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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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](image)

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 $\alpha = 0.001$ ($\Delta$ 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 \( \theta_{ij} \) is the individual value of the parameter (e.g., clearance [CL]) for the \( i^{th} \) individual at the \( j^{th} \) occasion, \( \theta_{TV} \) is the typical value model parameter, \( \eta_i \) denotes the interindividual random effect accounting for the \( i^{th} \) individual’s deviation from the typical value, and \( \kappa_{ij} \) denotes the intraindividual random effect accounting for the \( i^{th} \) individual’s deviation at the \( j^{th} \) occasion.

The \( \eta_i \)'s (\( \kappa_{ij} \)'s) are assumed to have a normal distribution with a zero mean and variance \( \omega^2 \) (\( \psi^2 \)). The approximate percent coefficient of variation (%CV) was reported as:

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

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 \( \Omega_{IIV} \). A diagonal \( \Omega \) 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 \( \varepsilon_{ij} \) denotes the residual random variable, which is assumed to have normal distribution with zero mean and variance \( \sigma^2 \).

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 $\theta_{REF}$ and $\theta_x$ 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:

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

where $\theta_{REF}$ and $\theta_x$ 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 $\theta_x$ 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 ($\Delta$ OFV) of two hierarchical models ($-2 \log$-likelihood) is asymptotically $\chi^2$ 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., $\Delta$ OFV < 10.8 [$\alpha = 0.001$, 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 (AUC0-12h,ss) and maximum plasma concentration over 12 hours (Cmax0-12h,ss) values were calculated for a morning dose at steady state. The mean AUC0-12h,ss and Cmax0-12h,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 14C-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 (KaMMF) (Run 68). In subsequent runs, both low- and medium-fat meal covariates were additionally applied to MMF bioavailability (F1) and to Ka of HES (KaHES) (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 KaMMF and on KaHES (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 (\(K_{a_{MMF}}\) and \(K_{a_{HES}}\)) 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 \(K_{a_{MMF}}\) and 30.9% for \(K_{a_{HES}}\). The corresponding IIV estimates for \(K_{a_{MMF}}\) and \(K_{a_{HES}}\) 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 \(K_{a_{HES}}\) was not well estimated (confidence interval of the estimate included zero). An additional model was tested in which IOV was estimated only for \(K_{a_{MMF}}\) (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 |
| \(K_{a_{MMF}}\) | PTST |
| \(K_{a_{HES}}\) | 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 $\alpha = 0.001$ (i.e., $\Delta$ 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     | $\Delta$ 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**

```plaintext
$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 RICRCNL 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 = (HESABS);6
  COMP = (MMFTABS);7
  COMP = (HESABS);8
  COMP = (MMFTABS);9
  COMP = (HESABS);10
  COMP = (MMFTABS);11
  COMP = (HESABS);12
