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ARTICLE

Population Pharmacokinetics of Fosdagrocorat (PF-04171327), a Dissociated Glucocorticoid Receptor Agonist, in Patients With Rheumatoid Arthritis

Barry Weatherley[1], Lynn McFadyen[1] and Brinda Tammara[2,*]

Dissociated agonists of the glucocorticoid receptor (DAGRs) show similar antiinflammatory effects but improved tolerability compared with standard glucocorticoid receptor (GR) agonists. The prodrug fosdagrocorat (PF-04171327), with active DAGR metabolite PF-00251802 (Metabolite-1), is postulated to show superior efficacy over placebo and prednisone in patients with moderate to severe rheumatoid arthritis (RA). We investigated the population pharmacokinetics of active Metabolite-1 and its active metabolite PF-04015475 (Metabolite-2) in patients with moderate to severe RA enrolled in a 12-week, phase II, randomized, double-blind study (NCT01393639). A simultaneous fit of a two-compartment model for Metabolite-1 and a one-compartment model for Metabolite-2 provided an adequate fit to the data. Significant covariates included weight, with an additional female effect on clearance of Metabolite-1 (~26%) and Metabolite-2 (~33%) compared with males. Age influenced clearance of Metabolite-1. In combination, age, weight, and sex predicted >twofold differences in area under the concentration–time curve of Metabolite-1 at the extremes.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ While glucocorticoids are frequently prescribed, as monotherapy or in combination with disease-modifying antirheumatic drugs, for treatment of rheumatoid arthritis (RA), their use is associated with adverse effects. Fosdagrocorat (PF-04171327) is a phosphate ester prodrug of PF-00251802, a high-affinity, selective glucocorticoid receptor ligand with potent antiinflammatory activity in nonclinical and preclinical models.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ We developed a pharmacokinetic (PK) model for Metabolite-1 and Metabolite-2 after oral administration of fosdagrocorat in RA patients, and performed a limited evaluation of covariates for the PK of Metabolite-1 and Metabolite-2 in the study population.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ This analysis provides an in-depth description of Metabolite-1 and Metabolite-2 PK characteristics of the prodrug fosdagrocorat in patients with RA.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ As part of the drug development process and the characterization of the PK of fosdagrocorat, population PK modeling is key to identifying factors affecting the dose–concentration relationship in a clinically relevant population; in this case, patients with RA.

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the presence of swollen and tender joints.[1] Glucocorticoids, both as monotherapy or in combination with disease-modifying antirheumatic drugs, are frequently prescribed as treatment for patients with RA in order to alleviate disease symptoms and slow disease progression.[2–4] Although glucocorticoids have demonstrated efficacy in RA, their use is associated with adverse effects, including weight gain, osteoporosis, elevated blood pressure, diabetes, gastrointestinal adverse events, and susceptibility to infections.[5–9] As such, new agents that demonstrate equivalent efficacy but have less association with adverse effects are required.

Dissociated agonists of the glucocorticoid receptor are a novel class of agents currently in development. Fosdagrocorat (PF-04171327) is a phosphate ester prodrug of PF-00251802 (hereafter referred to as Metabolite-1), a high-affinity, selective glucocorticoid receptor ligand with potent antiinflammatory activity in nonclinical and preclinical models.[10] Fosdagrocorat does not appear to be absorbed systemically after oral administration in humans, but is converted to Metabolite-1, by alkaline phosphatase in the gut wall lining, which is then absorbed. Metabolite-1 is further converted to the circulating metabolite PF-04015475 (the N-oxide, hereafter referred to as Metabolite-2). Metabolite-1 cannot be administered directly as its free-base form has

[1]Pharmacometrics, Pfizer Global Product Development, Sandwich, Kent, UK; [2]Clinical Pharmacology, Pfizer Inc., Collegeville, Pennsylvania, USA. *Correspondence: Brinda Tammara (brinda.tammara@pfizer.com)
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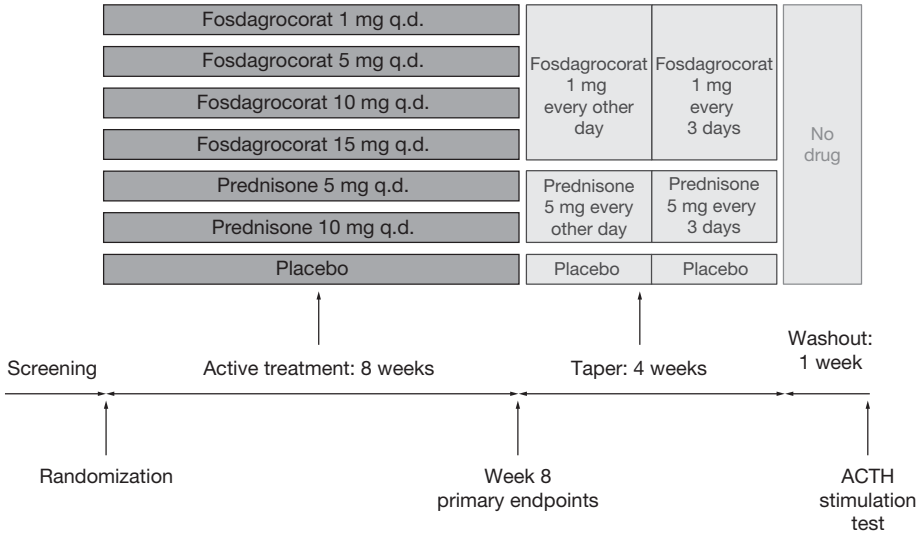

