SUPPLEMENTARY MATERIAL

Development of a Population Pharmacokinetic Model for the Diroximel Fumarate Metabolites Monomethyl Fumarate and 2-Hydroxyethyl Succinimide Following Oral Administration of Diroximel Fumarate in Healthy Participants and Patients with Multiple Sclerosis

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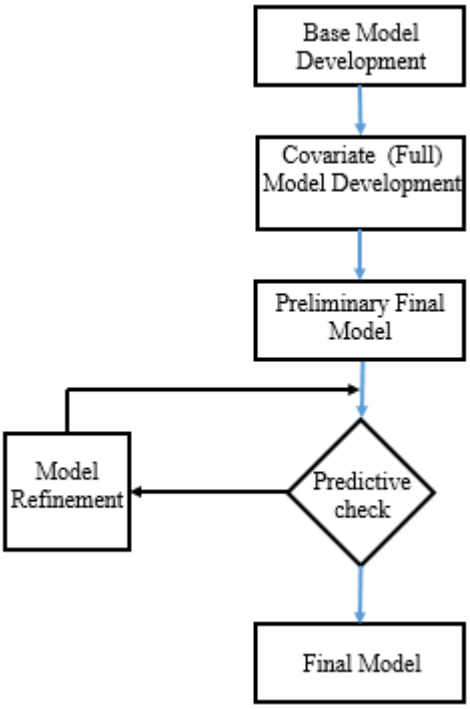
S1 SUPPLEMENTARY TEXT

METHODS

Modeling Strategy

The overall strategy for fitting and evaluating the population pharmacokinetics (PK) model for metabolite monomethyl fumarate (MMF) and 2-hydroxyethyl succinimide (HES) using pooled data from 11 clinical studies of diroximel fumarate (DRF) is shown in the flowchart. Because concentrations of MMF and HES were log-normally distributed, the dependent variable modeled was log(concentration) of MMF and HES.

Flowchart of Model Development



Data derived from five single-dose studies of DRF in healthy participants (Studies 001, A103, A105, A106, and A108) were used to develop the base model. Structural covariates were gradually introduced into the base model using data from studies with elements of greater complexity (i.e., multiple doses, high-fat meals, and patients with multiple sclerosis [MS]).

Selected covariates, based on observed parameter–covariate relationships, were added simultaneously to the base model to produce a full model. A backward elimination procedure with a significance level of $\alpha = 0.001$ (Δ objective function value [OFV] < 10.8 for 1 degree of freedom) was performed to identify a parsimonious preliminary final model. Standard goodness-

of-fit plots were used to assess model fit at each stage of development. The predictive performance of the final model was evaluated using an internal visual predictive check.

Nonlinear mixed effects modeling methodology was implemented in this analysis using the computer program NONMEM (version 7.3) [1]. The first-order conditional estimation with interaction method was utilized. Model development was based on: (1) successful minimization and completion of covariance steps in NONMEM; (2) assessment of standard goodness-of-fit plots; (3) reductions in NONMEM OFV for hierarchical models; and (4) reductions in interindividual variability (IIV) and residual variability.

Inspection of the covariance matrix of estimates at every stage of model development was performed to verify that extreme pairwise correlations ($\rho > 0.95$) of the parameters were not encountered. The condition number of the correlation matrix of the parameter estimates (i.e., the ratio of the largest to smallest eigenvalues) was also assessed to ensure values < 1000, which would indicate an ill-conditioned model.

Base Model Development

The disposition of MMF and HES was initially described as independent one-compartment models with a single transit absorption compartment and first-order elimination for each metabolite. Standard diagnostic plots, model stability, and changes in the OFV were considered when determining the most appropriate base model. Based on the goodness-of-fit diagnostics, additional model complexities (e.g., additional transit compartments) were explored. A sensitivity analysis was performed for both MMF and HES and eight transit absorption compartments achieved the lowest decrease in the OFV for both analytes. In addition, pertinent covariates (e.g., time of dosing [morning vs. evening] and food effects) were evaluated for inclusion into the base model.

A complete battery of diagnostic plots was generated to evaluate the adequacy of the base model fit. Plots of population-weighted residuals (WRES), individual-weighted residuals (IWRES), and conditional-weighted residuals (CWRES) versus time and model-predicted concentration were evaluated for random scatter around the zero line. The residual (WRES, IWRES, and CWRES) plots were also used to identify potential outliers as described in the Methods section of the main article. A total of 32 HES PK samples were deemed as outliers; however, they were still included in the base model to be further evaluated during final model development.

Random Effects Model Development

IIV and interoccasion variability (IOV) of the PK parameters were incorporated, when applicable, using a lognormal random effects model of the form:

$$\theta_{ij} = \theta_{TV} \cdot exp(\eta_i + \kappa_{ij})$$

where θ_{ij} is the individual value of the parameter (e.g., clearance [CL]) for the i^{th} individual at the j^{th} occasion, θ_{TV} is the typical value model parameter, η_i denotes the interindividual random effect accounting for the i^{th} individual's deviation from the typical value, and κ_{ij} denotes the intraindividual random effect accounting for the i^{th} individual's deviation at the j^{th} occasion.

The η_i's (κ_{ij}'s) are assumed to have a normal distribution with a zero mean and variance ω^2 (ψ^2). The approximate percent coefficient of variation (%CV) was reported as:

$$\%CV\ (IIV)\ = \sqrt{\omega^2} \cdot 100 \quad or \quad \%CV(IOV) = \sqrt{\psi^2} \cdot 100$$

IOV was evaluated on absorption rate constant (Ka). Unique occasions within a participant were assigned in sequential order for all dose intervals in which two or more PK samples were collected. IOV was estimated only for occasions with similar dietary fat conditions and when dosing was followed by serial PK sampling. The multivariate vector of interindividual random effects has a variance–covariance matrix Ω^{IIV}. A diagonal Ω was estimated.

Residual variability, a composite measure of assay error, dose/sample time collection errors, model misspecification, and any other unexplained variability within a participant, was modeled using the log-transformed error model:

$$\ln(Y_{ij}) = \ln(C_{ij}) + \varepsilon_{ij}$$

where Y_{ij} denotes the observed concentration for the i^{th} individual at time t_j, C_{ij} denotes the corresponding predicted concentration based on the PK model, and ε_{ij} denotes the residual random variable, which is assumed to have normal distribution with zero mean and variance σ^2.

Full Model Development

A full model was developed to explore the impact of covariates not included as structural covariates in the base model. Clinical judgment and mechanistic plausibility were used to determine which covariate–parameter relationships may be tested.

Covariates for Consideration in the Full Model

Parameter	Covariates
Ka, F	Patient population (healthy participant/patient), sex, dietary intake, dose, and dose time (morning or evening)
CL	Patient population (healthy participant/patient), sex, body weight, age, race, eGFR, total bilirubin, albumin, and AST
Vc	Patient population (healthy participant/patient), sex, body weight, age, race, total bilirubin, albumin, and AST

AST aspartate aminotransferase, *CL* clearance, *eGFR* estimated glomerular filtration rate, *F* relative bioavailability, *Ka* absorption rate constant, *Vc* central volume of distribution

Selected covariates, based on observed parameter–covariate relationships, were added simultaneously to the base model to produce a full model. The relationship between continuous

covariates and the typical value of PK parameters ($\theta_{TV,ij}$) for an individual *i* at time *j* was described using power models:

$$\theta_{TV,ij} = \theta_{REF}\left(\frac{x_{ij}}{x_{REF}}\right)^{\theta_x}$$

where θ_{REF} and θ_x are the fixed-effect parameters, x_{REF} is a reference value of covariate *x* in the population, and x_{ij} is the value of covariate *x* for individual *i* at time *j*. For time-invariant (stationary) covariates, the values of x_{ij} and $\theta_{TV,ij}$ were constant within individual *i* at all time points. For this analysis, the median value of the covariate was used for x_{REF}.

The relationship between categorical covariates and the typical value of PK parameters was modeled as:

$$\theta_{TV,ij} = \theta_{REF} \cdot (1 + \theta_x \cdot x_{ij})$$

where θ_{REF} and θ_x are fixed-effect parameters, and x_{ij} is the indicator variable defining the categorical assignment of individual *i* at time *j.* The lower bound for θ_x was constrained to a negative one, such that PK parameters will always be positive. For time-invariant continuous covariates, the value of $\theta_{TV,ij}$ was constant within individual *i* at all time points.

Final Model Development

A stepwise backward elimination procedure was used to identify a parsimonious PK model containing similar "information" content as the full model, but with fewer covariates than the full model. Statistical significance of covariate–parameter relationships was assessed with the likelihood ratio test, based on the property that the difference of the NONMEM OFV (Δ OFV) of two hierarchical models (–2 log-likelihood) is asymptotically χ^2 distributed. At each step of the backward elimination procedure, the covariate–parameter relationship that had the lowest change in OFV and did not meet the inclusion criteria (i.e., Δ OFV < 10.8 [α = 0.001, 1 degree of freedom]) was eliminated and the stepwise backward elimination procedure was repeated until all covariate-parameters met the inclusion criteria.

During the final model development, 33 PK samples, all associated with HES (0.34% of the total of HES samples) were deemed as outliers, with 88% in healthy volunteers and 12% in patients with MS. A total of 97% (32/33) of these PK samples were during the absorption phase of HES. Absorption phase was defined as elapsed time within 6 hours from the previous dose. Removal of the outliers had minimal impact on the PK parameter estimates for HES, thus the HES outlier PK samples were included in the final analysis.

Standard goodness-of-fit plots for the final model are shown in Fig. S3.

Final Model Evaluation

An internal visual predictive check [2] was performed on the final model. Parameter estimates were fixed to the estimates from the final model and used to generate 1000 datasets that

replicated the design, dose regimens, sample sizes, and covariate distributions from the observed dataset. The observed 5th, 50th, and 95th percentiles of MMF and HES concentrations were binned by time and overlaid with the 5th and 95th percentiles (90% confidence interval) of the 1000 simulated summary measures at corresponding percentiles (5th, 50th, and 95th) of the simulated data in order to provide a visual assessment of the predictive performance of the PK model.

Illustration of Covariate Effects

Using the final model, steady-state MMF and HES concentration–time profiles following administration of DRF 462 mg twice daily were simulated for virtual participants, differing only in specific test conditions relative to reference conditions, with all other factors being equal. Parameters were fixed to the estimates in the final model. Individual concentration–time profiles were then simulated for one participant per test or reference condition over 1000 iterations. For each virtual participant, area under the concentration–time profile (AUC) over a 12-hour dosing interval ($AUC_{0\text{-}12h,ss}$) and maximum plasma concentration over 12 hours ($C_{max0\text{-}12h,ss}$) values were calculated for a morning dose at steady state. The mean $AUC_{0\text{-}12h,ss}$ and $C_{max0\text{-}12h,ss}$ ratios (test/reference) and 90% prediction intervals were calculated for each comparison and presented in forest plots.

RESULTS

Base Model Development

The base model was initially fit with data from five single-dose studies (001, A103, A105, A106, A108) of DRF in healthy participants (Run 1). The stepwise addition of eight transit compartments for each metabolite was found to adequately describe the delayed absorption of both MMF and HES. Following inclusion of Study A110 (a multiple-dose administration study; evening dosing excluded), the model improved after placing an effect of body weight on volume and fixing the bioavailability of HES (F4) to the value of 0.6 based on the urinary recovery of ^{14}C-HES in a clinical mass balance study (Run 67). Next, participants on low- and medium-fat meals in Study A109 were incorporated into the model, where covariates describing the meal fat content were initially placed on Ka of MMF (Ka_{MMF}) (Run 68). In subsequent runs, both low- and medium-fat meal covariates were additionally applied to MMF bioavailability (F1) and to Ka of HES (Ka_{HES}) (Run 68.1–68.3).

A lag time was estimated for HES absorption when parent drug was dosed with a low-fat meal, whereas lag time estimates were nearly equal to zero for HES with a medium-fat meal and MMF with low- and medium-fat meals. Participants taking DRF with high-fat meals in Studies A102 and A104 were incorporated next, with the corresponding covariates related to high-fat meals ultimately being placed on F1 and Ka_{MMF} and on Ka_{HES} (Run 69–69.3). Lag time estimates for HES and MMF were nearly equal to zero when dosing the parent drug with a high-

fat meal. Data records associated with evening dosing in Studies A102 and A110 were then considered in the model build (Run 70.6–70.8). Evening dose covariates on Ka were estimated for both MMF and HES. A lag time was added for HES with evening dosing; however, the lag time estimate for MMF with evening dosing was not significant. Additionally, evening dosing did not appear to affect bioavailability of MMF or HES.

Model parameters were then re-estimated with evening dosing defined only by serial PK sampling data in Study A102 (Run 2). Study A110 data with evening dosing were not designated as evening samples, since only the pre dose samples on days 6 and 11 were obtained following an evening dose and these concentrations would not likely influence the estimation of evening dose effects on absorption rate (MMF and HES) or lag time (HES). A lag time for MMF with evening dosing was further explored (Runs 11–12) and estimates were near zero.

Patients in Studies EVOLVE-MS-1 [3] and EVOLVE-MS-2 [4], along with participants with renal impairment from Study A108 (Run 13) were then included in the model. Covariates describing the effects of dietary fat and evening dosing on absorption rate parameters were fixed to the estimates obtained with phase I data with serial sampling (Table S5). The parameters were fixed due to the large variability in exposure of MMF and HES during the absorption phase, which was anticipated to negatively impact the ability of the model to characterize the post-absorption phase of the PK profiles and identify factors that may influence CL and distribution volume of the metabolites. It was determined that estimated glomerular filtration rate (eGFR) was an appropriate covariate for describing the CL of HES, which is eliminated primarily by renal excretion. In addition, body weight was a significant covariate on CL of both metabolites. Parameter estimates for the base model developed using phase I data in healthy participants with normal renal function, participants with impaired renal function, and patients in phase III studies (Run 13) are provided in Table S6.

