Predictive Physiologically Based Pharmacokinetic (PBPK) Model Suggests Minimal Drug-drug Interaction (DDI) Between PPARδ Agonist Mavodelpar (REN001) and Rosuvastatin

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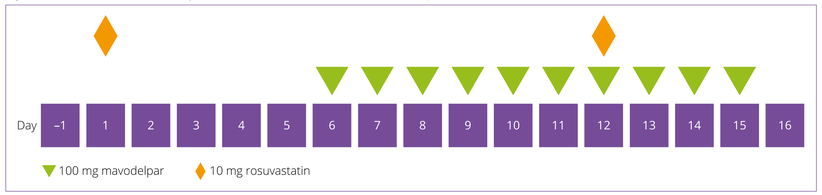
BACKGROUND

- Mavodelpar is a peroxisome proliferator–activated receptor delta (PPARδ) agonist being investigated for treating primary mitochondrial myopathy (PMM)[1]
- Statins carry a risk of causing myopathy, and increased systemic concentrations due to pharmacokinetic (PK) drug-drug interactions (DDIs) are a significant risk factor for statin-associated myopathy and myotoxicity[2,3]
- Statin-related myopathy may be a potential issue when administered to patients with PMM, and DDIs are likely important in defining risk-benefit for statins in PMM[2,3]
- Determinants of statin disposition are unique for each statin and include transporters for absorption, uptake, and excretion, as well as metabolizing enzymes[2,3]
- Although mavodelpar does not appear to inhibit cytochromes P450, in vitro data suggest that mavodelpar could be an inhibitor of transporters involved in the absorption and uptake of statins, including breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, and OATP1B3
- The in vitro profile data predicted that rosuvastatin was the statin most likely to be impacted by coadministration with mavodelpar
- Because of the potential for a transporter-based PK DDI, a predictive physiologically based PK (PBPK) model from in vitro data was developed and validated. This model was then used to predict the magnitude of an interaction for rosuvastatin, as well as atorvastatin, pravastatin, and a sensitive control substrate, methotrexate
- The prediction of the influence of mavodelpar on rosuvastatin PK was then tested in a clinical DDI study
- As coproporphyrin I (CP-I) is a sensitive biomarker for OATP1B1/OATP1B3 inhibition, the effect of mavodelpar on the disposition of CP-I was also assessed as a secondary end point[4,5]

METHODS

- A predictive PBPK model (Simcyp V21, Certara, Princeton, NJ) was developed and validated from clinical PK data generated from 2 phase 1 studies in healthy volunteers and in obese patients with dyslipidemia
- Simulations were then performed to predict the magnitude of the DDI of mavodelpar with rosuvastatin, atorvastatin, pravastatin, and methotrexate (Methotrexate is a control substrate that interacts with organic anion transporter 3 [OAT3], which is not affected by mavodelpar)
  - In the simulations, rosuvastatin, atorvastatin, pravastatin, and methotrexate (as object drugs) were administered as a single dose with and without coadministration of mavodelpar
  - Simulations of 10 different trials consisting of 16 healthy volunteers (50% female) aged 18 to 55 years consistent with a planned rosuvastatin clinical DDI trial were generated. For the other statins, simulations of 10 healthy volunteers were used
  - The simulated subjects received a single oral dose of 10 mg rosuvastatin (10 mg atorvastatin, 40 mg of pravastatin, or 200 mg methotrexate) in the absence of mavodelpar and a second dose coadministered with mavodelpar 100 mg daily at steady state.
  - A sensitivity analysis to evaluate the impact of the competitive inhibition constant values for unbound mavodelpar ($K_{i,u}$) was performed by reducing the $K_{i,u}$ values by 10- to 15-fold in the model
- On Day 1, subjects received a single 10-mg dose of rosuvastatin. From Day 6 to Day 15, subjects received 100 mg mavodelpar once daily. On Day 12, subjects received a repeat single 10-mg dose of rosuvastatin and 100 mg of mavodelpar (**Figure 1**)
- Plasma samples were analyzed by validated liquid chromatography tandem mass spectrometry methods
  - Statistical analysis of the derived PK parameters (area under the curve [AUC] and maximal drug concentration [C_{max}]) to estimate the DDI potential of mavodelpar were log-transformed and analyzed using an analysis of variance model including fixed effects for treatment and subject. Differences between treatments and their 90% confidence intervals (CIs) were ratios (test/reference) when back-transformed. Point estimates and 90% CIs were constructed for the contrasts of rosuvastatin alone on Day 1 versus rosuvastatin dosed simultaneously with mavodelpar on Day 12 following mavodelpar dosing to steady state
- In a separate group of subjects, plasma concentrations of CP-I were assessed over 2 days following a single dose of 100 mg mavodelpar in 14 subjects

Figure 1. Clinical and Simulated Study Schematic to Evaluate DDIs Between Mavodelpar and Rosuvastatin



Abbreviations: DDI, drug-drug interaction.