Figure 1 A9391010 study design. ACTH, adrenocorticotropic hormone; q.d., once daily.

relatively low aqueous solubility, resulting in low bioavailability due to dissolution rate-limiting absorption. Previous preclinical and phase I studies have demonstrated that the antiinflammatory effects of fosdagrocorat are observed without triggering the adverse events generally associated with activation of the glucocorticoid receptors by standard agonists.[10–17] An acceptable efficacy and safety profile has been demonstrated in two phase II studies.[18–20]

As part of the drug development process and the characterization of the pharmacokinetics (PK) of fosdagrocorat, population PK modeling is key to identifying factors affecting the dose–concentration relationship in a clinically relevant population[21]; in this case, patients with RA. Previous population modeling of Metabolite-1 in healthy volunteers (Study A9391002; NCT00812825) and in patients with RA (Study A9391005; NCT00938587), using a two-compartment model, suggested a larger clearance in healthy volunteers than in patients with RA (data on file).[20] The objective of this analysis was to develop a PK model for Metabolite-1 and Metabolite-2 after oral administration of fosdagrocorat in patients with RA. A further objective was to perform a limited evaluation of covariates for the PK of Metabolite-1 and Metabolite-2 in the study population.

METHODS

Study design

This study was conducted in accordance with applicable legal and regulatory requirements, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The Institutional Review Boards or Independent Ethics Committees at each investigational center approved the study. All patients provided written, informed consent.

Study A9391010 (NCT01393639) was a 12-week, phase II, randomized, double-blind, dose-ranging study that investigated the safety and efficacy of fosdagrocorat vs. prednisone and placebo in patients with RA who were receiving stable background methotrexate (**Figure 1**).[18] Patients were randomized (1:1:1:1:1:1:1) to receive fosdagrocorat 1, 5, 10, or 15 mg once daily (q.d.), prednisone 5 or 10 mg q.d., or matched placebo for 8 weeks, followed by blinded tapered therapy (all at 1 mg; Q48 h for 2 weeks and then Q72 h for 2 weeks) for 4 weeks and no drug or placebo for 1 week.

Assessments

Only PK data from the fosdagrocorat arms were modeled for Metabolite-1 and Metabolite-2. Blood samples from patients treated with fosdagrocorat 1, 5, 10, and 15 mg q.d. were collected during: the treatment period (Weeks 2, 4, 6, ±3 days) ~24 h after dosing (0 h) with patient-reported dosing; at the end of the treatment period (Week 8, ±3 days) at times 0 and at 1, 2, 3, and 4 h after dosing of study medication in the clinic; and single samples at the taper visits (Weeks 10, 12, ±3 days) at variable times after dose (patient-reported dosing). Plasma samples were extracted and stored at –20°C until analyzed for Metabolite-1 and Metabolite-2 using a validated liquid chromatography-tandem mass spectrometry method at WuXi App Tec (Shanghai, China). The calibration ranges for Metabolite-1 and Metabolite-2 were 1.00–500 ng/mL and 0.50–100 ng/mL, respectively. Any concentration below the level of quantitation (1.00 ng/mL for Metabolite-1 and 0.50 ng/mL for Metabolite-2; called BLQ), were set to 0 in the data set.

Population PK modeling strategy

Nonlinear mixed-effects modeling (NONMEM® 7.2, ICON Development Solutions, Ellicott City, MD) was used with first-order conditional estimation to fit Metabolite-1 and Metabolite-2 data (untransformed domain). R (v. 2.12.2, using R-Studio) was used for data manipulation, for postprocessing, and plotting.

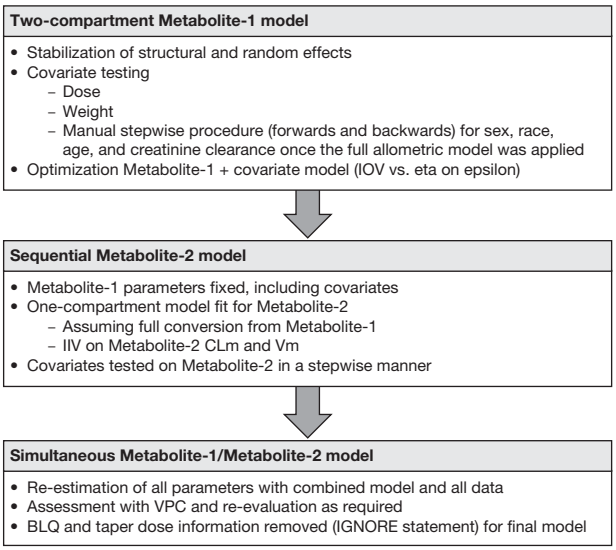

Figure 2 Modeling strategy. BLQ, below level of quantitation; CLm, apparent clearance of Metabolite-2; IIV, interindividual variability; IOV, interoccasion variability; Vm, volume of distribution of Metabolite-2; VPC, visual predictive check.