  COMP = (MMFTABS);13
  COMP = (HESABS);14
  COMP = (MMFTABS);15
  COMP = (HESABS);16
  COMP = (MMFTABS);17
  COMP = (HESABS);18
  COMP = (MMFTABS);19
  COMP = (HESABS);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
  TOCC=0
  IF(STUD.GE.110) TOCC=OCC+1
  IF(STUD.EQ.102.AND.NMID.GE.71.AND.OCC.LE.1) TOCC=1
  IF(STUD.EQ.102.AND.NMID.GE.71.AND.OCC.GE.2) TOCC=2
  BOVAM1=0
  BOVAM2=0
  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
$\text{ERROR (OBSERVATION ONLY)}$

\begin{align*}
\text{IF} & \ (\text{CMT.EQ.2.AND.PM1.EQ.0.AND.FAT.EQ.0}) \ W = \sqrt{\text{THETA}(4)^2} \\
\text{IF} & \ (\text{CMT.EQ.2.AND.PM1.EQ.0.AND.FAT.GE.1.AND.FAT.LE.3}) \ W = \sqrt{\text{THETA}(29)^2} \\
\text{IF} & \ (\text{CMT.EQ.2.AND.PM1.EQ.1.AND.FAT.EQ.0}) \ W = \sqrt{\text{THETA}(30)^2} \\
\text{IF} & \ (\text{CMT.EQ.2.AND.FAT.EQ.4}) \ W = \sqrt{\text{THETA}(31)^2} \\
\text{IF} & \ (\text{CMT.EQ.3.AND.PM1.EQ.0.AND.FAT.EQ.0}) \ W = \sqrt{\text{THETA}(5)^2} \\
\text{IF} & \ (\text{CMT.EQ.3.AND.PM1.EQ.0.AND.FAT.GE.1.AND.FAT.LE.3}) \ W = \sqrt{\text{THETA}(32)^2} \\
\text{IF} & \ (\text{CMT.EQ.3.AND.PM1.EQ.1.AND.FAT.EQ.0}) \ W = \sqrt{\text{THETA}(33)^2} \\
\text{IF} & \ (\text{CMT.EQ.3.AND.FAT.EQ.4}) \ W = \sqrt{\text{THETA}(34)^2} \\
\end{align*}

\begin{align*}
\text{IF} & \ (F.GT.0) \ \text{THEN} \\
\text{IPRED} & = \log(F) \\
Y & = \text{IPRED} + W*\text{ERR(1)} \\
\text{IRES} & = DV - \text{IPRED} \\
\text{IWRES} & = \text{IRES}/W \\
\text{ELSE} \\
Y & = 0 \\
\text{IPRED} & = 0 \\
\text{IRES} & = 0 \\
\text{IWRES} & = 0 \\
\text{ENDIF} \\
$\text{THETA}$ \\
\begin{align*}
(0,15) & ;1 \text{ CLMMF} \\
(0,30) & ;2 V2 \\
(0,5) & ;3 \text{ KAMMF} \\
(0,8) & ;4 \text{ RE MMF} \\
(0,0.3) & ;5 \text{ RE HES} \\
(0,3) & ;6 \text{ KAHES} \\
(0,2) & ;7 \text{ CLHES} \\
(0,6 \text{ FIX}) & ;8 \text{ F4} \\
(0,2,1) & ;9 \text{ F1} \\
(0,8) & ;10 \text{ WT ON V2} \\
(-0.592 \text{ FIX}) & ;11 \text{ PM DOSING ON KAM} \\
(-0.368 \text{ FIX}) & ;12 \text{ LOW FAT ON KAM} \\
(-0.512 \text{ FIX}) & ;13 \text{ MED FAT ON KAM} \\
(-0.666 \text{ FIX}) & ;14 \text{ HI FAT ON KAM} \\
(-1,0,1) & ;15 \text{ UNK FAT ON KAM} \\
(-0.296 \text{ FIX}) & ;16 \text{ LOW FAT ON F1} \\
(-0.301 \text{ FIX}) & ;17 \text{ MED FAT ON F1} \\
(-0.131 \text{ FIX}) & ;18 \text{ HI FAT ON F1} \\
(-0.267 \text{ FIX}) & ;19 \text{ PM DOSING ON KAH} \\
(-0.335 \text{ FIX}) & ;20 \text{ LOW FAT ON KAH} \\
(-0.492 \text{ FIX}) & ;21 \text{ MED FAT ON KAH} \\
(-0.621 \text{ FIX}) & ;22 \text{ HI FAT ON KAH} \\
(-1,0,1) & ;23 \text{ UNK FAT ON KAH} \\
(1.96 \text{ FIX}) & ;24 \text{ PM DOSING ON ALAG4} \\
(0,421 \text{ FIX}) & ;25 \text{ LOW FAT ON ALAG4} \\
(0,8) & ;26 \text{ EGFR ON CLH} \\
(0,7) & ;27 \text{ WT ON CLM} \\
(0,3) & ;28 \text{ WT ON CLH} \\
(0,9) & ;29 \text{ RE MMF PM=0 \& FAT>=1 <=3} \\
(0,9) & ;30 \text{ RE MMF PM=1} \\
(0,9) & ;31 \text{ RE MMF FAT=4} \\
(0,3) & ;32 \text{ RE HES PM=0 \& FAT>=1 <=3}
\end{align*}
$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

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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/m²) |     |      |      |      |      |      |      |      |      |             |             |       |     |
| 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  | 3.7  | 3.7  | 3.5  | 3.5  | 3.9  | 3.0  | 4.0         | 3.0         | 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 | 18.0        | 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    | 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   | 0.78   | 0.48   | 0.46   | 0.53   | 0.55   | 0.36   | 0.28   | 0.53   |        |        |        |