RESULTS

PBPK RESULTS

- Mean clinical and simulated plasma rosuvastatin concentrations following 1) a single oral dose in the absence of mavodelpar and 2) plasma rosuvastatin concentrations on the 7th day of 10 days of dosing of mavodelpar (**Figure 2**)
- Simulations were also performed with a single oral dose of 10 mg rosuvastatin (BCRP/OATP1B1/OATP1B3 inhibition) in the presence or absence of steady state mavodelpar (**Table 1**)
  - No clinically significant DDIs were predicted based on OATP1B1 and OATP1B3 transport
  - Preliminary PK results show that a weak DDI between rosuvastatin and mavodelpar was observed (<2-fold change in simulated area under the plasma concentration-time curve from time zero to the end of the dosing interval [AUC_{tau}] and [C_{max}]) and was well predicted by accounting for a 15-fold reduction in BCRP $K_{i,u}$
- Additional simulations performed with a single oral dose of 10 mg atorvastatin, 40 mg of pravastatin, and 200 mg methotrexate in the presence or absence of steady state mavodelpar (100 mg for 15 days) indicate no clinically significant DDIs (**Table 2**)

*Mavodelpar is an investigational treatment not yet approved by any regulatory agency.

Mavodelpar, a potent and selective PPARδ agonist is being evaluated as a potential treatment for PMM

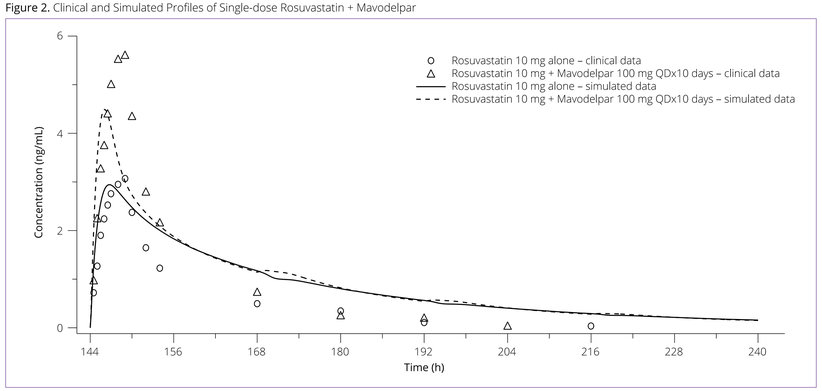
Mavodelpar showed a weak interaction with rosuvastatin based on PBPK modeling that could be predicted in the clinical setting and appears to be driven by BCRP inhibition

Mavodelpar coadministration with statins is unlikely to alter the statin risk-benefit ratio for patients with PMM based on an increase in statin exposure

CLINICAL RESULTS

- A weak interaction on rosuvastatin PK by mavodelpar was observed and consistent with the PBPK model predictions (AUC and C_{max} geometric least-square mean ratios < 2); clinical data is presented in **Table 3**
- No change in CP-I concentrations were observed with mavodelpar administration over 24 hours, suggesting that rosuvastatin DDI is primarily mediated by BCRP inhibition, and OATP1B1-mediated hepatic statin uptake was not significantly impacted (data not shown)

Figure 2. Clinical and Simulated Profiles of Single-dose Rosuvastatin + Mavodelpar



Geometric mean plasma concentration-time profiles of a single 10-mg dose of rosuvastatin and 10 mg rosuvastatin plus 100 mg once daily (QD) mavodelpar for 10 days in healthy subjects. Clinical results are depicted as open circles for rosuvastatin alone, and open triangles for rosuvastatin co-administered with mavodelpar. Lines represent the mean data for the 10 simulated trials of n = 16 volunteers. Plasma concentration-time profiles of rosuvastatin following a single oral dose in the absence of mavodelpar (solid line) and on the 7th day of 10 days of dosing of mavodelpar (dashed line).

Table 1. Simulated and Observed Rosuvastatin Geometric Mean AUC_{tau} and C_{max} Values in the Presence and Absence of Mavodelpar in Healthy Subjects and the Corresponding GMRs with Confidence Intervals