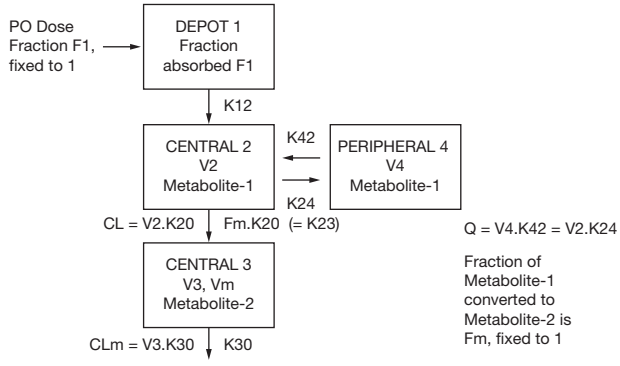

Figure 3 Structural model (sequential for two-compartment Metabolite-1 and one-compartment Metabolite-2). CL, clearance of Metabolite-1; CLm, clearance of Metabolite-2; F1, fraction of fosdagrocorat dose absorbed as Metabolite-1; Fm, fraction of Metabolite-1 converted to Metabolite-2; K12, absorption rate constant; PO, oral; V2, apparent volume of central compartment for Metabolite-1.

Key modeling assumptions applied in the analysis were: 100% of fosdagrocorat is converted to Metabolite-1; a two-compartment disposition model is appropriate for Metabolite-1, based on prior modeling of PK data from healthy volunteers (Study A9391002; NCT00812825) and patients with RA (Study A9391005; NCT00938587); and 100% of Metabolite-1 is converted to Metabolite-2. The 100% conversions were used to prevent overparameterization of the models.

The sequential and subsequent combined modeling strategy that was utilized for the two metabolites is summarized in **Figure 2**. A diagram of the combined models is shown in **Figure 3**. Metabolite-1 was evaluated first, including stabilization of the structural and random effects model, followed by covariate testing on Metabolite-1. A sequential one-compartment model was then applied to Metabolite-2, having fixed Metabolite-1 parameters. Covariates were then tested on the Metabolite-2 model.

The final simultaneous Metabolite-1 and Metabolite-2 model was developed in two stages. The first stage estimated as many parameters as possible for both Metabolite-1 and Metabolite-2 simultaneously. After assessment of the visual predictive check (VPC) diagnostic, the model was further optimized by systematically removing BLQ and taper samples. It was known from preliminary modeling (of 70% of the study data) that data for BLQ values and the taper dosing periods, where dosing times were reported by the patients, made significant contributions to residual variability. The effect of separate and combined exclusions of taper and BLQ data was assessed on variability estimates and VPC.

Predicted individual Metabolite-1 and Metabolite-2 profiles were generated using dummy data profiles. Maximum concentrations could be obtained directly from the dummy profiles and area under the concentration–time curves (AUCs) generated using the linear trapezoidal method of calculation. In addition, Metabolite-2 to Metabolite-1 AUC ratios were calculated.

Random effects

Interindividual variability (IIV) in the PK parameters (clearance (CL), apparent volume of central compartment (V2), and absorption rate constant (K12) for Metabolite-1; clearance (CLm) and central volume V3 (=Vm) for Metabolite-2) was modeled using multiplicative exponential random effects. Additive and proportional residual variabilities were modeled in ordinary space to allow the inclusion of BLQ values as zero concentrations.

IIV was assessed in two ways: by utilizing IIV on the residual variability terms (eta on epsilon) and subsequently removing this to test interoccasion variability (IOV) on the fraction of Metabolite-1 absorbed (F1) on each dosing occasion.

Covariate testing

The base model for covariate testing of Metabolite-1 included dose dependency on K12 and F1 (based on a preliminary population PK analysis of a previous patient study, which covered a larger dose range and showed a dose-dependent effect on K12), using both a power model scaling to, and a linear model centered on, the 10 mg dose, but these were found not to reach significance and were not included at the outset. Thereafter, sequential stepwise covariate modeling was performed manually for Metabolite-1 and Metabolite-2 sequentially, with baseline weight (reference of 70 kg) tested on all disposition parameters and, in addition, age, sex, race, and baseline creatinine clearance tested on Metabolite-1 CL as well as Metabolite-2 CLm. Univariate covariates were included if the objective function value (OFV) change was greater than 3.84 for one degree of freedom (the greater change of power or linear value chosen if both tested). After an allometric or other baseline weight inclusion, other covariates were tested one at a time, with the covariate with the largest change then going forward into the next round (including reintroducing the dose power effect on K12 because of the previous preliminary population PK analysis). After all significant covariates (OFV $>$3.84 for one degree of freedom) had been included, backwards covariate

Table 1 Patient demographics and baseline characteristics

	Fosdagrocorat dose group			
	1 mg	**5 mg**	**10 mg**	**15 mg**
Study patients (*n*)	44	45	45	45
Female (*n*) (%)	32 (72.7)	36 (80.0)	34 (75.6)	34 (75.6)
Mean age (range) (yrs)				
Males	54.8 (26–73)	54.2 (38–67)	52.6 (25–73)	52.4 (29–64)
Females	48.6 (18–78)	54.1 (29–73)	55.4 (34–80)	54.1 (27–84)
Mean weight (SD) (kg)				
Males	77.0 (14.2)	77.0 (15.0)	84.0 (22.7)	83.4 (15.7)
Females	70.5 (23.5)	72.9 (17.6)	70.1 (14.1)	78.0 (21.9)
Mean BCCL (SD) (mL/min)				
Males	107.5 (18.5)	95.1 (34.3)	122.7 (36.4)	128.8 (32.4)
Females	114.0 (41.6)	109.7 (32.5)	100.8 (33.5)	112.3 (38.9)