| Median                          | 0.51   | 0.48   | 0.53   | 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   | 0.12   | 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*
| 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            |
| Sex        |     |      |      |      |      |      |      |      |      |             |             | 389          |
| Male       |     | 15   | 27   | 25   | 27   | 10   | 24   | 16   | 22   | 20          | 10          | 197 (50.6)   |
| Female     |     | 39   | 34   | 10   | 15   | 0    | 6    | 16   | 25   | 10          | 34          | 192 (49.3)   |
| Race       |     |      |      |      |      |      |      |      |      |             |             |              |
| White      |     | 39   | 40   | 23   | 30   | 4    | 19   | 25   | 31   | 9           | 34          | 258 (66.3)   |
| Black      |     | 11   | 18   | 12   | 11   | 6    | 10   | 6    | 15   | 21          | 10          | 120 (30.8)   |
| Asian      |     | 3    | 1    | 0    | 1    | 0    | 1    | 0    | 0    | 0           | 0           | 6 (1.5)      |
| Other      |     | 1    | 2    | 0    | 0    | 0    | 0    | 1    | 1    | 0           | 0           | 5 (1.2)      |
| Ethnicity  |     |      |      |      |      |      |      |      |      |             |             |              |
| Not Hispanic |   | 30   | 36   | 20   | 21   | 8    | 28   | 30   | 29   | 27          | 37          | 270 (69.4)   |
| Hispanic   |     | 24   | 25   | 15   | 21   | 2    | 2    | 2    | 18   | 3           | 7           | 119 (30.5)   |
| Dose group |     |      |      |      |      |      |      |      |      |             |             |              |
| 49 mg      |     | 6    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| 105 mg     |     | 6    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| 210 mg     |     | 6    | 15   | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| 231 mg     |     | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 43   | 4           | 4           | 47           |
| 420 mg     |     | 18   | 31   | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| 462 mg     |     | 0    | 0    | 35   | 42   | 10   | 30   | 32   | 47   | 30          | 40          | 270          |
| 630 mg     |     | 6    | 15   | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| 840 mg     |     | 6    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| 924 mg     |     | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 29   | 0           | 0           | 29           |
| 980 mg     |     | 6    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| Fat content |     |      |      |      |      |      |      |      |      |             |             |              |
| None       |     | 54   | 61   | 35   | 0    | 10   | 30   | 32   | 0    | 30          | 0           | 0            |
| Low        |     | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 47   | 0           | 0           | 0            |
| Moderate   |     | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 47   | 0           | 0           | 0            |
| High       |     | 0    | 16   | 0    | 42   | 0    | 0    | 0    | 0    | 0           | 0           | 0            |
| Unknown    |     | 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            |
| Fed        |     | 0    | 16   | 0    | 42   | 0    | 0    | 0    | 47   | 0           | 0           | 0            |

