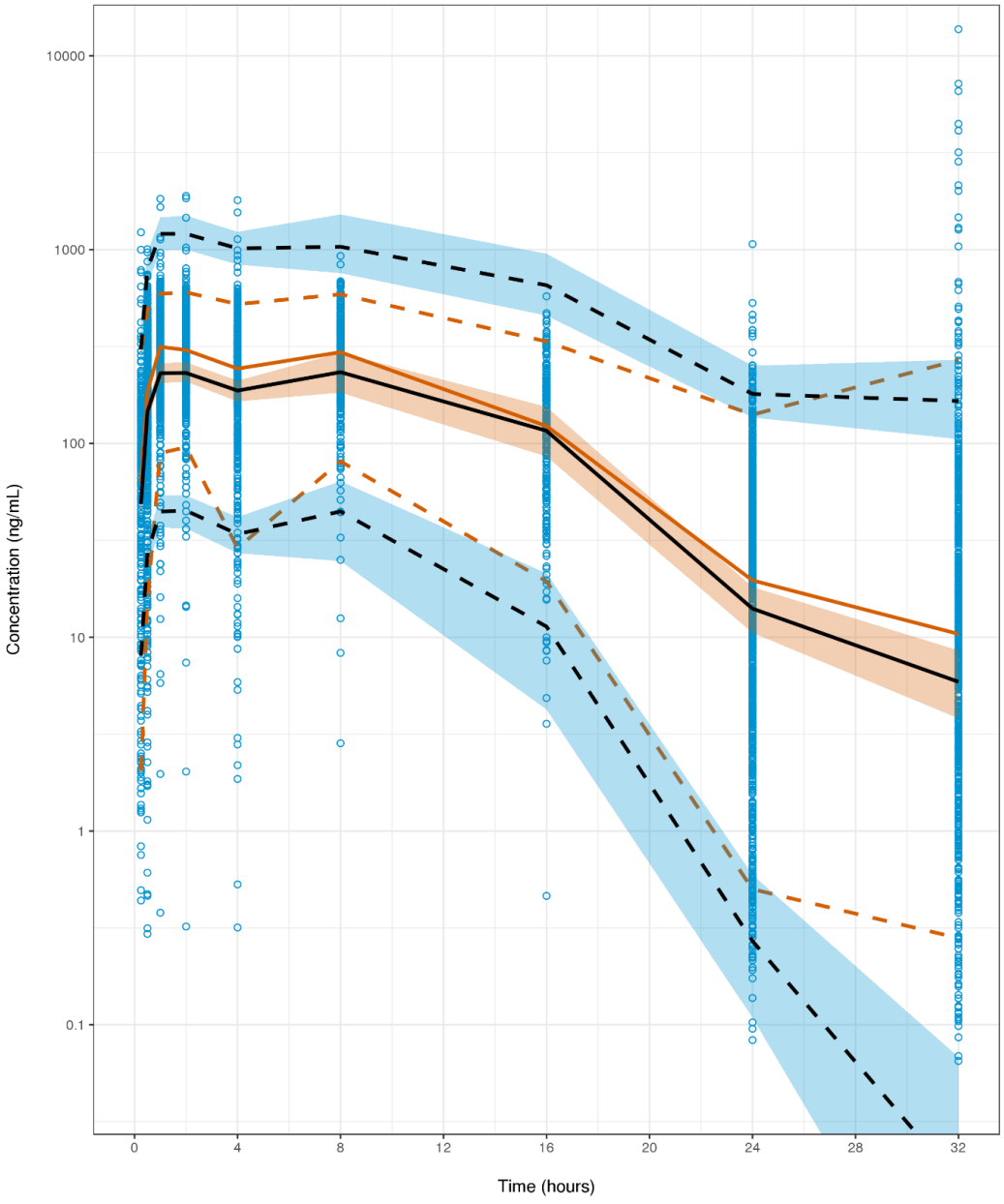
```
$TABLE PROT ID TIME AMT CMT MDV EVID KA CL V K
  ETAS(1:LAST) IPRED PRED CWRES
  DOSE FORM FOOD RACE PTST BWT
  NOPRINT ONEHEADER FILE = run1.fit
; ------------------------------------------------------------
```