BCCL, baseline creatinine clearance; *n*, number of patients included in the analysis; SD, standard deviation.

deletion was manually undertaken for an increase of OFV of less than 6.64 for one degree of freedom. For body weight effects, a test of simplification by standard allometric scaling was made, with fixed powers of 1.00 for volume terms and 0.75 for clearance terms.

RESULTS

Patients

Demographics and baseline characteristics of patients included in the study by dose are described in **Table 1**. Blood samples from 179 patients were used in this analysis, of which 1,607 each of Metabolite-1 and Metabolite-2 concentrations were obtained (on average nine per subject per analyte including BLQ and taper concentrations). Metabolite-1 had 69 BLQ concentrations in total, 322 taper concentrations in total, and 42 of the BLQ concentrations during the reduced dose taper period. Metabolite-2 had 65 BLQ concentrations in total, 323 taper concentrations in total, and 37 of the BLQ concentrations during the reduced dose taper period. The majority (76%) of patients were female (contributing 1,224 observations per analyte) and this was consistent across all doses. Although no gender difference was observed in age and creatinine clearance at baseline, mean weight was lower for females compared with males (72.9 and 80.4 kg, respectively).

Base and covariate model for Metabolite-1

Production of Metabolite-1 from fosdagrocorat (100% conversion assumed) was described by a first-order rate constant (K12) without a lag time. Previous modeling of Metabolite-1 had shown that a two-compartment disposition model was appropriate. The model required a fixed value of peripheral volume (initially fixed at 248 L from previous modeling) for the production of a successful covariance step. IIV could only be estimated on CL and K12. When univariate testing with estimation of allometric weight exponents was found to be significant for three of four disposition parameters, a fixed standard allometric scaling simplification was applied (power 0.75 for CL and Metabolite-1 intercompartmental clearance (Q) and power 1.0 for V2 and Metabolite-1 peripheral volume (V4)) (OFV of –41.934). Reestimation of V4 to 209 L produced a further drop in OFV (0.464), so V4 was refixed at this value.

This fixed standard allometric base model was then used for sequential forward and backward testing of the following covariates: dose on K12, age, baseline creatinine clearance, sex and race on CL, and sex on V2. In the forward search, sex on CL entered in round 1 (OFV of –21.695) followed by age on CL in round 2 (OFV of –7.887) and sex on V2 in round 3 (OFV of –3.671) to produce the full model. Sex on CL and age on CL were retained in a backward deletion step. In order to improve individual subject level fits to the data, eta on epsilon (53%) was removed and IOV (33%) was introduced on Metabolite-1 F1 with relatively small effects on fixed-effect parameters, an increase in IIV on CL (42–50%), and a decrease in additive residual error (1.25 ng/mL to 0.998 ng/mL). This model was carried forward for modeling of Metabolite-2.

Metabolite-2 sequential model

The Metabolite-2 data were fit to a one-compartment model with Metabolite-1 parameters fixed to those estimated with Metabolite-1 data alone, as described above and including Metabolite-1 concentrations. Assuming a 100% conversion of Metabolite-1 to Metabolite-2, the fraction of Metabolite-1 (Fm) converted to Metabolite-2 was arbitrarily set to 1; the input rate constant K23 to V3 was therefore the output rate constant from V2, leaving just two Metabolite-2 parameters to be estimated, namely, Metabolite-2 clearance (CLm) and volume of distribution of Metabolite-2 (Vm). The results of the Metabolite-2 model (with Metabolite-1 parameters all fixed) produced a CLm estimate for Metabolite-2 of 12.9 L/h and Vm of 62.7 L, with IIV of 45% and 19%, respectively (after model stability required the Metabolite-2 additive error to be fixed to the metabolite BLQ of 0.5 ng/mL and the proportional error fixed to the typical bioanalytical standard value of 15%).

Weight effects on CLm and Vm were tested, but only weight (power model) on CL was included in the base model for testing of the other covariates. The weight effect on Vm was not significant (and the power estimate was 0.241, far from the expected standard allometric value of 1.0); therefore, standard allometric scaling was not utilized for Metabolite-2 (unlike Metabolite-1). Sex on CLm was significant with no further covariate inclusions.