Table S2  Categorical covariate data summary by study
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|---------|---|---|---|---|---|---|---|---|---|---|---|
| Renal function (CRCL)<sup>a</sup> | | | | | | | | | | | |
| Normal | 53 | 57 | 34 | 41 | 9 | 28 | 8 | 47 | 28 | 35 | 3 |
| Mild | 1 | 4 | 1 | 1 | 1 | 2 | 10 | 0 | 2 | 8 | 1 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 1 | 0 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal function (eGFR)<sup>b</sup> [1] | | | | | | | | | | | |
| Normal | 46 | 49 | 27 | 36 | 9 | 21 | 7 | 41 | 26 | 29 | 3 |
| Mild | 8 | 12 | 8 | 6 | 1 | 9 | 10 | 6 | 3 | 14 | 1 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 0 | 1 | 1 | 0 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| Participant type | | | | | | | | | | | |
| Healthy participants | 54 | 61 | 35 | 42 | 10 | 30 | 32 | 47 | 30 | 0 | 0 |
| Patients | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 44 | 4 |
| Dose prior to serial PK samples | | | | | | | | | | | |
| Morning dose | 54 | 61 | 35 | 42 | 10 | 30 | 32 | 47 | 30 | 44 | 4 |
| Evening dose | 0 | 45 | 0 | 0 | 0 | 0 | 29 | 22 | 1 | 97 | 4 |

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

<sup>a</sup> CRCL calculated using Cockcroft-Gault equation

<sup>b</sup> 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

| Study       | 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         | 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

|                   | PK samples | Quantifiable (> LLOQ) | Total BLQ | BLQ by sampling time |
|-------------------|------------|-----------------------|-----------|----------------------|
|                   | n          | No. of samples        | n         | No. of samples       | n          | No. of samples |
| 001               | 42         | 588                   | 42        | 192                  | 42         | 150           |
| A102              | 61         | 2844                  | 61        | 322                  | 61         | 260           |
| A103              | 35         | 594                   | 35        | 142                  | 35         | 107           |
| A104              | 42         | 882                   | 42        | 257                  | 42         | 215           |
| A105              | 10         | 160                   | 10        | 45                   | 10         | 35            |
| A106              | 30         | 508                   | 30        | 121                  | 30         | 91            |
| A108              | 32         | 670                   | 32        | 515                  | 31         | 28            |
| A109              | 47         | 1903                  | 47        | 296                  | 47         | 224           |
| A110              | 30         | 708                   | 30        | 708                  | 0          | 0             |
| EVOLVE-MS-1       | 44         | 811                   | 44        | 113                  | 44         | 38            |
| EVOLVE-MS-2       | 4          | 78                    | 4         | 15                   | 4          | 11            |
| Total             | 377        | 9746                  | 377       | 8088                 | 346        | 335           |

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<sub>MMF</sub> | 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<sub>MMF</sub> | 4.85    | 0.156 | 3.2   | (4.55, 5.16) | h<sup>-1</sup> |     |
| 6 Ka<sub>HES</sub> | 3.17     | 0.0818 | 2.6 | (3.01, 3.33) | h<sup>-1</sup> |     |