Samples obtained following evening dosing in EVOLVE-MS-1 and EVOLVE-MS-2 were not considered in the estimation of the evening dosing covariate on Ka_{MMF}, Ka_{HES}, or the HES lag time with evening dosing, since sparse sampling may not have adequately characterized the absorption phase in these studies. Furthermore, observed trough samples did not indicate any consistent trend with morning or evening dosing in Study A110, EVOLVE-MS-1, or EVOLVE-MS-2.

Additional investigation was performed for the estimated HES lag time for dosing with a low-fat meal (Runs 14–15, 17). The HES lag time was combined for all dietary fat conditions that resulted in an estimate near zero. Setting the HES lag time equal to zero for dosing with a low-fat meal resulted in an increase in OFV. Although an HES lag time with the specific low-fat dietary condition could not be explained, it was concluded that the HES lag time with a low-fat meal was required for model stability.

The residual error structure was described as log-additive, with separate values determined for each metabolite upon stratification by morning/evening dosing and meal fat content. Additionally, IOV of absorption rate (Ka_{MMF} and Ka_{HES}) was incorporated into the model, accounting for two dosing periods with matched dietary restrictions (Studies A102 and A110 and EVOLVE-MS-1 and EVOLVE-MS-2). In the base model, IOV estimates were 42.6% for Ka_{MMF} and 30.9% for Ka_{HES}. The corresponding IIV estimates for Ka_{MMF} and Ka_{HES} were reduced by ~3 percentage points when IOV was also estimated. Residual error for MMF (unknown fat/phase III studies) was ~8 percentage points lower in the base model incorporating IOV. When IOV was included in the final model (Run 7), the IOV for Ka_{HES} was not well estimated (confidence interval of the estimate included zero). An additional model was tested in which IOV was estimated only for Ka_{MMF} (Run 20); however, the model was unstable. Parameter estimates for the final model were similar with and without IOV, and therefore IOV was considered to be not important in the model.

Representative goodness-of-fit plots for the 420 mg or 462 mg dose of DRF in each study are shown in Fig. S4.

Full Model and Covariate Selection Procedures

The covariate analysis was performed using a full model approach with simultaneous addition of covariates. Base model ETA plots were examined to identify covariate–parameter relationships for testing in subsequent covariate analysis. R^2 values were calculated to assess the correlation between continuous covariates and parameter values, and categorical covariates were assessed by visual inspection. There were no continuous covariates with $R^2 > 0.05$, hence none were evaluated further during covariate analysis. From among the prespecified covariates considered, excluding those identified as structural covariates, four covariate–parameter relationships were selected for evaluation using a full model approach. Note that the patient status covariate combines the conditions of patient status and dietary intake of unknown fat content.

Covariates Included in Full Model Development

Parameter	Covariate
CL_{MMF}	PTST
CL_{HES}	PTST
Ka_{MMF}	PTST
Ka_{HES}	PTST

CL clearance, *HES* 2-hydroxyethyl succinimide, *Ka* absorption rate constant, *MMF* monomethyl fumarate, *PTST* patient status

From inspection of the ETA plots, a difference in MMF clearance (CL_{MMF}) was noted with evening dosing; however, this covariate was not selected for testing in the full model because the apparent effect may be a result of the study design and not an actual effect of evening dosing on CL_{MMF}. Following evening dosing in Study A102, the absorption of MMF was delayed and prolonged relative to morning dosing. However, the serial PK sampling was stopped after 10 hours post dose. Due to the prolonged and delayed absorption, the elimination phase would not have been captured with the 0–10-hour PK samples following evening dosing, and this could lead to a lower CL_{MMF} estimate for evening dosing.

The full model included patient status covariates on CL_{MMF}, clearance of HES (CL_{HES}), Ka_{MMF}, and Ka_{HES}. A stepwise backward elimination procedure was then performed on the full model containing the four additional covariates to identify a parsimonious final model. The table below summarizes the backward elimination procedure where all four covariate–parameter relationships met the inclusion criteria at a significance level of α = 0.001 (i.e., Δ OFV >10.8; $p < 0.001$) and none of these covariates were removed from the model.

Full Model Backward Elimination Algorithm Results

Step	Description	Thetas	OFV	Δ OFV
	Full model	22	–3227.483	–
1	PTST on CL_{HES}	21	–3212.623	14.860
1	PTST (UNK) on Ka_{HES}	21	–3204.82	22.663
1	PTST on CL_{MMF}	21	–3193.525	33.958
1	PTST (UNK) on Ka_{MMF}	21	–3179.547	47.936

CL clearance, *HES* 2-hydroxyethyl succinimide, *Ka* absorption rate constant, *MMF* monomethyl fumarate, *OFV* objective function value, *PTST* patient status, *UNK* administration with or without meal of unknown fat content

Model Evaluation

A visual predictive check was performed on the final model in order to determine if the model adequately characterized the MMF and HES concentration–time data in healthy participants and patients with MS. Fig. S5 shows observed and predicted dose-normalized MMF and HES concentration–time profiles.