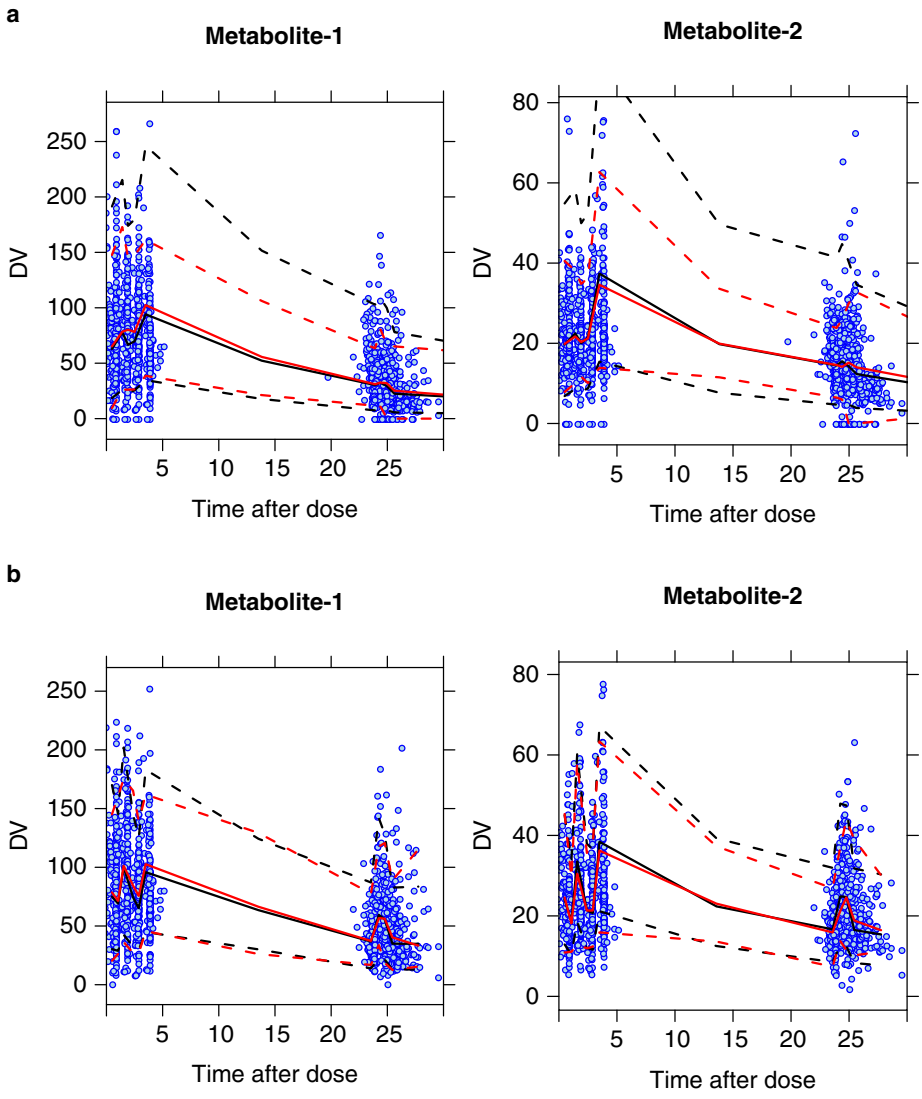

Figure 4 Prediction-corrected VPC of simultaneous Metabolite-1 and Metabolite-2 model. (**a**) Full data set. (**b**) Final reduced data set without BLQ and taper observations (overlapping subsets with $n = 700$ removed). Red lines: data medians (solid) and lower 5% and upper 95% lines (broken); black lines: equivalent model-simulated lines. BLQ, below level of quantitation; DV, dependent variable; VPC, visual predictive check.

Simultaneous Metabolite-1 and Metabolite-2 model

In the simultaneous fitting of Metabolite-1 and -2 data together, all parameters were estimated in the final run, except for the following fixed values: V4 = 209 L, absorption lag time (ALAG) 1 = 0, F1 = 1, and Fm = 1, as well as the standard allometric body weight effects on Metabolite-1 parameters. In a comparison of the simultaneous model to the sequential model parameters, the main structural and covariate parameters are little changed. The primary differences between sequential and simultaneous fitting (reduction of 447.278 in the OFV) were on variability parameters, as follows: increase Metabolite-1 IOV (from 33% to 51%); increase IIV on Metabolite-2 Vm (from 20% to 41%); reduce Metabolite-1 IIV on CL (from 50% to 43%); and to almost halve residual error parameters for Metabolite-2 that were previously fixed (proportional error from 15% to 7.6% and 0.5 to 0.29 ng/mL), while reducing Metabolite-1 additive error from 0.998 to 0.54 ng/mL. Standard errors of parameters were all <20%, with only the age effect on Metabolite-1 CL remaining greater than 20%.

Assessment of simultaneous Metabolite-1 and Metabolite-2 model

From examination of the individual fitted profiles of parent and metabolite, it was clear that using IOV (rather than eta on epsilon structure) gave visually acceptable parent and metabolite profiles, and so examinations of VPCs were undertaken to ascertain a final model suitable for generation of individual patient exposure parameters (AUC, maximum concentration (C_{max}) and minimum concentration (C_{min})).