| 7 CL<sub>HES</sub> | 1.54     | 0.0175 | 1.1  | (1.51, 1.58) | L/h   |                 |
| 8 F4            | 0.6 FIXED | 0.0175 | 1.1  | (0.59, 0.67) | L/h   |                 |
| 9 F1            | 0.166     | 0.00732 | 4.4  | (0.152, 0.181) | L/h   |                 |
| 10 WT on Vc     | 0.813     | 0.0772 | 9.5  | (0.661, 0.964) | L/h   |                 |
| 11 PM dosing on Ka<sub>MMF</sub> | −0.592 | 0.0141 | 2.3  | (−0.620, −0.565) | h<sup>-1</sup> |     |
| 12 LOW on Ka<sub>MMF</sub> | −0.368 | 0.0455 | 12.3 | (−0.457, −0.279) | h<sup>-1</sup> |     |
| 13 MED on Ka<sub>MMF</sub> | −0.512 | 0.0332 | 6.4  | (−0.577, −0.447) | h<sup>-1</sup> |     |
| 14 HI on Ka<sub>MMF</sub> | −0.666 | 0.0182 | 2.6  | (−0.702, −0.630) | h<sup>-1</sup> |     |
| 17 LOW on F1    | −0.296    | 0.0489 | 16.4 | (−0.392, −0.200) | h<sup>-1</sup> |     |
| 18 MED on F1    | −0.301    | 0.0478 | 15.8 | (−0.395, −0.208) | h<sup>-1</sup> |     |
| 19 HI on F1     | −0.131    | 0.0569 | 42.6 | (−0.241, −0.0213) | h<sup>-1</sup> |     |
| 26 PM dosing on Ka<sub>HES</sub> | −0.267 | 0.0492 | 18.3 | (−0.364, −0.171) | h<sup>-1</sup> |     |
| 27 LOW on Ka<sub>HES</sub> | −0.335 | 0.0432 | 12.8 | (−0.420, −0.251) | h<sup>-1</sup> |     |
| 28 MED on Ka<sub>HES</sub> | −0.492 | 0.0315 | 6.3  | (−0.554, −0.43) | h<sup>-1</sup> |     |
| 29 HI on Ka<sub>HES</sub> | −0.621 | 0.00847 | 1.3  | (−0.638, −0.604) | h<sup>-1</sup> |     |
| 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<sub>MMF</sub> | 26.8     | (22.7, 30.3) | %CV | 27.7 |
| 2 ETA2 - Vc | 17.3 | (14.8, 19.5) | %CV | 23.7 |
| 5 ETA5 - CLHES | 16.2 | (14.3, 17.8) | %CV | 17.3 |
| 3 ETA3 - KaMMMF | 36.2 | (32.2, 39.8) | %CV | 13.1 |
| 4 ETA4 - KaHES | 38.2 | (34.7, 41.3) | %CV | 5.2 |

| OFV | -1460.77 |

%CV: percent coefficient of variation, AลาAG4: 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

* Shrinkage estimate for epsilon was 5.2%

Model equations:

\[ CL_{MMF,i} = 14.1 \cdot \exp(\eta_i^{CLMMF}) \]
\[ CL_{HES,i} = 1.54 \cdot \exp(\eta_i^{CLHES}) \]
\[ V_{Cl} = 30.7 \cdot \left(\frac{WT}{78}\right)^{0.813} \cdot \exp(\eta_i^{Vc}) \]
\[ Ka_{MMF,i} = 4.85 \cdot \left(1 + PM \cdot (-0.592)\right) \cdot \left(1 + LOW \cdot (-0.368)\right) \cdot \left(1 + MED \cdot (-0.512)\right) \cdot \left(1 + HI \cdot (-0.666)\right) \cdot \exp(\eta_i^{KaMMF}) \]
\[ Ka_{HES,i} = 3.17 \cdot \left(1 + PM \cdot (-0.267)\right) \cdot \left(1 + LOW \cdot (-0.335)\right) \cdot \left(1 + MED \cdot (-0.492)\right) \cdot \left(1 + HI \cdot (-0.621)\right) \cdot \exp(\eta_i^{KaHES}) \]

\[ F1 = 0.166 \cdot \left(1 + LOW \cdot (-0.296)\right) \cdot \left(1 + MED \cdot (-0.301)\right) \cdot \left(1 + HI \cdot (-0.131)\right) \]
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 (%) |
|-----------------|----------|------|-------|--------------|-------|---------------|
| 1 CL<sub>MMF</sub> | 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 K<sub>MMF</sub> | 5.38     | 0.151 | 2.8   | (5.08, 5.68) | h<sup>-1</sup> |   |
| 6 K<sub>HES</sub> | 3.38     | 0.078 | 2.3   | (3.22, 3.53) | h<sup>-1</sup> |   |
| 7 CL<sub>HES</sub> | 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 K<sub>MMF</sub> | −0.592 FIXED | |     |              |       |               |
| 12 LOW on K<sub>MMF</sub> | −0.368 FIXED | |     |              |       |               |
| 13 LOW on K<sub>MMF</sub> | −0.512 FIXED | |     |              |       |               |
| 14 HI on K<sub>MMF</sub> | −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 K<sub>HES</sub> | −0.267 FIXED | |     |              |       |               |