PK Final Model NONMEM Control Stream

```
$PROB BIOGEN BIIB098 BASE MODEL DEVELOPMENT OF MMF & HES METABOLITES

$INPUT C LINE NMID=ID SUBJID STUD TIME ATFD ATFDT=DROP NTFD ATLD NTLD DAY
PM DOSE AMT ADDL II CONC LCONC=DV MDV EVID CMT BLQ AGE RACE SEXF ETHN BBSA BBMI
BWT BHT BALB BALT BAST BBILI BCRCL BEGFR SDMD PTST CNTY DIGOX FAT FOOD
LLOQ RICRCLN RIEGFRN OCC SERIAL NDOSNO=DROP CONCBLQ=DROP LCONCBLQ=DROP
MDVBLQ=DROP
```

```
$DATA ../../../DerivedData/PK_COMBINED_19DEC2019V19.csv
        IGNORE=@
        IGNORE(DIGOX.EQ.1)

$SUBROUTINE ADVAN5 TRANS1
$MODEL
COMP = (MMFDOS1);1
COMP = (PLMMF);2
COMP = (PLHES);3
COMP = (HESABS);4
COMP = (MMFTABS);5
COMP = (HESTABS);6
COMP = (MMFTABS2);7
COMP = (HESTABS2);8
COMP = (MMFTABS3);9
COMP = (HESTABS3);10
COMP = (MMFTABS4);11
COMP = (HESTABS4);12
COMP = (MMFTABS5);13
 COMP = (HESTABS5);14
COMP = (MMFTABS6);15
COMP = (HESTABS6);16
COMP = (MMFTABS6);17
COMP = (HESTABS6);18
COMP = (MMFTABS6);19
COMP = (HESTABS6);20

$PK
AGEM=35         ;MEDIAN AGE
IF(AGE.GT.0) AGEM=AGE
PM1=PM
IF(STUD.GE.110) PM1=0  ; PM IS ONLY FOR STUD 102
EGFR=111.9 ;MEDIAN BEGFR
IF(BEGFR.GT.0) EGFR=BEGFR
WT=78 ;MEDIAN WT
IF(BWT.GT.0) WT=BWT
BFAT1=0
IF(FAT.EQ.1) BFAT1=1
BFAT2=0
IF(FAT.EQ.2) BFAT2=1
BFAT3=0
IF(FAT.EQ.3) BFAT3=1
BFAT4=0
IF(FAT.EQ.4) BFAT4=1
; IOV FOR REPEAT ADMIN STUDIES
TOCC=0
IF(STUD.GE.110) TOCC=OCC+1
IF(STUD.EQ.102.AND.NMID.GE.71.AND.OCC.LE.1) T0CC=1
IF(STUD.EQ.102.AND.NMID.GE.71.AND.OCC.GE.2) T0CC=2
; SPARSE PK SAMPLING NO IOV
BOVAM1=0
BOVAM2=0
; 1ST OCCASION OF SERIAL PK SAMPLING TOCC=1
IF(TOCC.EQ.1.AND.SERIAL.EQ.1) THEN
BOVAM1=ETA(6)
```

```
BOVAM2=ETA(9)
ENDIF
; 2ND OCCASION OF SERIAL PK SAMPLING TOCC=2
IF(TOCC.EQ.2.AND.SERIAL.EQ.1) THEN
BOVAM1=ETA(7)
BOVAM2=ETA(10)
ENDIF
TVCL = THETA(1)*EXP(ETA(1))
TVV2 = THETA(2)*EXP(ETA(2))
TVKAM= THETA(3)*EXP(ETA(5)+BOVAM1)
TVKAH= THETA(6)*EXP(ETA(8)+BOVAM2)
TVCLH= THETA(7)*EXP(ETA(4))
F4 = THETA(8)*EXP(ETA(3))
F1 = THETA(9)

F1=F1*(1+BFAT1*THETA(16))*(1+BFAT2*THETA(17))*(1+BFAT3*THETA(18))

ALAG1=0

ALAG4=0+(PM1*THETA(24))+(BFAT1*THETA(25))

CLM=TVCL*((WT/78)**THETA(27))*(1+PTST*THETA(35))
V2=TVV2*((WT/78)**THETA(10))
KAM=TVKAM*(1+PM1*THETA(11))*(1+BFAT1*THETA(12))*(1+BFAT2*THETA(13)) &
*(1+BFAT3*THETA(14))*(1+BFAT4*THETA(15))
K15=KAM
K57=KAM
K79=KAM
K9T11=KAM
K11T13=KAM
K13T15=KAM
K15T17=KAM
K17T19=KAM
K19T2=KAM
KAH=TVKAH*(1+PM1*THETA(19))*(1+BFAT1*THETA(20))*(1+BFAT2*THETA(21)) &
*(1+BFAT3*THETA(22))*(1+BFAT4*THETA(23))
K46=KAH
K68=KAH
K8T10=KAH
K10T12=KAH
K12T14=KAH
K14T16=KAH
K16T18=KAH
K18T20=KAH
K20T3=KAH
CLH=TVCLH*((EGFR/111.9)**THETA(26))*((WT/78)**THETA(28))&
*(1+PTST*THETA(36))


V3 = V2

S2= V2/1000              ; dose = mg, conc = ng/mL= mcg/L
S3= V3/1000

K20=CLM/V2
K30=CLH/V3
```

```
$ERROR (OBSERVATION ONLY)
IF (CMT.EQ.2.AND.PM1.EQ.0.AND.FAT.EQ.0) W = SQRT(THETA(4)**2)
IF (CMT.EQ.2.AND.PM1.EQ.0.AND.FAT.GE.1.AND.FAT.LE.3) W = SQRT(THETA(29)**2)
IF (CMT.EQ.2.AND.PM1.EQ.1.AND.FAT.EQ.0) W = SQRT(THETA(30)**2)
IF (CMT.EQ.2.AND.FAT.EQ.4) W = SQRT(THETA(31)**2)
IF (CMT.EQ.3.AND.PM1.EQ.0.AND.FAT.EQ.0) W = SQRT(THETA(5)**2)
IF (CMT.EQ.3.AND.PM1.EQ.0.AND.FAT.GE.1.AND.FAT.LE.3) W = SQRT(THETA(32)**2)
IF (CMT.EQ.3.AND.PM1.EQ.1.AND.FAT.EQ.0) W = SQRT(THETA(33)**2)
IF (CMT.EQ.3.AND.FAT.EQ.4) W = SQRT(THETA(34)**2)

IF (F.GT.0) THEN
IPRED = LOG(F)
Y = IPRED + W*ERR(1)
IRES = DV - IPRED
IWRES = IRES/W
ELSE
Y = 0
IPRED = 0
IRES = 0
IWRES = 0
ENDIF

$THETA
(0,15)          ;1  CLMMF
(0,30)          ;2  V2
(0,5)           ;3  KAMMF
(0.8)           ;4  RE MMF
(0,0.3)         ;5  RE HES
(0,3)           ;6  KAHES
(0,2)           ;7  CLHES
(0.6 FIX)       ;8  F4
(0,.2,1) ;9  F1
(0.8)           ;10 WT ON V2
(-0.592 FIX)    ;11 PM DOSING ON KAM
(-0.368 FIX)    ;12 LOW FAT ON KAM
(-0.512 FIX)    ;13 MED FAT ON KAM
(-0.666 FIX)    ;14 HI  FAT ON KAM
(-1,0.1) ;15 UNK FAT ON KAM
(-0.296 FIX)    ;16 LOW FAT ON F1
(-0.301 FIX)    ;17 MED FAT ON F1
(-0.131 FIX)    ;18 HI  FAT ON F1
(-0.267 FIX)    ;19 PM DOSING ON KAH
(-0.335 FIX)    ;20 LOW FAT ON KAH
(-0.492 FIX)    ;21 MED FAT ON KAH
(-0.621 FIX)    ;22 HI  FAT ON KAH
(-1,0.1) ;23 UNK FAT ON KAH
(1.96 FIX)      ;24 PM DOSING ON ALAG4
(0.421 FIX)     ;25 LOW FAT ON ALAG4
(0.8)           ;26 EGFR ON CLH
(0.7)           ;27 WT ON CLM
(0.3)           ;28 WT ON CLH
(0.9)           ;29 RE MMF PM=0 & FAT>=1 <=3
(0.9)           ;30 RE MMF PM=1
(0.9)           ;31 RE MMF FAT=4
(0.3)           ;32 RE HES PM=0 & FAT>=1 <=3
```

```
(0.3)              ;33 RE HES PM=1
(0.2)              ;34 RE HES FAT=4
(-1,-0.2);35 PTST ON CLM
(-1,0.1) ;36 PTST ON CLH
$OMEGA
0.05               ;1 ETA1 - CL MMF
0.04               ;2 ETA2 - V2
0 FIX              ;3 ETA3 - F4
0.03               ;4 ETA4 - CL HES
$OMEGA 0.15  ;5 ETA5 - KAMMF IIV
$OMEGA BLOCK(1) 0 FIX
;;                          ;6 ETA6 -KAMMF IOV OCC1
$OMEGA BLOCK(1) SAME