Results of a prediction-corrected VPC, stratified by Metabolite-1/Metabolite-2 compartment with time after dose (h) as the independent variable are shown in **Figure 4**. In the full data set model (**Figure 4a**), although the simulated

Table 2 Final simultaneous Metabolite-1 and Metabolite-2 covariate model

Parameter	All data (% SE)	Without BLQ (% SE)[a]	Without taper (% SE)[a]	Without BLQ or taper (% SE)
Metabolite-1[b]				
Fraction of dose absorbed (F1)	1 FIXED	1 FIXED	1 FIXED	1 FIXED
Metabolite-1 CL (L/h)	8.13 (3.0)	6.70 (–)	8.24 (–)	7.29 (7.5)
Female on CL (% change)	–32.9 (12)	–25.2 (–)	–31.2 (–)	–26.8 (19)
Age on CL (change in L/h every year above 40)	–0.00627 (30)	–0.00589 (–)	–0.00675 (–)	–0.00633 (30)
Metabolite-1 central volume (V2) (L)	98.7 (7.7)	92.3 (–)	98.4 (–)	85.9 (19)
Metabolite-1 absorption rate constant (K12) (/h)	0.489 (3.2)	0.424 (–)	0.531 (–)	0.377 (24)
Metabolite-1 absorption lag time (ALAG1) (h)	0 FIXED	0 FIXED	0 FIXED	0 FIXED
Metabolite-1 intercompartmental clearance (Q) (L/h)	14.3 (14)	13.7 (–)	11.6 (–)	11.6 (51)
Metabolite-1 peripheral volume (V4) (L)	209 FIXED	209 FIXED	209 FIXED	209 FIXED
Interindividual variability				
On Metabolite-1 CL (%)	43 (18)	32 (–)	42 (–)	33 (8.6)
On Metabolite-1 absorption rate constant (K12) (%)	208 (9.0)	233 (–)	229 (–)	249 (10)
Interoccasion variability				
On Metabolite-1 F1 (%)	51 (13)	33.5 (–)	39.9 (–)	23.8 (9.8)
Residual error parameters				
Metabolite-1 proportional (%)	18.5 (4.6)	21.0 (–)	18.4 (–)	19.9 (5.1)
Metabolite-1 additive (ng/mL)	0.54 (11)	0.00014 (–)	0.805 (–)	0.305 (172)
Metabolite-2				
Fraction of Metabolite-1 converted to Metabolite-2 (Fm)	1 FIXED	1 FIXED	1 FIXED	1 FIXED
Metabolite-2 volume of distribution (Vm) (L)	61.2 (7.3)	56.9 (–)	62.4 (–)	62.8 (21)
Metabolite-2 clearance (CLm) (L/h)	18.9 (4.8)	16.1 (–)	19.0 (–)	17.2 (6.0)
BWT power on CLm	0.421 (17)	0.388 (–)	0.528 (–)	0.450 (30)
Female on CLm (% change)	−39.5 (4.3)	−33.7 (–)	−37.7 (–)	−34.1 (9.6)
Interindividual variability				
On Metabolite-2 Vm (%)	41 (15)	38 (–)	41 (–)	44 (14)
On Metabolite-2 CLm (%)	32 (19)	25 (–)	34 (–)	26 (7.0)
Residual error parameters				
Metabolite-2 proportional (%)	7.6 (5.5)	7.7 (–)	7.6 (–)	7.8 (6.0)
Metabolite-2 additive (ng/mL)	0.29 (8.3)	0.11 (–)	0.34 (–)	0.10 (0.0008)[c]

[a]No SE as NONMEM $COV step failed.
[b]Allometric model (Fixed BWT power 0.75 on CL and Q and Fixed BWT power 1 on V2 and V4).
[c]Lower boundary of 0.1 reached; if boundary reduced, $COV step failed.
Parameters are described with: all data with BLQ set to zero; exclusion of BLQ observations; exclusion of taper observations; and exclusion of both (final model; reference: male, 70 kg, 40 years old).
ALAG, absorption lag time; BLQ, below level of quantitation (PK value set to 0 in data); BWT, body weight; CL, clearance; CLm, clearance of Metabolite-2; F1, fraction of parent dose absorbed; K12, absorption rate constant; NONMEM, nonlinear mixed-effects modeling; PK, pharmacokinetics; Q, Metabolite-1 intercompartmental clearance; SE, standard error; V2, apparent volume of central compartment for Metabolite-1; V4, Metabolite-1 peripheral volume; Vm, volume of distribution of Metabolite-2.

and observed 5th and 50th percentiles overlap, the 95th simulated percentile shows that the model overestimates variability for Metabolite-1 and Metabolite-2. Removal of BLQ and taper observations had major effects (overlapping subsets, $n = 700$) and improved VPC (**Figure 4b**). This resulted in a reduction in Metabolite-1 IOV from 51% to 24%. In addition, moderate reductions in IIV of Metabolite-1 CL (from 43% to 33%) and CLm (from 32% to 26%), and a decrease in reference CL from 8.13 to 7.29 L/h for Metabolite-1 and in reference CLm from 18.9 to 17.2 L/h, were observed. Finally, none of the covariate effects changed substantially following removal of BLQ and taper observations. The model using the reduced data set (without BLQ and without taper concentrations) was selected as the final model for prediction.

The estimates for the final simultaneous Metabolite-1/Metabolite-2 model using the full data set and three reduced data subsets (exclusion of BLQ observations and/or taper dose concentrations) are described in **Table 2**.