| 20 LOW on K<sub>HES</sub> | −0.335 FIXED | |     |              |       |               |
| 21 MED on K<sub>HES</sub> | −0.492 FIXED | |     |              |       |               |
| 22 HI on K<sub>HES</sub> | −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<sub>HES</sub> | 0.546 | 0.0329 | 6.0 | (0.481, 0.61) |       |               |
| 27 WT on CL<sub>MMF</sub> | 0.824 | 0.101 | 12.2 | (0.627, 1.02) |       |               |
| 28 WT on CL<sub>HES</sub> | 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<sup>a</sup>) | 103 | 2.09 | 2.0 | (98.8, 107) | % |
| 30 RE MMF (PM dose, fasted) | 111 | 3.69 | 3.3 | (104, 118) | % |
|   | RE MMF (UNK) | RE HES (AM dose, fed) | RE HES (PM dose, fasted) | RE HES (UNK) |
|---|--------------|-----------------------|--------------------------|--------------|
| 1 | 102          | 46.9                  | 18.4                     | 37.4         |
| 2 | 3.45         | 0.745                 | 0.407                    | 1.09         |
| 3 | (3.4)        | (1.6)                 | (2.2)                    | (2.9)        |
| 4 | (94.9, 108)  | (45.4, 48.3)          | (17.6, 19.2)             | (35.3, 39.6) |

IIV

|   | ETA1 - CL\text{MMF} | ETA2 - Vc | ETA5 - CL\text{HES} | ETA3 - K\text{MMF} | ETA4 - K\text{HES} |
|---|----------------------|-----------|----------------------|---------------------|---------------------|
| 1 | 24.5                 | 19.6      | 18.4                 | 39.8                | 43.7                |
| 2 | (20.8, 27.7)         | (17.2, 21.8) | (16.7, 20.0)         | (35.8, 43.4)       | (40.3, 46.8)       |
| 3 | %CV 29.2             | %CV 19.8  | %CV 14.1             | %CV 13.4           | %CV 4.42           |

OFV \text{–} 3112.3

%CV percent coefficient of variation, \text{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}

\* Shrinkage estimate for epsilon was 5.6\%

\^ 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\text{MMF}; low fat, medium fat, high fat on F1; low fat, medium fat, high fat, and PM dosing on Ka\text{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\text{MMF}, WT on CL\text{HES}, WT on Vc, eGFR on CL\text{HES}

Model equations:

\[
\text{CL}_{\text{MMF},i} = 12.7 \cdot \left(\frac{WT}{78}\right)^{0.824} \cdot \exp(\eta_{i\text{CL\text{MMF}}})
\]

\[
\text{CL}_{\text{HES},i} = 1.47 \cdot \left(\frac{\text{eGFR}}{111.9}\right)^{0.546} \cdot \left(\frac{WT}{78}\right)^{0.335} \cdot \exp(\eta_{i\text{CL\text{HES}}})
\]

\[
\text{Vc}_i = 30.4 \cdot \left(\frac{WT}{78}\right)^{0.884} \cdot \exp(\eta_{i\text{Vc}})
\]

\[
\text{Ka}_{\text{MMF},i} = 5.38 \cdot (1 + PM \cdot (-0.592)) \cdot (1 + LOW \cdot (-0.368)) \cdot (1 + MED \cdot (-0.512)) \cdot (1 + HI \cdot (-0.666)) \cdot \exp(\eta_{i\text{K\text{AMMF}}})
\]

\[
\text{Ka}_{\text{HES},i} = 3.38 \cdot (1 + PM \cdot (-0.267)) \cdot (1 + LOW \cdot (-0.335)) \cdot (1 + MED \cdot (-0.492)) \cdot (1 + HI \cdot (-0.621)) \cdot \exp(\eta_{i\text{K\text{AHES}}})
\]

\[
F1 = 0.158 \cdot (1 + LOW \cdot (-0.296)) \cdot (1 + MED \cdot (-0.301)) \cdot (1 + HI \cdot (-0.131))
\]
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$_{0-12h,ss}$ area under the concentration–time profile from 0 to 12 h at steady state, C$_{\text{max}0-12h,ss}$ maximum plasma concentration over 12 h at steady state, eGFR estimated glomerular filtration rate, HES 2 hydroxyethyl succinimide, MMF monomethyl fumarate, MS multiple sclerosis
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.
**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.