;;                          ;7 ETA7 -KAMMF IOV OCC2
$OMEGA 0.21  ;8 ETA8 - KAHES IIV
$OMEGA BLOCK(1) 0 FIX
;;                          ;9 ETA9-KAHES IOV OCC1
$OMEGA BLOCK(1) SAME
;;                          ;10 ETA10-KAHES IOV OCC2
$SIGMA
 1 FIXED

$EST METHOD=1 INTERACTION PRINT=1 MAXEVAL=9999 NOABORT POSTHOC MSF=Run.msf
$COV MATRIX=R COMPRESS PRINT=E

$TABLE STUD ID NTLD ATLD ATFD NTFD DOSE CONC PM PM1
MDV EVID CMT BLQ AGE RACE SEXF ETHN BBSA BBMI BWT BHT BALB
BALT BAST BBILI BCRCL BEGFR SDMD PTST CNTY DIGOX
FAT FOOD LLOQ RICRCLN RIEGFRN
IWRES IPRED CWRES IRES
CLM V2 KAM KAH CLH F1 F4
ETA1 ETA2 ETA4 ETA5 ETA6 ETA8 ETA9
ONEHEADER NOPRINT FILE=fit.tab FORMAT=s1PE19.11
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Table S1 Continuous covariate data summary by study

Study	001	A102	A103	A104	A105	A106	A108	A109	A110	EVOLVE-MS-1	EVOLVE-MS-2	Total
n	**54**	**61**	**35**	**42**	**10**	**30**	**32**	**47**	**30**	**44**	**4**	**389**
Age (years)												
Mean	31.0	33.1	34.0	35.9	31.2	42.4	65.1	33.6	31.0	45.5	55.5	38.0
Median	28.5	32.0	33.0	35.5	30.5	44.5	68.0	31.0	30.0	48.5	56.0	35.0
SD	9.80	8.72	7.73	9.26	7.86	9.57	8.05	9.67	6.84	10.20	5.51	13.10
Min	18	20	19	21	19	25	44	18	19	24	49	18
Max	53	53	50	51	42	54	75	49	45	61	61	75
Body weight (kg)												
Mean	71.5	76.1	81.7	77.0	80.4	81.1	82.6	79.4	75.0	79.0	77.4	77.8
Median	70.1	75.8	82.5	78.9	79.7	81.0	82.8	78.2	76.0	79.3	80.6	78.0
SD	14.9	13.2	13.3	15.2	12.6	9.4	15.5	12.0	11.2	18.4	15.0	14.3
Min	49.1	50.6	54.7	47.4	58.5	58.1	51.9	59.4	56.3	48.5	56.4	47.4
Max	112.3	120.6	108.1	99.1	98.0	99.4	119.0	112.0	98.1	126.3	91.8	126.3
Body mass index (kg/m^2)												
Mean	26.3	26.4	27.5	26.3	26.6	26.0	29.4	27.7	25.4	28.1	26.9	27.0
Median	26.6	26.4	27.6	26.7	26.6	26.5	27.9	27.9	25.5	25.8	26.2	26.9
SD	3.47	3.36	2.65	3.18	3.59	2.46	4.08	2.73	3.20	6.91	4.73	3.93
Min	18.6	20.8	21.8	18.5	20.2	22.5	21.1	21.8	19.4	17.9	22.0	17.9
Max	32.0	32.5	31.6	31.7	31.8	30.1	38.9	31.8	30.1	44.0	33.1	44.0
Albumin (g/dL)												
Mean	4.43	4.43	4.52	4.37	4.41	4.42	4.22	4.42	4.38	4.32	4.53	4.4
Median	4.4	4.4	4.5	4.4	4.5	4.5	4.3	4.5	4.4	4.4	4.7	4.4
SD	0.24	0.26	0.24	0.25	0.37	0.25	0.28	0.27	0.32	0.38	0.36	0.29
Min	4.0	3.8	4.1	3.8	3.7	3.7	3.5	3.5	3.9	3.0	4.0	3.0
Max	5.0	5.1	5.0	4.8	5.0	4.8	4.7	4.9	5.1	5.1	4.8	5.1
Alanine aminotransferase (IU/L)												
Mean	15.3	16.5	18.5	19.3	14.8	21.3	17.7	17.0	17.1	24.4	21.3	18.3
Median	14.0	14.0	16.0	19.5	12.5	19.0	17.0	15.0	13.0	13.0	18.0	15.0
SD	7.04	8.15	9.17	8.07	6.12	9.92	7.10	8.92	10.60	63.30	12.70	22.70
Min	6	8	5	9	8	8	7	8	6	7	10	5
Max	41	44	44	41	27	51	38	50	55	433	39	433

Aspartate aminotransferase (IU/L)												
Mean	16.8	16.6	19.1	17.8	17.2	22.7	19.9	17.0	17.3	19.6	20.0	18.2
Median	16.0	16.0	17.0	17.0	17.0	23.0	19.5	16.0	16.0	16.0	19.5	17.0
SD	4.12	4.42	5.81	4.47	2.90	5.56	6.21	4.33	4.91	19.50	6.48	8.11
Min	10	9	11	12	13	14	12	12	9	9	13	9
Max	29	34	33	31	22	36	44	34	28	141	28	141
Bilirubin (mg/dL)												
Mean	0.59	0.52	0.59	0.59	0.78	0.48	0.46	0.53	0.55	0.36	0.28	0.53
Median	0.51	0.48	0.53	0.56	0.75	0.44	0.40	0.48	0.50	0.30	0.25	0.49
SD	0.25	0.18	0.23	0.22	0.40	0.23	0.22	0.20	0.16	0.15	0.10	0.23
Min	0.23	0.25	0.25	0.25	0.25	0.12	0.20	0.23	0.30	0.20	0.20	0.12
Max	1.38	1.11	1.20	1.34	1.68	0.94	0.90	1.23	1.00	0.80	0.40	1.68
Estimated glomerular filtration rate (mL/min)												
Mean	114.0	115.1	115.1	115.8	115.4	108.3	67.8	116.5	116.4	108.0	109.1	110.0
Median	114.9	113.8	115.0	113.0	114.0	108.5	67.3	111.8	114.6	102.3	117.4	111.4
SD	21.4	20.4	20.0	18.5	14.5	15.6	35.8	21.2	19.3	32.1	22.6	26.3
Min	74.7	76.4	68.6	75.0	99.5	76.2	15.2	81.6	63.5	55.0	76.3	15.2
Max	170.8	166.5	152.7	162.9	147.6	135.8	131.2	172.8	150.5	185.8	125.3	185.8

Max maximum, *min* minimum, *SD* standard deviation

Table S2 Categorical covariate data summary by study

Study	001	A102	A103	A104	A105	A106	A108	A109	A110	EVOLVE-MS-1	EVOLVE-MS-2	Total, *n* (%)
n	**54**	**61**	**35**	**42**	**10**	**30**	**32**	**47**	**30**	**44**	**4**	**389**
Sex												
Male	15	27	25	27	10	24	16	22	20	10	1	197 (50.6)
Female	39	34	10	15	0	6	16	25	10	34	3	192 (49.3)
Race												
White	39	40	23	30	4	19	25	31	9	34	4	258 (66.3)
Black	11	18	12	11	6	10	6	15	21	10	0	120 (30.8)
Asian	3	1	0	1	0	1	0	0	0	0	0	6 (1.5)
Other	1	2	0	0	0	0	1	1	0	0	0	5 (1.2)
Ethnicity												
Not Hispanic	30	36	20	21	8	28	30	29	27	37	4	270 (69.4)
Hispanic	24	25	15	21	2	2	2	18	3	7	0	119 (30.5)
Dose group												
49 mg	6	0	0	0	0	0	0	0	0	0	0	6
105 mg	6	0	0	0	0	0	0	0	0	0	0	6
210 mg	6	15	0	0	0	0	0	0	0	0	0	21
231 mg	0	0	0	0	0	0	0	0	0	43	4	47
420 mg	18	31	0	0	0	0	0	0	0	0	0	49
462 mg	0	0	35	42	10	30	32	47	30	40	4	270
630 mg	6	15	0	0	0	0	0	0	0	0	0	21
840 mg	6	0	0	0	0	0	0	0	0	0	0	6
924 mg	0	0	0	0	0	0	0	0	29	0	0	29
980 mg	6	0	0	0	0	0	0	0	0	0	0	6
Fat content												
None	54	61	35	0	10	30	32	0	30	0	0	252