6. M3 Sensitivity Analysis Results

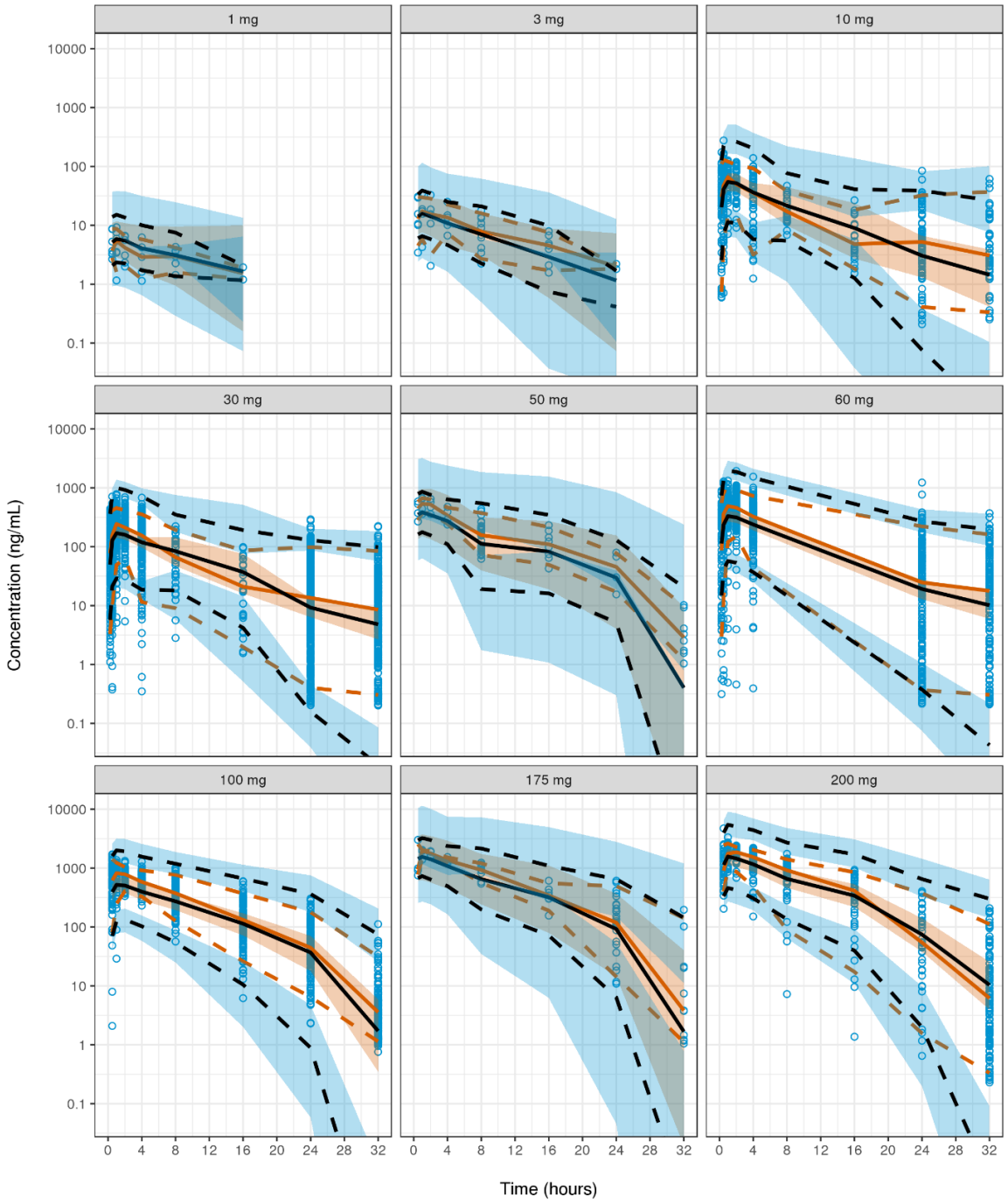
Parameter	Final Model Bootstrap Median (95% CI)	M3 Model Bootstrap Median (95% CI)
Population Parameter		
First-order absorption rate constant (k_a; hr^{-1})	3.51 (3.13 – 4.10)	3.34 (2.82 – 3.87)
Apparent clearance (CL/F; L/hr)	18.7 (17.1 – 20.6)	19.6 (17.7 – 21.7)
Apparent volume of distribution (Vc/F; L)	136 (125 – 148)	135 (123 – 148)
Absorption lag (A_{lag}; hr)	0.240 (0.228 – 0.273)	0.240 (0.203 – 0.264)
Effect of weight on CL/F (70 kg reference)	0.750 (Fixed)	0.750 (Fixed)
Effect of weight on Vc/F (70 kg reference)	1.00 (Fixed)	1.00 (Fixed)
Effect of suspension formulation on A_{lag}	-1.00 (Fixed)	-1.00 (Fixed)
Effect of high-fat meal on k_a	-0.701 (-0.831 – -0.329)	-0.690 (-0.823 – -0.289)
Effect of dose on F_{rel} (dose ≥ 175 mg)	0.348 (0.186 – 0.508)	0.336 (0.180 – 0.509)
Effect of Asian subjects on CL/F	-0.235 (-0.346 – -0.113)	-0.236 (-0.364 – -0.097)
Effect of high-fat meal on F_{rel}	-0.279 (-0.391 – -0.169)	-0.280 (-0.390 – -0.169)
Inter-individual Variability		
$\omega_{CL/F}$ (% CV)	76.9 (68.1 – 89.4)	62.3 (50.4 – 78.1)
$\omega_{Vc/F}$ (% CV)	59.5 (45.3 – 79.0)	59.2 (46.2 – 77.9)
Correlation		
$\rho_{CL/F\text{-}Vc/F}$	0.759 (0.651 – 0.840)	0.781 (0.675 – 0.853)
Random Unexplained Variability		
Proportional RUV (Phase 1; CV)	0.517 (0.441 – 0.605)	0.555 (0.464 – 0.662)
Proportional RUV (Phase 2; CV)	0.873 (0.813 – 0.937)	0.909 (0.844 – 0.984)
ε_{res}	1.00 (Fixed)	1.00 (Fixed)

A_{lag}: absorption lag time; CL/F: apparent clearance; CI: confidence interval; CV: coefficient of variation; F: absolute bioavailability; F_{rel}: relative bioavailability; k_a: absorption rate constant;

7. Visual Predictive Checks



Prediction-corrected visual predictive check. The binned prediction-corrected observed brepocitinib concentrations are represented by blue circles and the black lines (solid line - median; dashed lines - 5th and 95th percentiles). The binned prediction-corrected simulated brepocitinib concentrations based on 1000 simulations of the index population is represented by the red solid line and red ribbon (median and 95% prediction interval (PI) of the median, respectively) and by the red dashed lines and blue ribbons (median and 95% PI of the 5th and 95th percentiles respectively).



Visual predictive check stratified by dose. The binned observed brepocitinib concentrations are represented by blue circles and the black lines (solid line - median; dashed lines - 5th and 95th percentiles). The binned simulated brepocitinib concentrations based on 1000 simulations of the index population is represented by the red solid line and red ribbon (median and 95% prediction interval (PI) of the median, respectively) and by the red dashed lines and blue ribbons (median and 95% PI of the 5th and 95th percentiles respectively).