Covariate effects for final model

The reduction in CL and CLm for females compared with males (after weight is taken into account) translates to higher exposure in females for both Metabolite-1 and Metabolite-2. Compared with a reference male aged 40 years weighing 70 kg (CL = 7.29 L/h and CLm = 17.2 L/h, **Table 2**), the reference female of the same age and weight had a 27% reduction in Metabolite-1 clearance (CL = 5.4 L/h) and a 34% decrease in Metabolite-2 clearance (CLm = 11.4 L/h). At the extremes of weight, and particularly when combined with age, large differences in exposure were predicted. **Figure 5** illustrates the population predictions for Metabolite-1 AUC in male and female patients (reference age 40 years), by weight and for a 10 mg dose of fosdagrocorat. At the extremes of the weight

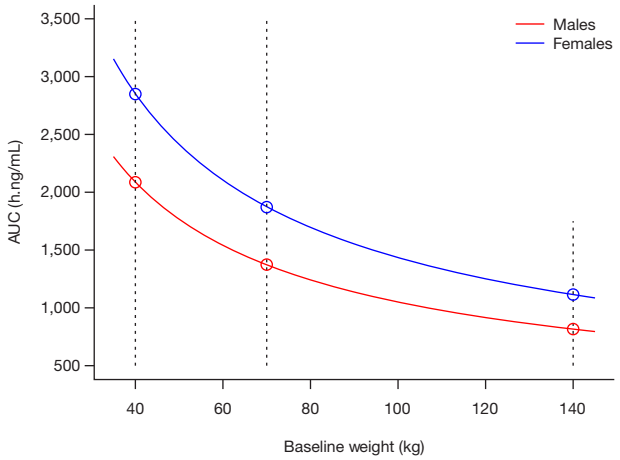

Figure 5 Population predictions for Metabolite-1 AUC. Data are shown for a 40-year-old male (red) and female patients (blue), by weight and for a 10-mg dose of fosdagrocorat. AUC, area under the concentration–time curve.

covariate values (140 kg male vs. 40 kg female, both 40 years old), there is a greater than twofold difference in AUC. However, the typical male weighing 70 kg would have a 26.8% lower AUC (1,875 vs. 1,373 h.ng/mL) than a typical female weighing 70 kg.

Because both Metabolite-1 CL and Metabolite-2 CLm values were reduced, only a small difference in Metabolite-2/Metabolite-1 AUC ratios between male and female patients (40% vs. 44%, respectively) was found.

To examine if the sex difference could be observed in the raw Metabolite-1 concentration data, a graphical examination of the concentrations at Week 8 was made. Metabolite-1 concentrations were scaled by dose to allow data for all doses to be combined. Normalized concentrations by sex vs. time after dose illustrate the gender differences in the absence of any model (**Supplementary Figure 1**).

DISCUSSION

The objectives of this analysis were to develop a population PK model for PF-00251802 (Metabolite-1) and its active metabolite PF-04015475 (Metabolite-2) after oral administration of the prodrug, fosdagrocorat, to patients with RA.

A simultaneously fitted two-compartment model for Metabolite-1 with assumed 100% conversion to Metabolite-2 in a single compartment was considered a satisfactory model for both Metabolite-1 and Metabolite-2. Regarding assumed 100% conversion of fosdagrocorat to Metabolite-1 (F1), this corresponds to the standard practice for an oral drug of all parameters being apparent (CL/F, V/F, Q/F, etc.) and in the case of Metabolite-1 this F is the product of both absorption and conversion of the prodrug. Any other value assumed would simply scale all the Metabolite-1 parameters and have no effect on proportional or power covariates or their consequences regarding concentrations. Similar reasoning applies to an assumed 100% Fm metabolism for Metabolite-2 production. This one-compartment concentration profile shape is determined by both the input shape of Metabolite-1 concentrations and by a single output rate constant independent of the scale of the concentrations, which is determined by Vm (output rate constant is Clm/Fm divided by Vm/Fm). Hence, any other value of Fm assumed would simply scale the Metabolite-2 parameters and similarly have no effect on proportional or power covariates or their consequences regarding Metabolite-2 concentrations.

Additive and proportional residual error in untransformed space was utilized based on many experiences with late-phase studies (of other drugs), sparse data, and patient-reported dosing. The strategy was to obtain good fits to individual patient profiles for Metabolite-1 and Metabolite-2 with acceptable NONMEM parameter gradients (with a single minimum in the OFV) and, if possible, a successful covariance step. Although log-normal concentrations are generally assumed in order to always keep values positive, experience has shown that using log-transformed space puts too much emphasis on low concentrations and not enough emphasis on higher concentrations. When comparing results from rich data that allowed noncompartmental analysis of the same data, the NONMEM results using log-transformed data underestimated noncompartmental AUCs, sometimes by a large fraction, depending on the size of the residual error. Additive and proportional residual error in untransformed space was therefore chosen for this analysis. Individual patient-fitted values (IPRED) were acceptable at the higher concentrations and were reasonable in capturing terminal phases, both in the predose samples and in the proximity to the BLQ cutoff. It was assumed, but not tested, that the additive error term also reduced the sensitivity of the assumption of zero for BLQ rather than one-half of BLQ.