Low	0	0	0	0	0	0	0	47	0	0	0	47
Moderate	0	0	0	0	0	0	0	47	0	0	0	47
High	0	16	0	42	0	0	0	0	0	0	0	58
Unknown	0	0	0	0	0	0	0	0	0	44	4	48
Administration with food												
Fasted	54	61	35	0	10	30	32	0	30	0	0	252
Fed	0	16	0	42	0	0	0	47	0	0	0	105

Unknown	0	0	0	0	0	0	0	0	0	44	4	48
Renal function (CRCL)[a]												
Normal	53	57	34	41	9	28	8	47	28	35	3	343 (88.1)
Mild	1	4	1	1	1	2	10	0	2	8	1	31 (7.9)
Moderate	0	0	0	0	0	0	10	0	0	1	0	11 (2.8)
Severe	0	0	0	0	0	0	4	0	0	0	0	4 (1.0)
Renal function (eGFR)[b] [1]												
Normal	46	49	27	36	9	21	7	41	26	29	3	294 (75.5)
Mild	8	12	8	6	1	9	10	6	3	14	1	78 (20.0)
Moderate	0	0	0	0	0	0	7	0	1	1	0	9 (2.3)
Severe	0	0	0	0	0	0	8	0	0	0	0	8 (2.0)
Participant type												
Healthy participants	54	61	35	42	10	30	32	47	30	0	0	341 (87.6)
Patients	0	0	0	0	0	0	0	0	0	44	4	48 (12.3)
Dose prior to serial PK samples												
Morning dose	54	61	35	42	10	30	32	47	30	44	4	389
Evening dose	0	45	0	0	0	0	0	0	29	22	1	97

CRCL creatinine clearance, *eGFR* estimated glomerular filtration rate, *PK* pharmacokinetics

[a] CRCL calculated using Cockcroft-Gault equation

[b] eGFR calculated using Modification of Diet in Renal Disease equation and expressed in absolute units (mL/min) following denormalization using individual participant body surface area

1. Renal function categories are based on US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling. Draft, September 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and.

Table S3 Number of participants and PK samples with MMF concentrations included in the population PK dataset by study

							BLQ by sampling time			
	PK samples		Quantifiable (> LLOQ)		Total BLQ		Pre dose BLQ (prior to first dose)		Post dose BLQ	
Study	*n*	No. of samples	*n*	No. of samples	*n*	No. of samples	*n*	No. of samples	*n*	No. of samples
001	54	756	54	321	54	435	54	54	54	381
A102	61	2844	61	1360	61	1484	61	107	61	1377
A103	35	595	35	222	35	373	35	35	35	338
A104	42	882	42	415	42	467	42	42	42	425
A105	10	160	10	69	10	91	10	10	10	81
A106	30	508	30	194	30	314	30	30	30	284
A108	32	671	32	184	32	487	32	32	32	455
A109	47	1903	47	905	47	998	47	94	47	904
A110	30	708	30	503	30	205	20	21	30	184
EVOLVE-MS-1	44	802	44	485	43	317	43	127	42	190
EVOLVE-MS-2	4	78	4	36	4	42	4	14	4	28
Total	389	9907	389	4694	388	5213	378	566	387	4647

BLQ below limit of quantification, *LLOQ* lower limit of quantification, *MMF* monomethyl fumarate, *PK* pharmacokinetics

Table S4 Number of participants and PK samples with HES concentrations included in the population PK dataset by study

							BLQ by sampling time			
	PK samples		Quantifiable (> LLOQ)		Total BLQ		Pre dose BLQ (prior to first dose)		Post dose BLQ	
	n	No. of samples	*n*	No. of samples	*n*	No. of samples	*n*	No. of samples	*n*	No. of samples
001	42	588	42	396	42	192	42	42	42	150
A102	61	2844	61	2522	61	322	61	62	61	260
A103	35	594	35	452	35	142	35	35	35	107
A104	42	882	42	625	42	257	42	42	42	215
A105	10	160	10	115	10	45	10	10	10	35
A106	30	508	30	387	30	121	30	30	28	91
A108	32	670	32	515	31	155	31	31	28	124
A109	47	1903	47	1607	47	296	47	72	47	224
A110	30	708	30	708	0	0	0	0	0	0
EVOLVE-MS-1	44	811	44	698	44	113	44	44	38	69
EVOLVE-MS-2	4	78	4	63	4	15	4	4	4	11
Total	377	9746	377	8088	346	1658	346	372	335	1286

BLQ below limit of quantification, *HES* 2-hydroxyethyl succinimide, *LLOQ* lower limit of quantification, *PK* pharmacokinetics

Table S5 PK parameter estimates for the base model estimating absorption parameters using phase I data in healthy participants following serial PK sampling

Theta/parameter	Estimate	ASE	% RSE	95% CI	Units	Shrinkage (%)[a]
1 CL_{MMF}	14.1	0.560	4.0	(13.0, 15.2)	L/h	
2 Vc	30.7	0.416	1.4	(29.9, 31.6)	L	
3 Ka_{MMF}	4.85	0.156	3.2	(4.55, 5.16)	h^{-1}	
6 Ka_{HES}	3.17	0.0818	2.6	(3.01, 3.33)	h^{-1}	
7 CL_{HES}	1.54	0.0175	1.1	(1.51, 1.58)	L/h	
8 F4	0.6 FIXED					
9 F1	0.166	0.00732	4.4	(0.152, 0.181)		
10 WT on Vc	0.813	0.0772	9.5	(0.661, 0.964)		
11 PM dosing on Ka_{MMF}	–0.592	0.0141	2.3	(–0.620, –0.565)		
12 LOW on Ka_{MMF}	–0.368	0.0455	12.3	(–0.457, –0.279)		
13 MED on Ka_{MMF}	–0.512	0.0332	6.4	(–0.577, –0.447)		
14 HI on Ka_{MMF}	–0.666	0.0182	2.6	(–0.702, –0.630)		
17 LOW on F1	–0.296	0.0489	16.4	(–0.392, –0.200)		
18 MED on F1	–0.301	0.0478	15.8	(–0.395, –0.208)		
19 HI on F1	–0.131	0.0559	42.6	(–0.241, –0.0213)		
26 PM dosing on Ka_{HES}	–0.267	0.0492	18.3	(–0.364, –0.171)		
27 LOW on Ka_{HES}	–0.335	0.0432	12.8	(–0.420, –0.251)		
28 MED on Ka_{HES}	–0.492	0.0315	6.3	(–0.554, –0.43)		
29 HI on Ka_{HES}	–0.621	0.00847	1.3	(–0.638, –0.604)		
36 HES ALAG4 with PM dosing	1.96	0.301	15.4	(1.37, 2.55)	h	
37 HES ALAG4 with LOW	0.421	0.0541	12.8	(0.315, 0.527)	h	
Residual variability						
4 RE MMF	97.0	1.22	1.3	(94.6, 99.4)	%	
5 RE HES	33.5	0.312	0.9	(32.9, 34.1)	%	
IIV						
1 ETA1 - CL_{MMF}	26.8			(22.7, 30.3)	%CV	27.7

2	ETA2 - Vc	17.3	(14.8, 19.5)	%CV	23.7
5	ETA5 - CL_{HES}	16.2	(14.3, 17.8)	%CV	17.3
3	ETA3 - Ka_{MMF}	36.2	(32.2, 39.8)	%CV	13.1
4	ETA4 - Ka_{HES}	38.2	(34.7, 41.3)	%CV	5.2
OFV		–1460.77			

%CV percent coefficient of variation, *ALAG4* lag time for HES absorption with low-fat meal, *ASE* asymptotic standard error, *CI* confidence interval, *CL* clearance, *F1* bioavailability of MMS, *F4* bioavailability of HES, *HES* 2-hydroxyethyl succinimide, *HI* administration of high-fat meal, *IIV* interindividual variability, *Ka* absorption rate constant, *LOW* administration of low-fat meal, *MED* administration of medium-fat meal, *MMF* monomethyl fumarate, *OFV* objective function value, *PK* pharmacokinetic, *PM* evening dose, *RE* residual error, *RSE* relative standard error, *Vc* central volume of distribution, *WT* body weight

[a] Shrinkage estimate for epsilon was 5.2%

Model equations:

$$CL_{MMF,i} = 14.1 \cdot exp(\eta_i{}^{CL_{MMF}})$$

$$CL_{HES,i} = 1.54 \cdot exp(\eta_i{}^{CL_{HES}})$$

$$Vc_i = 30.7 \cdot \left(\frac{WT}{78}\right)^{0.813} \cdot exp(\eta_i{}^{Vc})$$

$$Ka_{MMF,i} = 4.85 \cdot \big(1 + PM \cdot (-0.592)\big) \cdot (1 + LOW \cdot (-0.368)) \cdot (1 + MED \cdot (-0.512)) \cdot (1 + HI \cdot (-0.666)) \cdot exp(\eta_i{}^{KA_{MMF}})$$

$$Ka_{HES,i} = 3.17 \cdot \big(1 + PM \cdot (-0.267)\big) \cdot (1 + LOW \cdot (-0.335)) \cdot (1 + MED \cdot (-0.492)) \cdot (1 + HI \cdot (-0.621)) \cdot exp(\eta_i{}^{KA_{HES}})$$

$$F1 = 0.166 \cdot (1 + LOW \cdot (-0.296)) \cdot (1 + MED \cdot (-0.301)) \cdot (1 + HI \cdot (-0.131))$$

Table S6 PK parameter estimates for the base model using phase I and phase III data

Theta/parameter	Estimate	ASE	% RSE	95% CI	Units	Shrinkage (%)[a]
1 CL_{MMF}	12.7	0.392	3.1	(12.0, 13.5)	L/h	
2 Vc	30.4	0.384	1.3	(29.6, 31.1)	L	
3 Ka_{MMF}	5.38	0.151	2.8	(5.08, 5.68)	h^{-1}	
6 Ka_{HES}	3.38	0.078	2.3	(3.22, 3.53)	h^{-1}	
7 CL_{HES}	1.47	0.0163	1.1	(1.44, 1.50)	L/h	
8 F4	0.6 FIXED					
9 F1	0.158	0.00496	3.1	(0.149, 0.168)		
10 WT on Vc	0.884	0.0691	7.8	(0.749, 1.02)		
11 PM dosing on Ka_{MMF}	–0.592 FIXED					
12 LOW on Ka_{MMF}	–0.368 FIXED					
13 LOW on Ka_{MMF}	–0.512 FIXED					
14 HI on Ka_{MMF}	–0.666 FIXED					
16 LOW on F1	–0.296 FIXED					
17 MED on F1	–0.301 FIXED					
18 HI on F1	–0.131 FIXED					
19 PM dosing on Ka_{HES}	–0.267 FIXED					
20 LOW on Ka_{HES}	–0.335 FIXED					
21 MED on Ka_{HES}	–0.492 FIXED					
22 HI on Ka_{HES}	–0.621 FIXED					
24 HES ALAG4 with PM dosing	1.96 FIXED				h	
25 HES ALAG4 with LOW	0.421 FIXED				h	
26 eGFR on CL_{HES}	0.546	0.0329	6.0	(0.481, 0.61)		
27 WT on CL_{MMF}	0.824	0.101	12.2	(0.627, 1.02)		
28 WT on CL_{HES}	0.335	0.0616	18.4	(0.214, 0.455)		
Residual variability						
4 RE MMF (AM dose, fasted)	90.4	1.62	1.8	(87.3, 93.6)	%	
5 RE HES (AM dose, fasted)	25.2	0.332	1.3	(24.5, 25.8)	%	
29 RE MMF (AM dose, fed[a])	103	2.09	2.0	(98.8, 107)	%	
30 RE MMF (PM dose, fasted)	111	3.69	3.3	(104, 118)	%	

31 RE MMF (UNK)	102	3.45	3.4	(94.9, 108)	%	
32 RE HES (AM dose, fed[a])	46.9	0.745	1.6	(45.4, 48.3)	%	
33 RE HES (PM dose, fasted)	18.4	0.407	2.2	(17.6, 19.2)	%	
34 RE HES (UNK)	37.4	1.09	2.9	(35.3, 39.6)	%	
IIV						
1 ETA1 - CL_{MMF}	24.5			(20.8, 27.7)	%CV	29.2
2 ETA2 - Vc	19.6			(17.2, 21.8)	%CV	19.8
5 ETA5 - CL_{HES}	18.4			(16.7, 20.0)	%CV	14.1
3 ETA3 - Ka_{MMF}	39.8			(35.8, 43.4)	%CV	13.4
4 ETA4 - Ka_{HES}	43.7			(40.3, 46.8)	%CV	4.42
OFV	–3112.3					

%CV percent coefficient of variation, *ALAG4* lag time for HES absorption with low-fat meal, *AM* morning dose, *ASE* asymptotic standard error, *CI* confidence interval, CL clearance, *eGFR* estimated glomerular filtration rate, *F1* bioavailability of MMS, *F4* bioavailability of HES, *HES* 2-hydroxyethyl succinimide, *HI* administration of high-fat meal, *IIV* interindividual variability, *Ka* absorption rate constant, *LOW* administration of low-fat meal, *MED* administration of medium-fat meal, *MMF* monomethyl fumarate, *OFV* objective function value, *PK* pharmacokinetic, *PM* evening dose, *RE* residual error, *RSE* relative standard error, *UNK* administration with or without meal of unknown fat content (patients only), *Vc* central volume of distribution, *WT* body weight

[a] Shrinkage estimate for epsilon was 5.6%

[b] Fed refers to drug administration with a meal of low, medium, or high fat content

Covariate parameters fixed to values estimated in the base model using phase I data: low fat, medium fat, high fat, and PM dosing on Ka_{MMF}; low fat, medium fat, high fat on F1; low fat, medium fat, high fat, and PM dosing on Ka_{HES}; HES ALAG4 with PM dosing; HES ALAG4 with low fat

Covariate parameters estimated in base model using phase I and phase III data: WT on CL_{MMF}, WT on CL_{HES}, WT on Vc, eGFR on CL_{HES}

Model equations:

$$CL_{MMF,i} = 12.7 \cdot \left(\frac{WT}{78}\right)^{0.824} \cdot exp(\eta_i{}^{CL_{MMF}})$$

$$CL_{HES,i} = 1.47 \cdot \left(\frac{eGFR}{111.9}\right)^{0.546} \cdot \left(\frac{WT}{78}\right)^{0.335} \cdot exp(\eta_i{}^{CL_{HES}})$$

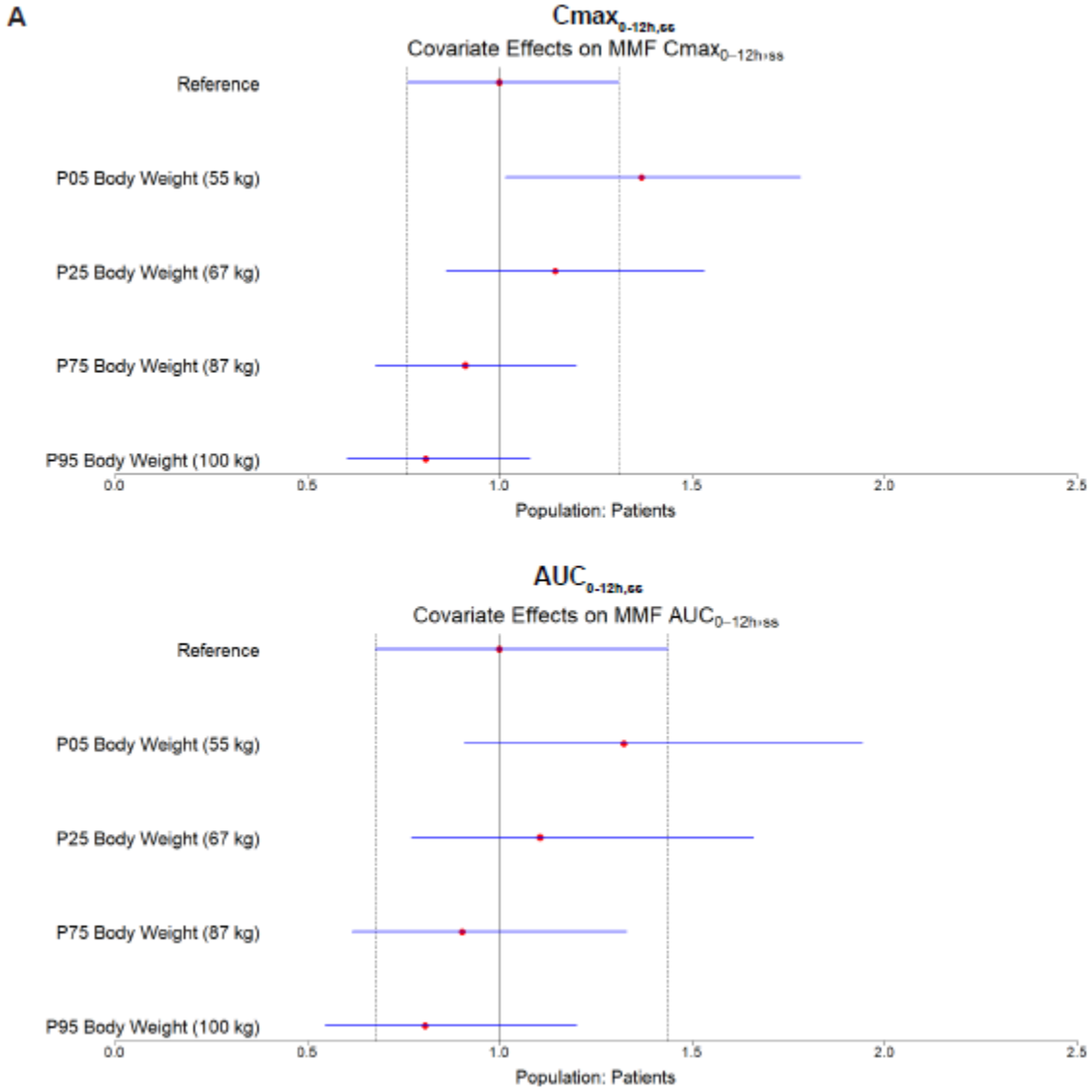
$$Vc_i = 30.4 \cdot \left(\frac{WT}{78}\right)^{0.884} \cdot exp(\eta_i{}^{Vc})$$

$$Ka_{MMF,i} = 5.38 \cdot \big(1 + PM \cdot (-0.592)\big) \cdot (1 + LOW \cdot (-0.368)) \cdot (1 + MED \cdot (-0.512)) \cdot (1 + HI \cdot (-0.666)) \cdot exp(\eta_i{}^{KA_{MMF}})$$

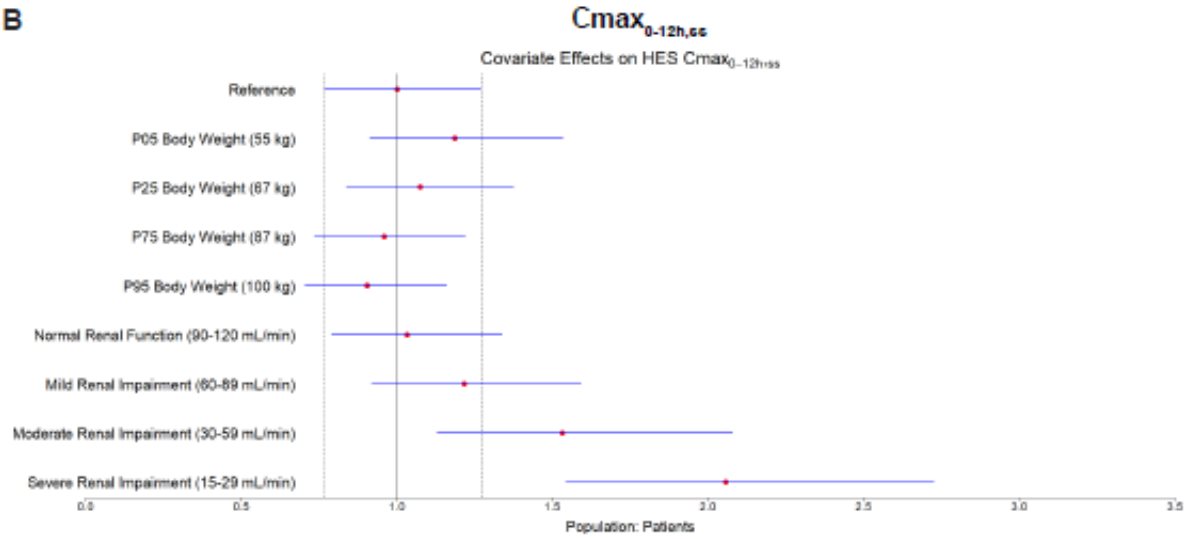
$$Ka_{HES,i} = 3.38 \cdot \big(1 + PM \cdot (-0.267)\big) \cdot (1 + LOW \cdot (-0.335)) \cdot (1 + MED \cdot (-0.492)) \cdot (1 + HI \cdot (-0.621)) \cdot exp(\eta_i{}^{KA_{HES}})$$

$$F1 = 0.158 \cdot (1 + LOW \cdot (-0.296)) \cdot (1 + MED \cdot (-0.301)) \cdot (1 + HI \cdot (-0.131))$$

Fig. S1 Illustration of covariate effects on steady state exposure of MMF (**a**) and HES (**b**) in patients with MS. Red circles show the ratio of the median parameter value under the test conditions compared with the reference patient with MS with median body weight of 78 kg and median eGFR of 111.9 mL/min. Test conditions for body weight include the 5th, 25th, 75th, and 95th percentiles of body weight among participants in the analysis dataset. Test conditions for renal function include four values of eGFR within each renal function category: normal (eGFR = 120, 110, 100, 90 mL/min); mild impairment (eGFR = 89, 80, 70, 60 mL/min), moderate impairment (eGFR = 59, 50, 40, 30 mL/min), and severe impairment (eGFR = 29, 25, 20, 15 mL/min), summarized within each category. The blue line segments represent the corresponding 90% prediction interval. Vertical dashed lines indicate the 90% prediction interval for the reference conditions. Simulations (*N* = 1000) were performed for virtual participants (one per test condition and reference), with parameter values fixed to the final model parameter estimates and incorporating interindividual variability (i.e., individual population-predicted–derived concentration–time profiles were generated). $AUC_{0\text{-}12h,ss}$ area under the concentration–time profile from 0 to 12 h at steady state, $C_{max0\text{-}12h,ss}$ maximum plasma concentration over 12 h at steady state, *eGFR* estimated glomerular filtration rate, *HES* 2 hydroxyethyl succinimide, *MMF* monomethyl fumarate, *MS* multiple sclerosis



B


Cmax0-12h,ss
Covariate Effects on HES Cmax0-12h,ss
Reference
P05 Body Weight (55 kg)
P25 Body Weight (67 kg)
P75 Body Weight (87 kg)
P95 Body Weight (100 kg)
Normal Renal Function (90-120 mL/min)
Mild Renal Impairment (60-89 mL/min)
Moderate Renal Impairment (30-59 mL/min)
Severe Renal Impairment (15-29 mL/min)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Population: Patients

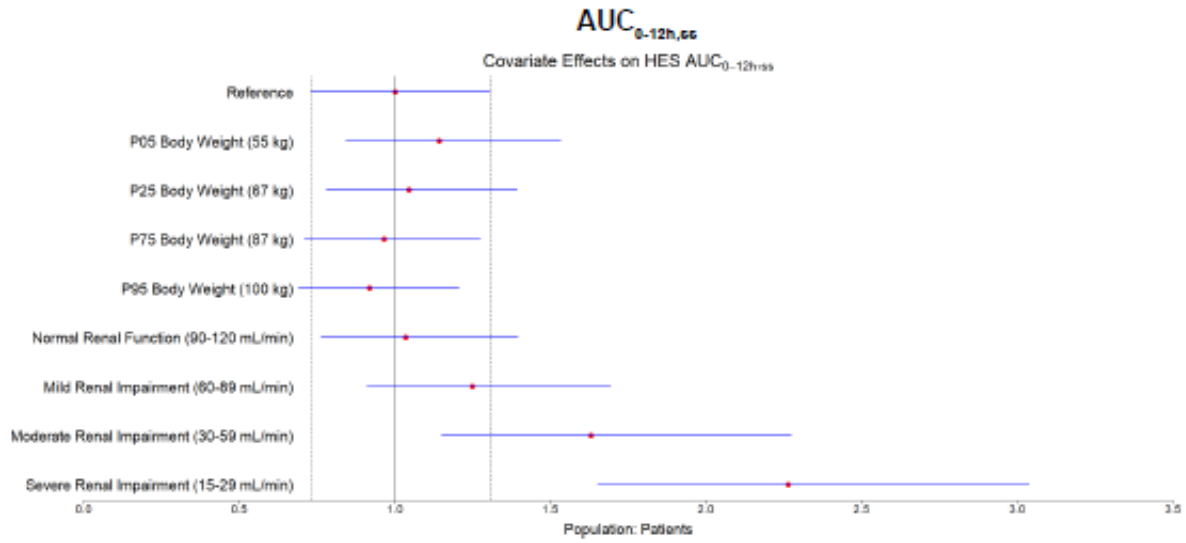

AUC0-12h,ss
Covariate Effects on HES AUC0-12h,ss
Reference
P05 Body Weight (55 kg)
P25 Body Weight (67 kg)
P75 Body Weight (87 kg)
P95 Body Weight (100 kg)
Normal Renal Function (90-120 mL/min)
Mild Renal Impairment (60-89 mL/min)
Moderate Renal Impairment (30-59 mL/min)
Severe Renal Impairment (15-29 mL/min)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Population: Patients

Fig. S2 Model-based simulation of steady state MMF and HES concentration–time profiles in healthy participants following administration of DRF 462 mg twice daily. *DRF* diroximel fumarate, *HES* 2 hydroxyethyl succinimide, *MMF* monomethyl fumarate, *PM* evening dose

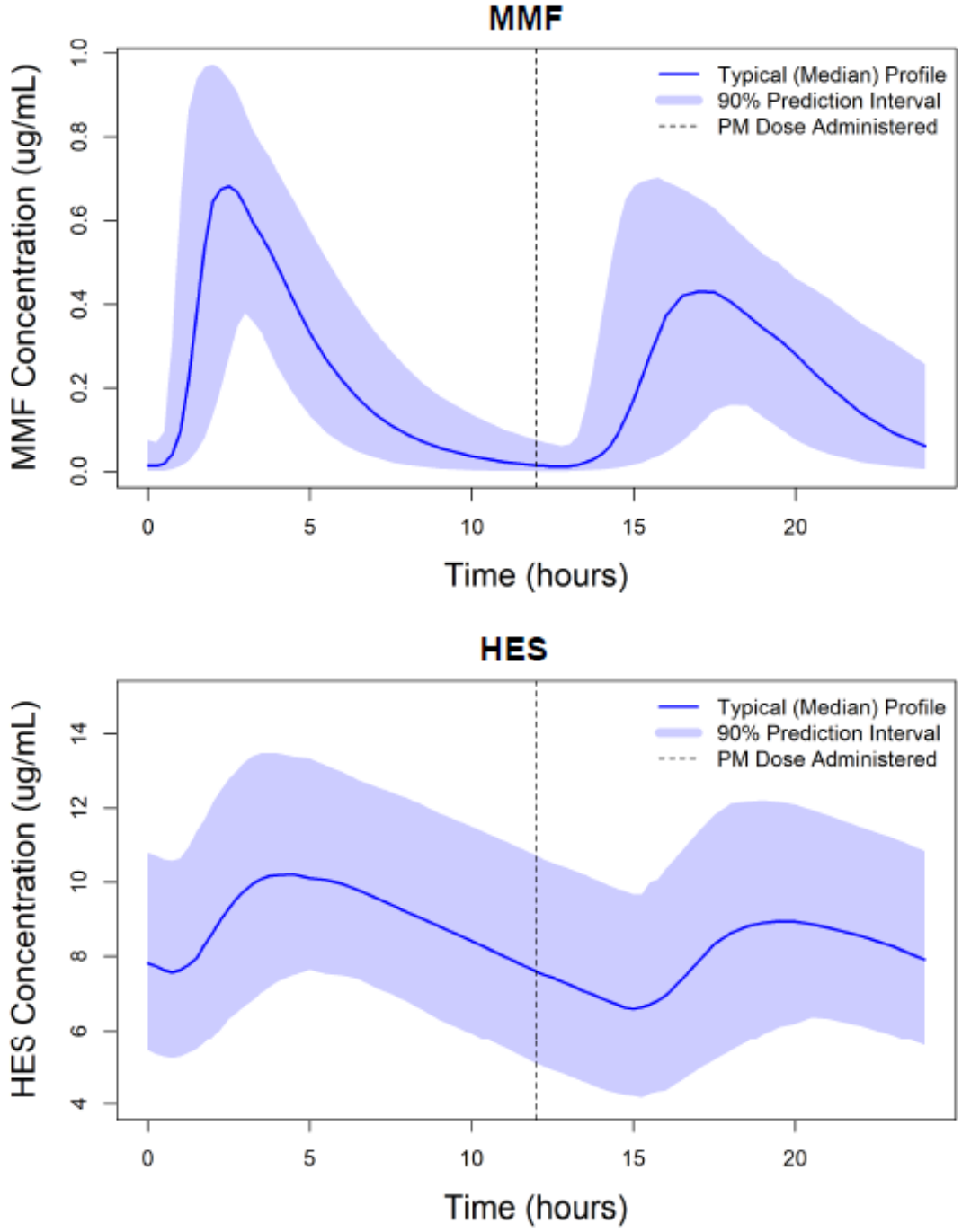


Fig. S3 Standard goodness-of-fit plots for the final model. *CWRES* conditional weighted residual, *DRF* diroximel fumarate, *DV* dependent variable, *HES* 2 hydroxyethyl succinimide, *iPRED* individual predicted value, *MMF* monomethyl fumarate, *OBS* observed, *PM* evening dose, *PRED* predicted value, *WRES* weighted residual

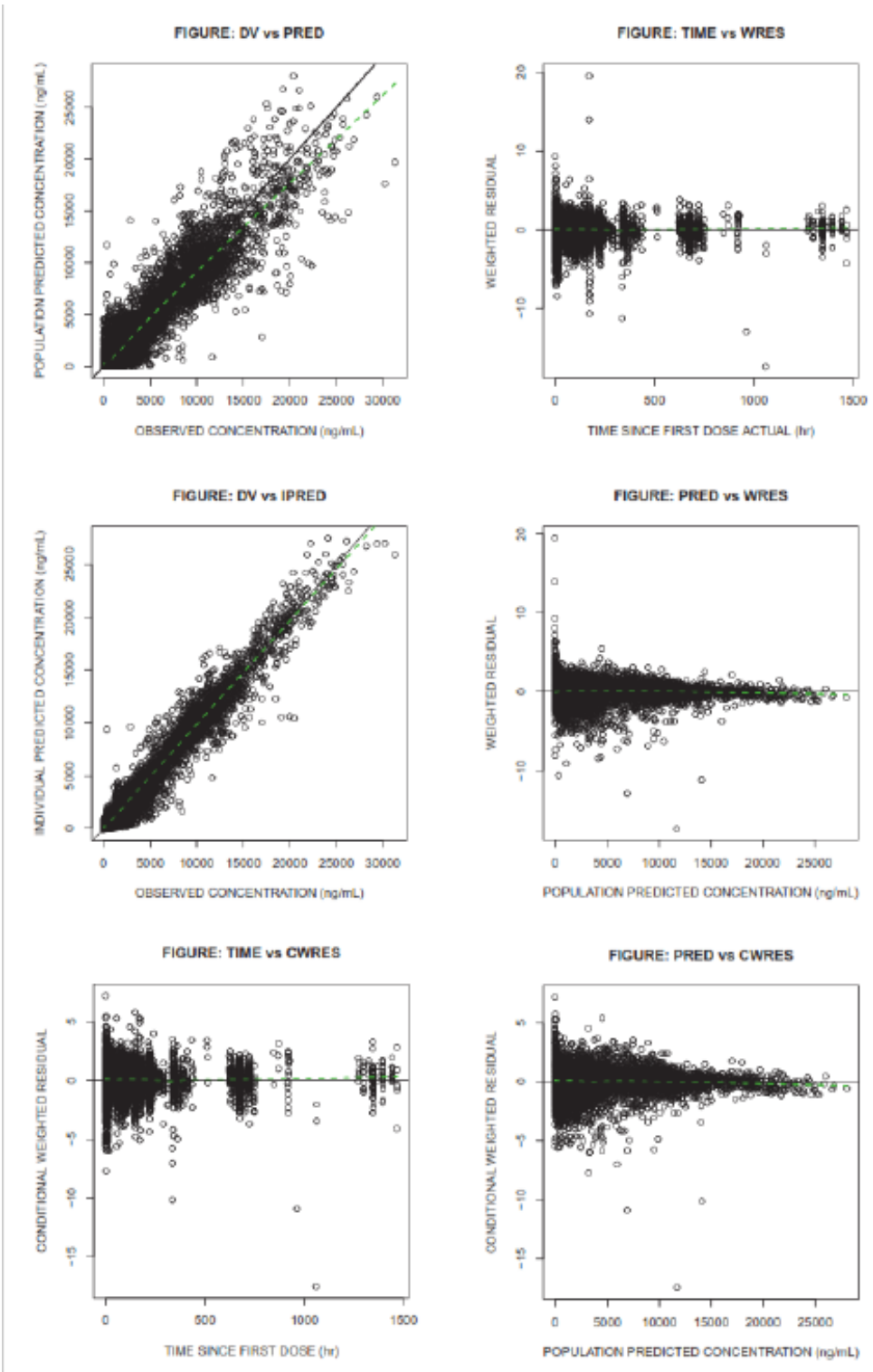
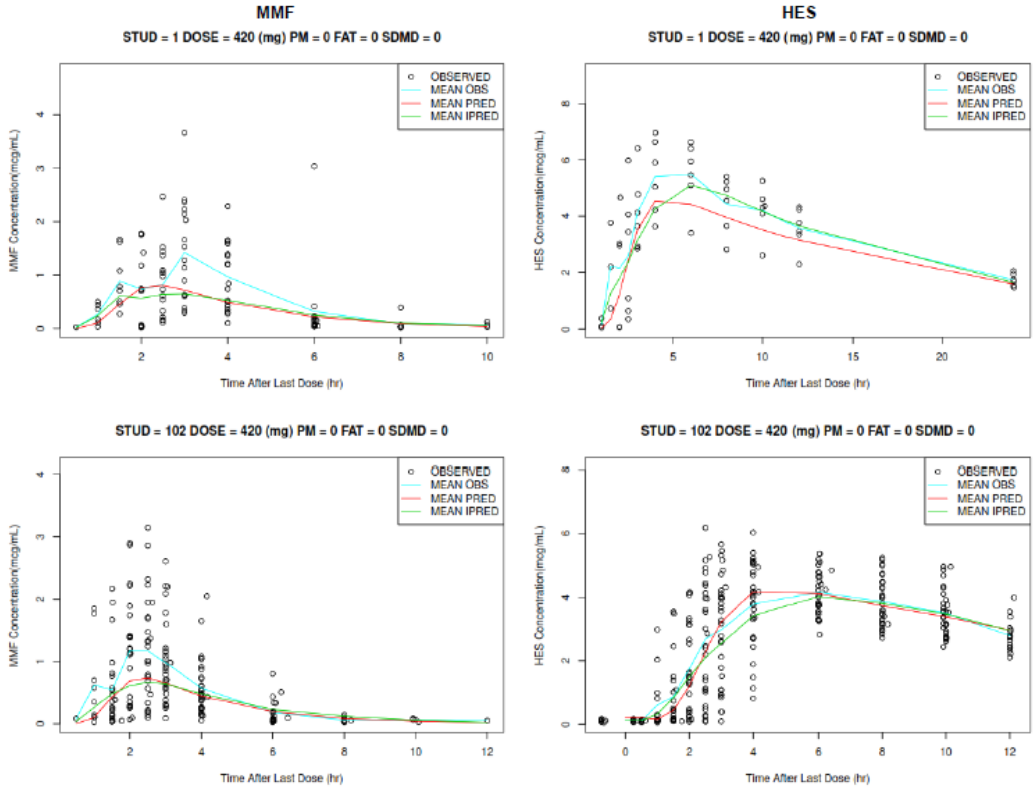
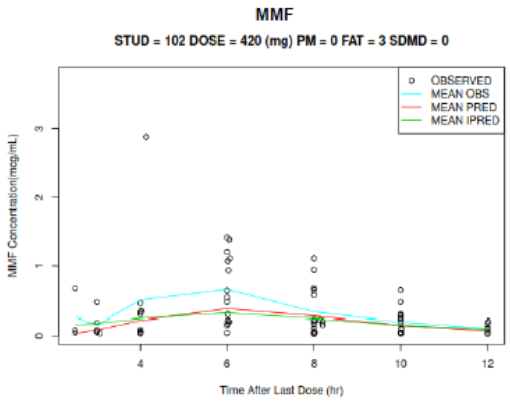
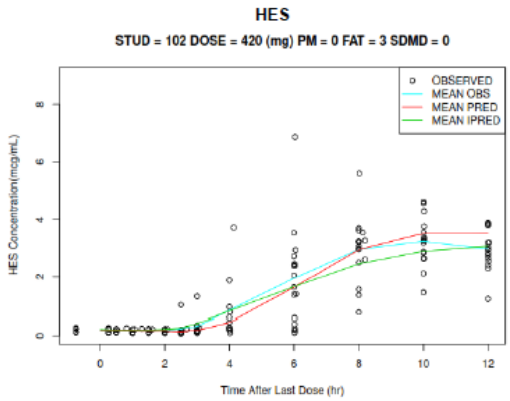
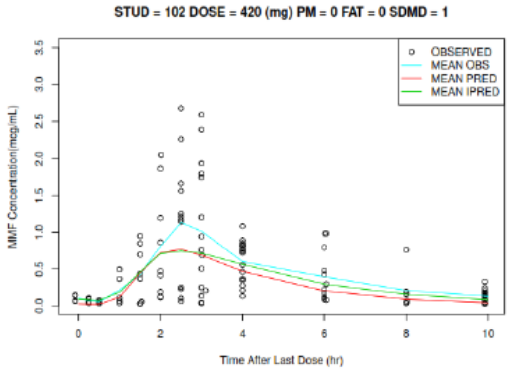


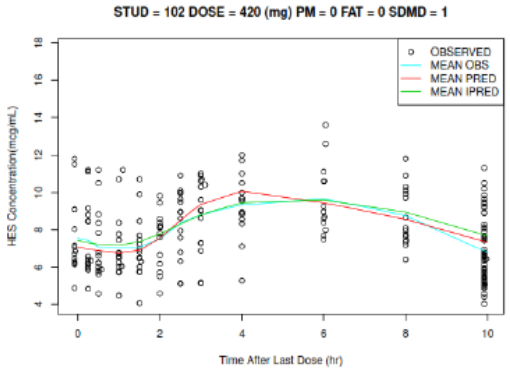
Fig. S4 Goodness-of-fit plots for the MMF and HES base model by study at DRF 420 or 462 mg. *DRF* diroximel fumarate, *HES* 2 hydroxyethyl succinimide, *iPRED* individual predicted value, *MMF* monomethyl fumarate, *OBS* observed, *PM* evening dose, *PRED* predicted value, *SDMD* single dose/multiple dose, *STUD* study

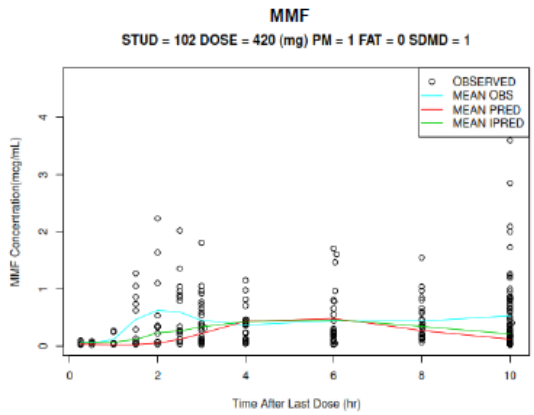


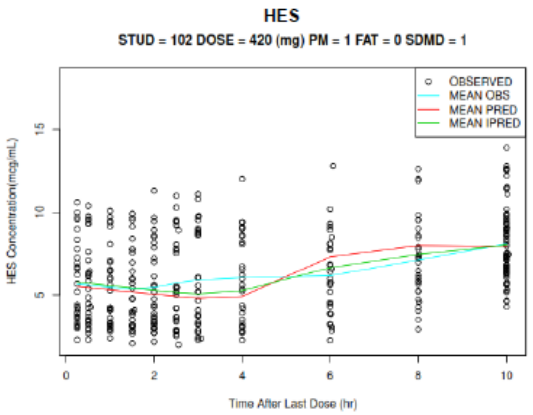

MMF
STUD = 102 DOSE = 420 (mg) PM = 0 FAT = 3 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

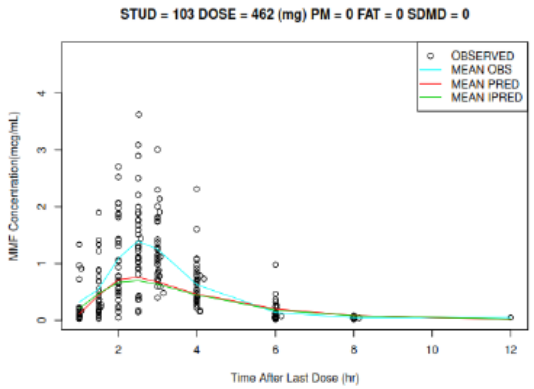

HES
STUD = 102 DOSE = 420 (mg) PM = 0 FAT = 3 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