Variability, particularly IOV, appeared to be overestimated (shown by VPC) with inclusion of BLQ and taper concentrations. Exclusion of these data (measured after patient-reported dosing) had little influence on structural parameters or covariate effects. Overestimation of variability (observed as overdispersion of the upper 95th percentile from the VPC) may be problematic when using such model outputs and including such a large IOV for simulation purposes. In this specific case, exclusion of samples measured as BLQ—many from the taper phase of sampling and taper concentrations where accurate dosing history was also difficult to obtain—resulted in a potentially more useful model.

The use of IOV on F1 was essential to produce good fits to both Metabolite-1 and Metabolite-2 data in each individual on each sampling occasion. It was included for this purpose in place of an eta on epsilon structure, as although the latter produced a good population fit and helped model stability, it was not helpful for individual subject fits. In particular, IOV on F1 takes into account problems that arise in studies where patient-reported dosing times may be unreliable. Alternative error structures that put these errors in the residual variability (such as eta on epsilon) do not address the source of the variability.

A further objective of this analysis was to perform a limited evaluation of covariates for Metabolite-1 and Metabolite-2 in the study population. All covariates were tested as prespecified in NONMEM (eta plots were not used for selecting covariates), and covariate selection based on OFV changes was therefore not influenced by eta shrinkage. The IIV eta

shrinkages for Metabolite-1 were 7.6% and 28% for CL and absorption rate constant K12, respectively, and for Metabolite-2 were 39% and 9.7% for Vm and CLm, respectively. These were low for the clearance terms that are the main determinants of exposures. The F1 IOV eta shrinkages ranged from 16–35%, with a median of 26%. Epsilon shrinkages were 12.6% for Metabolite-1 and 30% for Metabolite-2. The covariate effects, after allometric scaling of Metabolite-1, were age and sex on Metabolite-1 CL and sex and weight on Metabolite-2 CLm. Covariates of age, weight, and sex, in combination, predicted AUC differences >two fold at their extremes. From predicted individual Metabolite-1 and Metabolite-2 profiles, the covariate with the largest impact on exposure was the clearance difference between male and female patients, such that generally higher exposures (as judged by predicted AUCs) were apparent for female compared with male patients when an equivalent dose of fosdagrocorat was given. However, reasons for this sex difference are unclear. In preclinical studies, female rats had consistently higher mean PF-00251802 systemic exposure than male rats, whereas there was no apparent gender-related difference in exposure in dogs. Results of *in vitro* studies, using liver microsomes and hepatocytes from preclinical species and from humans, indicated that PF-00251802 undergoes both oxidative and conjugative metabolism. With respect to oxidative metabolism, PF 00251802 is metabolized by cytochrome P450 (CYP)3A to an N-oxide metabolite, PF-04015475, which is also present in the circulation of humans. However, no gender-related differences in CYP4503A4 have been reported in the literature. The single and multiple ascending dose PK studies in healthy volunteers enrolled only male subjects. The reason for the age effect is also not well understood. However, the age on CL effect is rather small (30 years' difference, ~3% difference in CL) and, although statistically significant, it is probably not clinically significant and could have been left out of the final model. Since the population treated is generally in the older age group, age effects may become more relevant with more subjects in older age groups (>70 years). In this study, more female than male patients were randomized and, although mean age was similar, it was noted that female patients had a lower mean body weight at baseline, which could in part explain the higher exposure levels in these patients. However, this was accounted for in the model by the allometric scaling of CL. After accounting for weight, the model still predicted an additional independent effect of sex. This sex difference in CL may account for the previous observation of a lower CL in Study A9391005 in RA patients, the majority of whom were female, compared with Study A9391002 in healthy male volunteers (data on file; Stock T *et al.*[20]). Neither of these previous studies had Metabolite-2 measurements, and although incorporation of the rich data from the phase I study in healthy volunteers may have stabilized the Metabolite-1 two-compartment model, in the interest of metabolite balance, it was decided to complete this analysis in a single study.

One limitation of this analysis was methodology for sample collection within the study, which limited the ability to precisely estimate Metabolite-1 peripheral volume (V4) and Q, as no samples were collected between 4 and 24 h postdose. Also, it was clear that the C_{max} for Metabolite-2 was beyond 4 h postdose in most patients. However, the use of simultaneous Metabolite-1 and Metabolite-2 data fitting along with the flexibility of the IOV structure on F1 (on every dose), and the IIV on CLm and Vm, allowed extrapolation of Metabolite-2 to dummy data points between 4 and 24 h. Metabolite-2 borrowing information from Metabolite-1 allowed estimation of C_{max} and AUC for the former that was not available from the Metabolite-2 data alone.

Another limitation was the treatment of BLQ values. There are alternative approaches to handling BLQ values.[22] The gold standard is the so-called M3 method, or, in the case of this analysis, where the data are in untransformed space, the M4 method. Preliminary testing showed that this method would work in principle but that model convergence was a problem and run times were excessive (this may have been partly due to the requirement to use the LAPLACE method instead of FOCE in NONMEM). For these reasons, this approach was not pursued. Another alternative would have been to treat the IOV on F1 as being different in magnitude for BLQ and particularly for taper occasions. This was not attempted, as it would have resulted in much more model complexity.

CONCLUSION

In summary, this analysis provides an in-depth description of Metabolite-1 and Metabolite-2 PK characteristics of the prodrug fosdagrocorat in patients with RA. Our results suggest higher exposures in female than male patients for the same weight that remained unexplained.

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