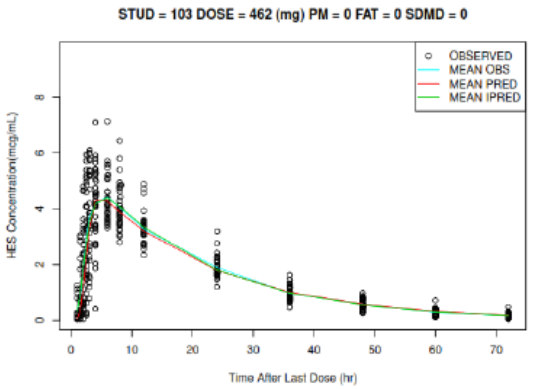

STUD = 102 DOSE = 420 (mg) PM = 0 FAT = 0 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

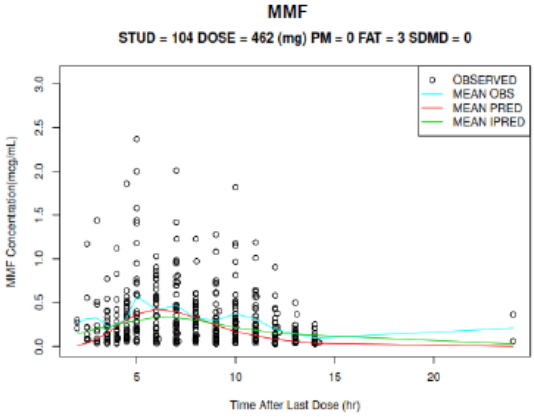

STUD = 102 DOSE = 420 (mg) PM = 0 FAT = 0 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

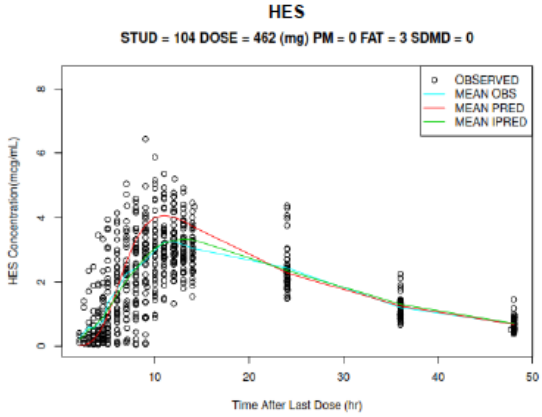

MMF
STUD = 102 DOSE = 420 (mg) PM = 1 FAT = 0 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

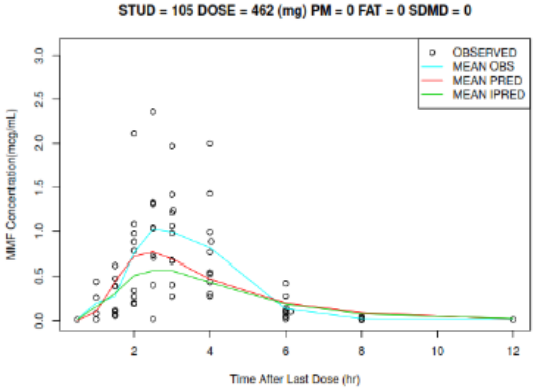

HES
STUD = 102 DOSE = 420 (mg) PM = 1 FAT = 0 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

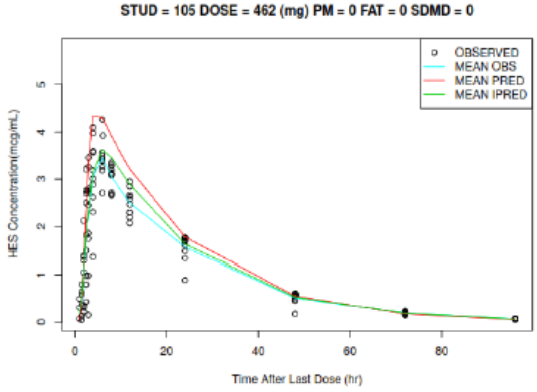

STUD = 103 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

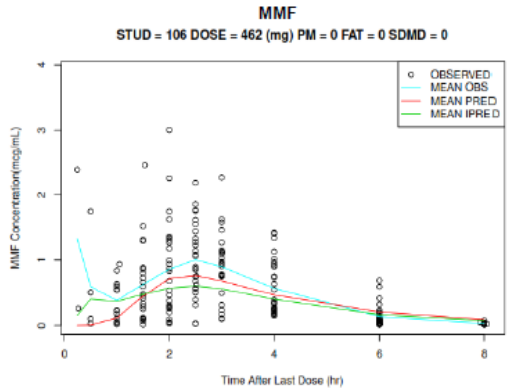

STUD = 103 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

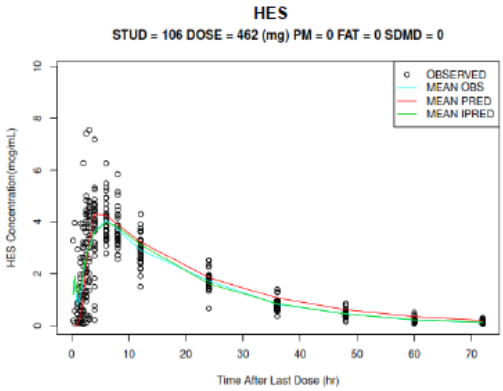

MMF
STUD = 104 DOSE = 462 (mg) PM = 0 FAT = 3 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

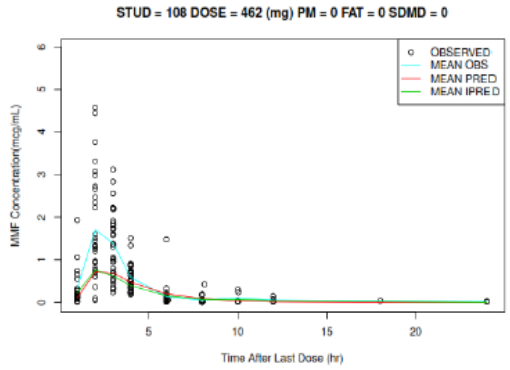

HES
STUD = 104 DOSE = 462 (mg) PM = 0 FAT = 3 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

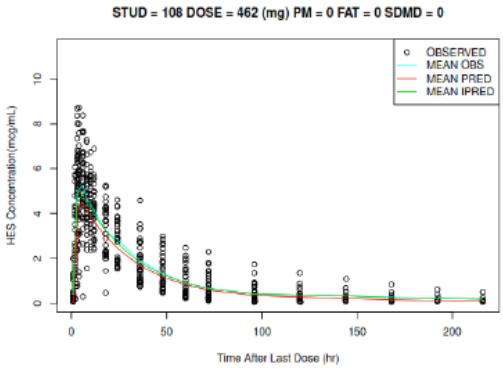

STUD = 105 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

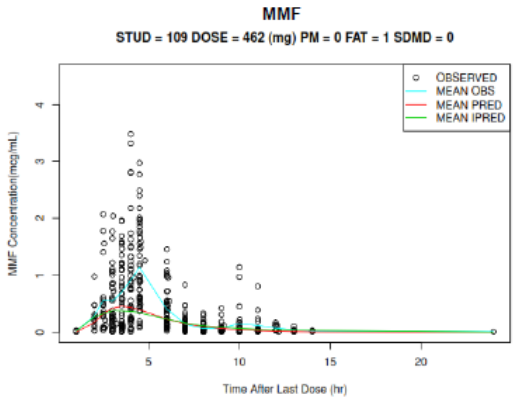

STUD = 105 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

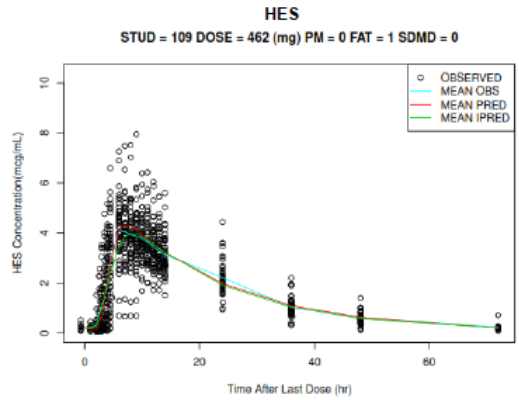

MMF
STUD = 106 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

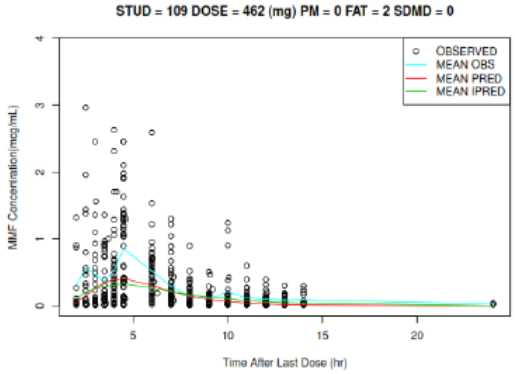

HES
STUD = 106 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)


STUD = 108 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)


STUD = 108 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)


MMF
STUD = 109 DOSE = 462 (mg) PM = 0 FAT = 1 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)


HES
STUD = 109 DOSE = 462 (mg) PM = 0 FAT = 1 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)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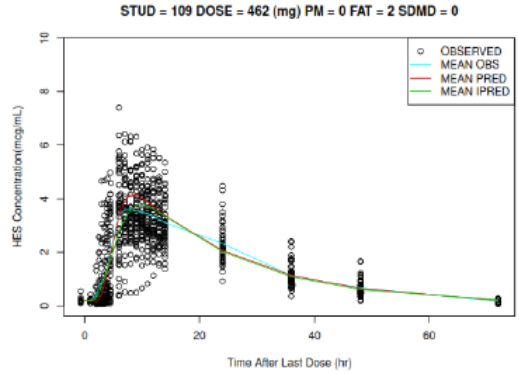
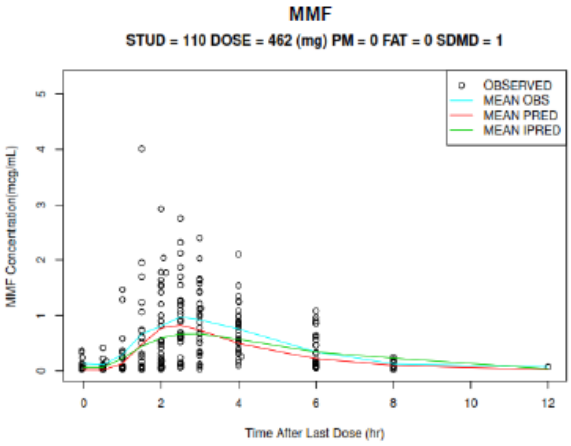
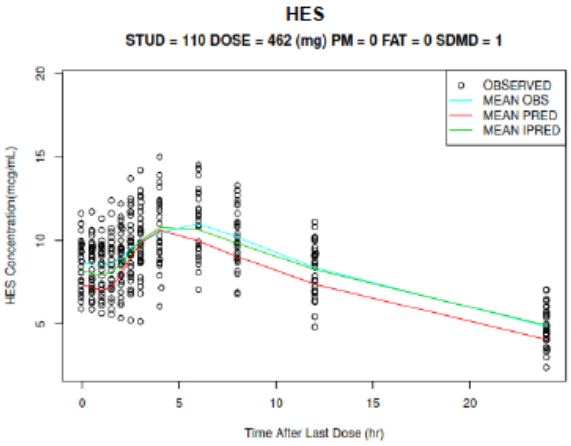
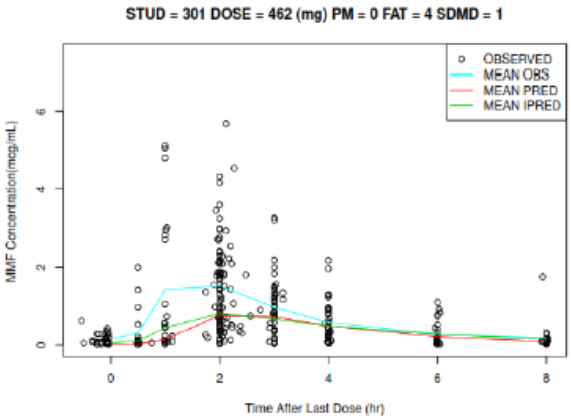
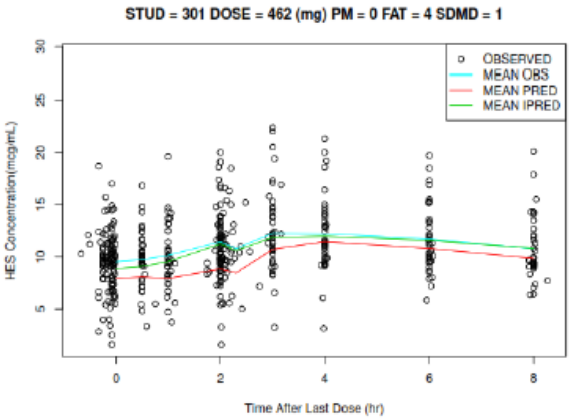
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

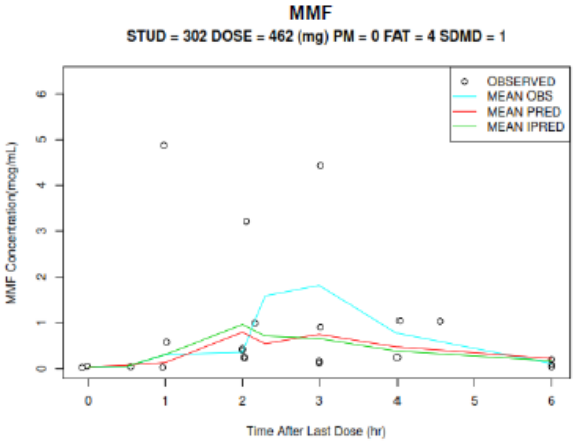

STUD = 109 DOSE = 462 (mg) PM = 0 FAT = 2 SDMD = 0
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)


MMF
STUD = 110 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)


HES
STUD = 110 DOSE = 462 (mg) PM = 0 FAT = 0 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)


STUD = 301 DOSE = 462 (mg) PM = 0 FAT = 4 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)


STUD = 301 DOSE = 462 (mg) PM = 0 FAT = 4 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)


MMF
STUD = 302 DOSE = 462 (mg) PM = 0 FAT = 4 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
MMF Concentration(mcg/mL)
Time After Last Dose (hr)

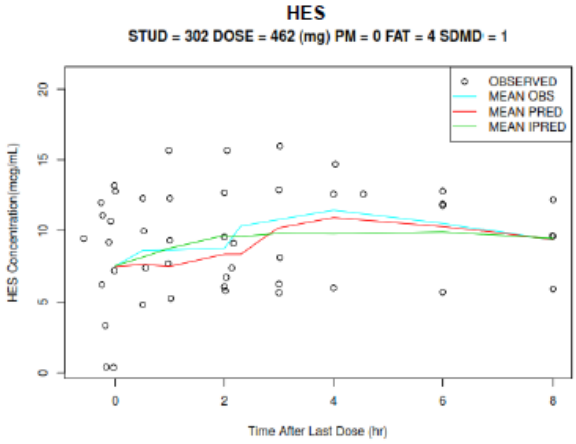
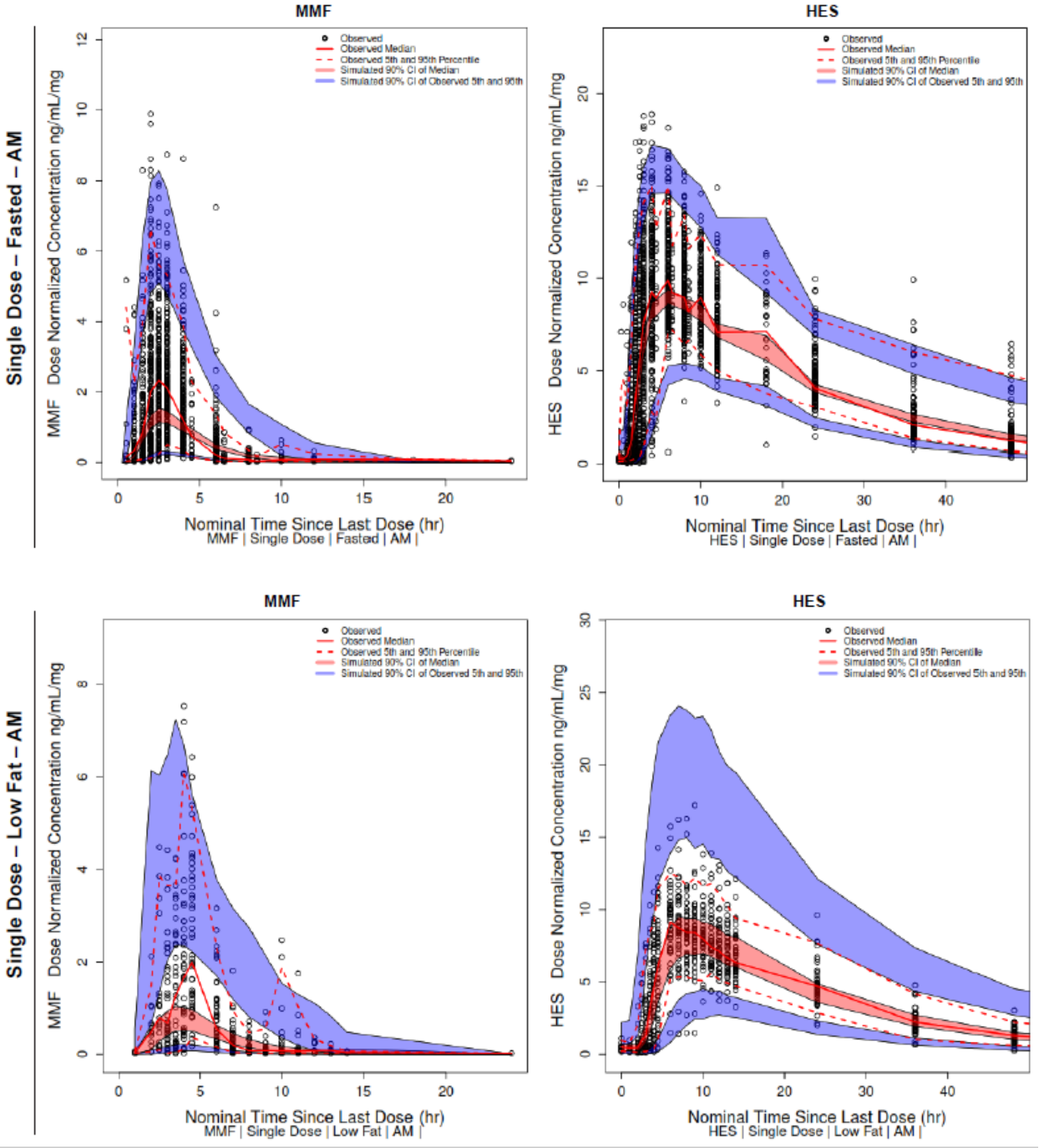
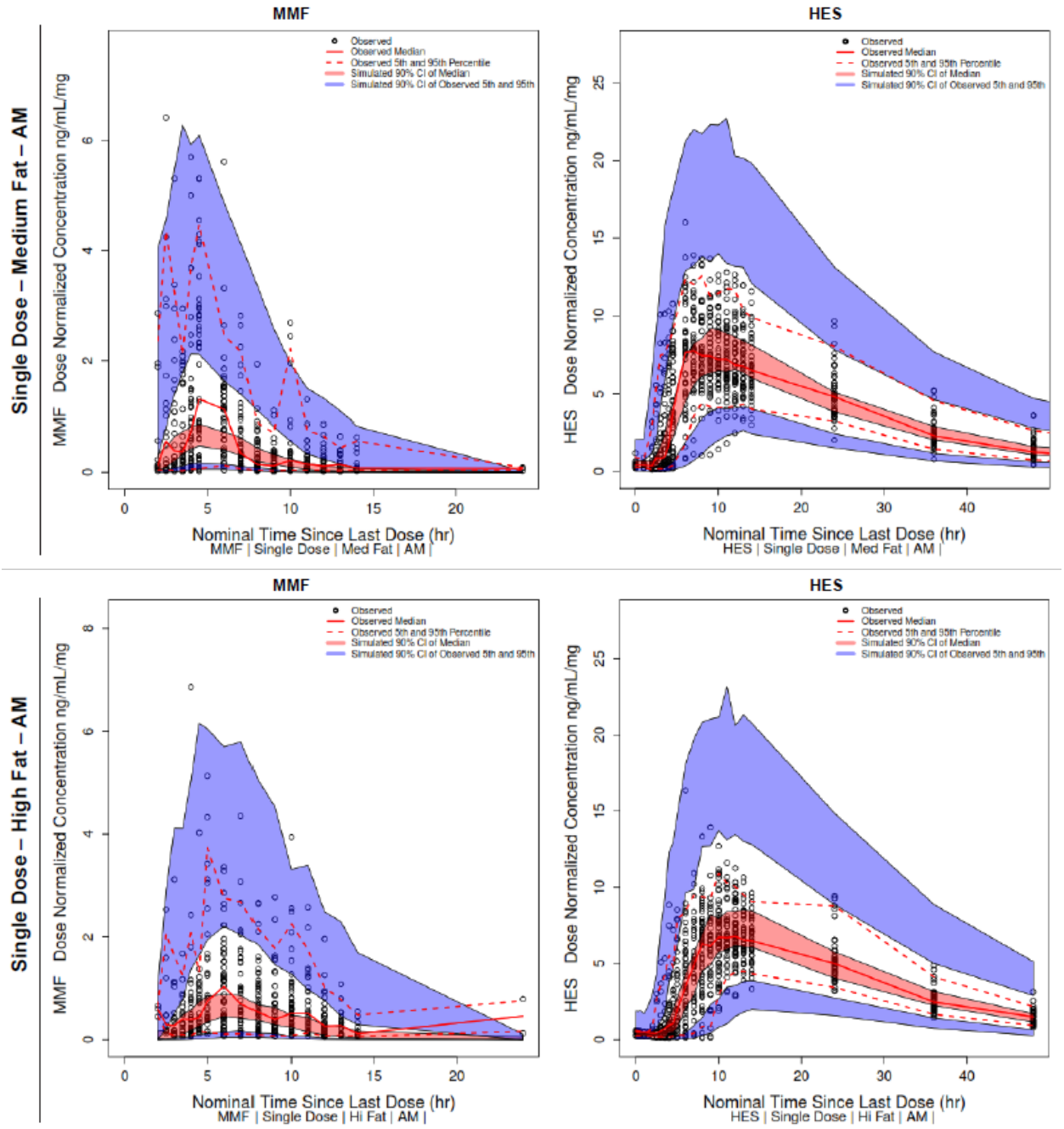
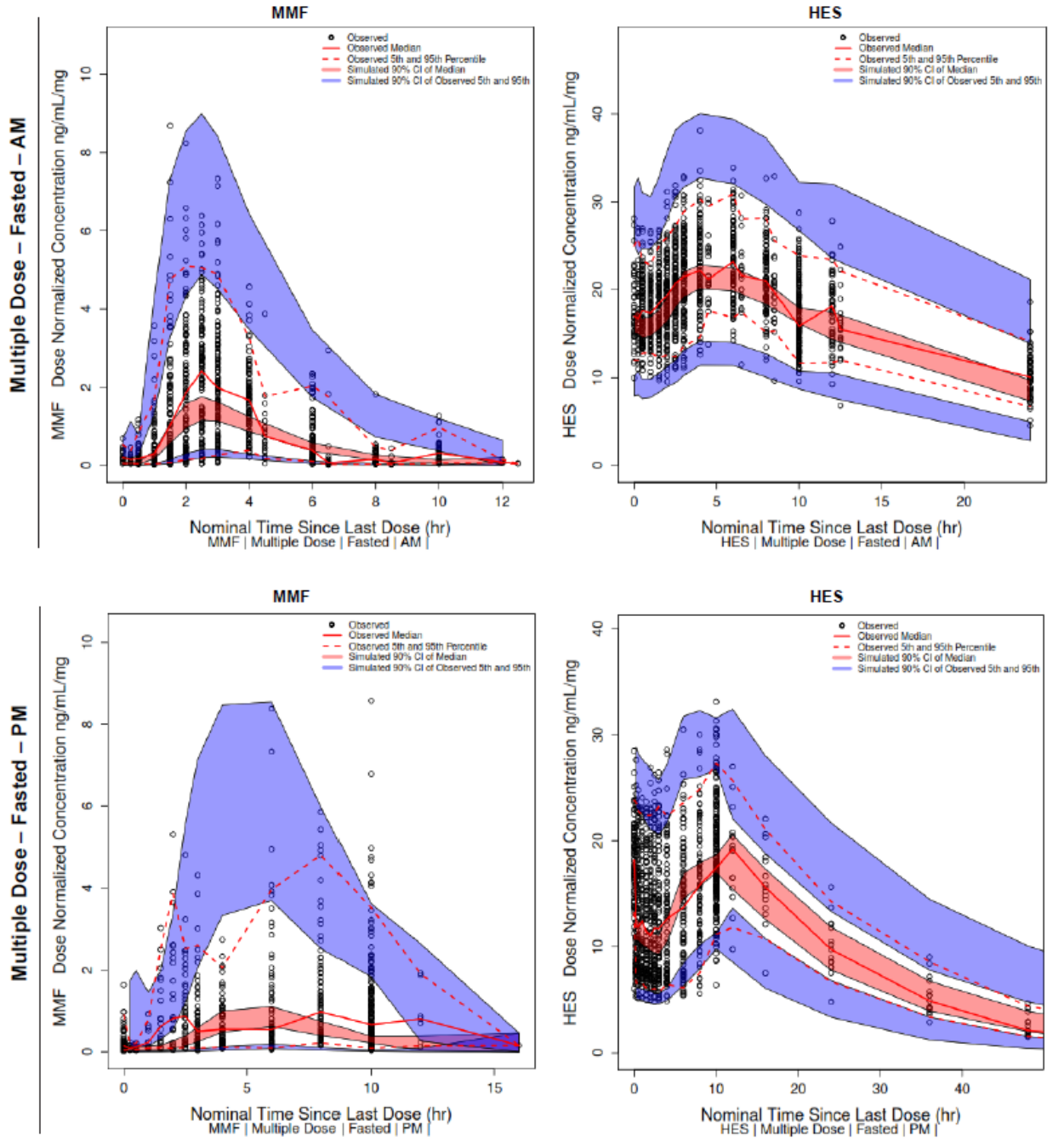
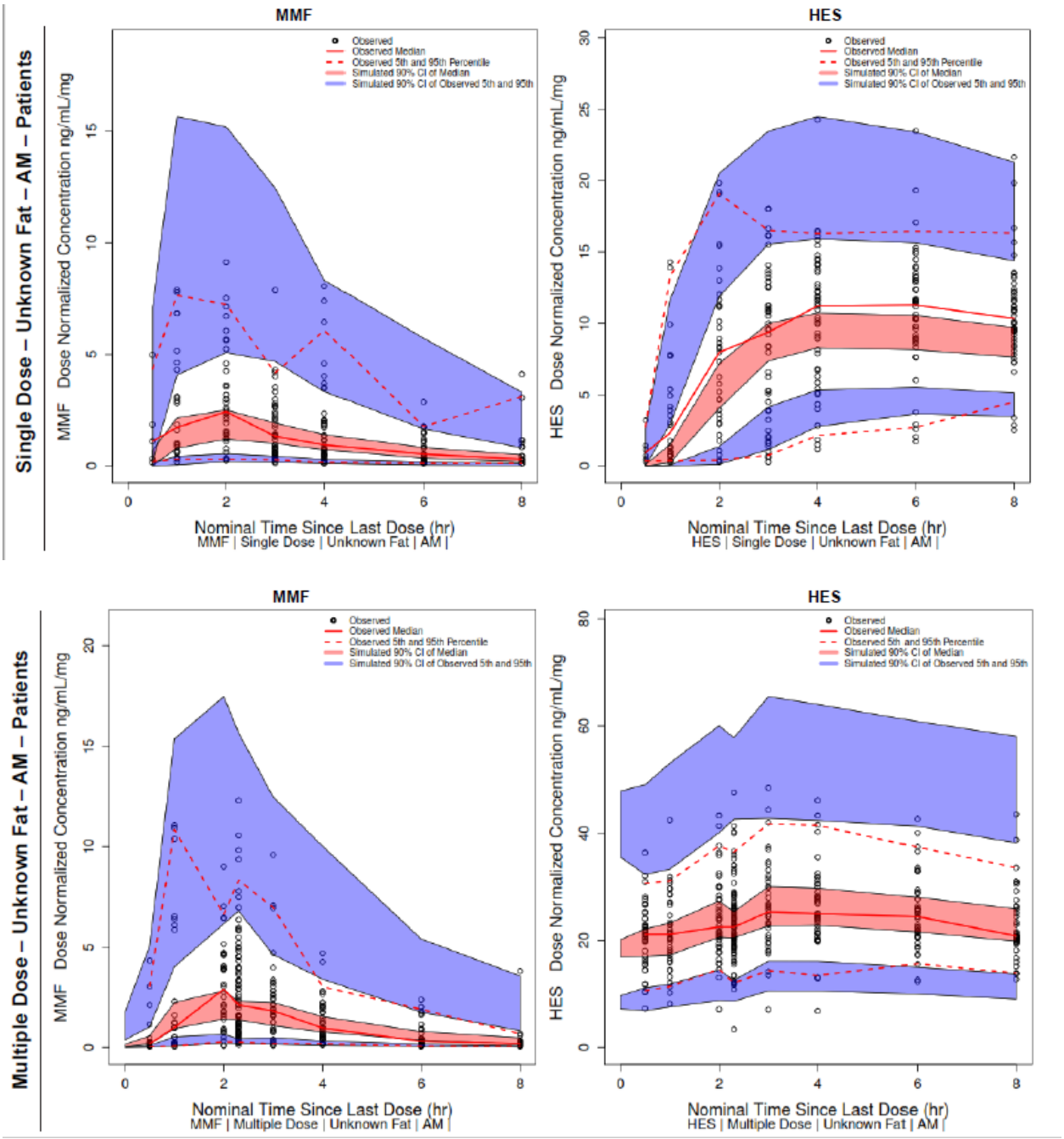

HES
STUD = 302 DOSE = 462 (mg) PM = 0 FAT = 4 SDMD = 1
OBSERVED
MEAN OBS
MEAN PRED
MEAN IPRED
HES Concentration(mcg/mL)
Time After Last Dose (hr)

Fig. S5 Visual predictive check for the MMF and HES final model. *AM* morning dose, *CI* confidence interval, *HES* 2 hydroxyethyl succinimide, *Hi* high, *Med* medium, *MMF* monomethyl fumarate, *PM* evening dose




Single Dose – Medium Fat – AM
MMF
HES
Observed
Observed Median
Observed 5th and 95th Percentile
Simulated 90% CI of Median
Simulated 90% CI of Observed 5th and 95th
MMF Dose Normalized Concentration ng/mL/mg
HES Dose Normalized Concentration ng/mL/mg
Nominal Time Since Last Dose (hr)
MMF | Single Dose | Med Fat | AM |
HES | Single Dose | Med Fat | AM |
Single Dose – High Fat – AM
MMF | Single Dose | Hi Fat | AM |
HES | Single Dose | Hi Fat | AM |


Multiple Dose – Fasted – AM
MMF
HES
Observed
Observed Median
Observed 5th and 95th Percentile
Simulated 90% CI of Median
Simulated 90% CI of Observed 5th and 95th
MMF Dose Normalized Concentration ng/mL/mg
HES Dose Normalized Concentration ng/mL/mg
Nominal Time Since Last Dose (hr)
MMF | Multiple Dose | Fasted | AM |
HES | Multiple Dose | Fasted | AM |
Multiple Dose – Fasted – PM
MMF | Multiple Dose | Fasted | PM |
HES | Multiple Dose | Fasted | PM |


Single Dose – Unknown Fat – AM – Patients
MMF
HES
Observed
Observed Median
Observed 5th and 95th Percentile
Simulated 90% CI of Median
Simulated 90% CI of Observed 5th and 95th
MMF Dose Normalized Concentration ng/mL/mg
HES Dose Normalized Concentration ng/mL/mg
Nominal Time Since Last Dose (hr)
MMF | Single Dose | Unknown Fat | AM |
HES | Single Dose | Unknown Fat | AM |
Multiple Dose – Unknown Fat – AM – Patients
MMF | Multiple Dose | Unknown Fat | AM |
HES | Multiple Dose | Unknown Fat | AM |