Transporter	Sensitive Substrate		Rosuvastatin		Mavodelpar + Rosuvastatin		GMR	
			AUC_{tau} ng/mL.h	C_{max} ng/mL	AUC_{tau} ng/mL.h	C_{max} ng/mL	AUC_{tau}	C_{max}
	Rosuvastatin Observed	Geometric Mean 95% CI – lower 95% CI – upper	32.4 28.9 36.3	3.02 2.73 3.34	55.2 49.3 61.9	5.47 4.95 6.04	1.70 1.49 1.94	1.81 1.61 2.03
BCRP	Rosuvastatin Predicted	Geometric mean 90% CI – lower 90% CI – upper	64.4 59.1 70.2	2.40 2.19 2.64	65.9 60.5 71.8	2.74 2.51 2.99	1.02 1.02 1.03	1.14 1.13 1.16
		S/O	1.99	0.794	1.19	0.501	0.601	0.631
BCRP	**Rosuvastatin Predicted sensitivity analysis 15-fold reduction K_i**	**Geometric mean 90% CI – lower 90% CI – upper**	64.4 59.1 70.2	2.40 2.19 2.64	71.9 66.2 78.0	3.78 3.48 4.09	1.12 1.11 1.13	**1.57 1.53 1.62**
		S/O	1.99	0.794	1.30	0.691	0.655	0.869
OATP1B1/ OATP1B3	Rosuvastatin Predicted	Geometric mean 90% CI – lower 90% CI – upper	64.4 59.1 70.2	2.40 2.19 2.64	64.6 59.3 70.5	2.42 2.20 2.65	1.00 1.00 1.00	1.01 1.01 1.01
		S/O	1.99	0.794	1.17	0.442	0.589	0.557
OATP1B1	Rosuvastatin Predicted sensitivity analysis 10-fold reduction K_i	Geometric mean 90% CI – lower 90% CI – upper	64.4 59.1 70.2	2.40 2.19 2.64	66.4 60.9 72.3	2.56 2.34 2.81	1.03 1.03 1.03	1.07 1.06 1.07
		S/O	1.99	0.794	1.20	0.468	0.605	0.590
OATP1B3	Rosuvastatin Predicted sensitivity analysis 10-fold reduction K_i	Geometric mean 90% CI – lower 90% CI – upper	64.4 59.1 70.2	2.40 2.19 2.64	64.7 59.3 70.5	2.42 2.21 2.66	1.00 1.00 1.00	1.01 1.01 1.01
		S/O	1.99	0.794	1.17	0.443	0.590	0.558

Abbreviations: AUC_{tau}, area under the plasma concentration-time curve from time zero to the end of the dosing interval; BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximal drug concentration; GMR, geometric mean ratio; K_i, inhibition constant; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3; S/O, simulated/observed.

Table 2. Simulated Geometric Mean AUC_{tau} and C_{max} Values and Corresponding GMRs for Atorvastatin, Pravastatin, and Methotrexate in the Absence and Presence of Mavodelpar in Healthy Subjects

Transporter	Sensitive Substrate		Substrate		Mavodelpar + Substrate		GMR	
			AUC_{tau} ng/mL.h	C_{max} ng/mL	AUC_{tau} ng/mL.h	C_{max} ng/mL	AUC_{tau}	C_{max}
OATP1B1/ OATP1B3	Atorvastatin	Geometric mean 90% CI – lower 90% CI – upper	16 14.7 17.4	3.27 3.01 3.54	16.2 14.9 17.6	3.3 3.04 3.58	1.01 1.01 1.01	1.01 1.01 1.01
OATP1B1/ OATP1B3	Pravastatin	Geometric mean 90% CI – lower 90% CI – upper	290 269 313	83.2 76.8 90.1	293 271 316	84 77.6 91	1.01 1.01 1.01	1.01 1.01 1.01
OAT3	Methotrexate	Geometric mean 90% CI – lower 90% CI – upper	41126 39622 42688	109689 108124 111276	41149 39644 42711	109689 108124 111276	1.00 1.00 1.00	1.00 1.00 1.00

Abbreviations: AUC_{tau}, area under the plasma concentration-time curve from time zero to the end of the dosing interval; C_{max}, maximal drug concentration; GMR, geometric mean ratio; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3; OAT3, organic anion transporter 3

Table 3. Interactions Between Rosuvastatin and Mavodelpar in a Clinical Trial

Parameter	Number in Comparison	Rosuvastatin (10 mg) (Day 1) GLSM (95% CI) (n=16)	Rosuvastatin (10 mg) + Mavodelpar (100 mg) (Day 12) GLSM (95% CI) (n=15)	GLSM Ratio (%) (90% CI) Day 12/Day 1	Within-Subject CV% From ANOVA
C_{max} ng/mL	15	3.0226 (2.7363 - 3.3388)	5.4676 (4.9497 - 6.0396)	180.89 (161.15 - 203.05)	18.1
AUC_{0-t} ng/mL.h	15	32.4069 (28.9212 - 36.3128)	55.2092 (49.2708 - 61.8633)	170.36 (149.27 - 194.43)	20.8
AUC_{inf} ng/mL.h	11	46.6267 (41.9482 - 51.8270)	73.6472 (66.2574 - 81.8611)	157.95 (139.86 - 178.38)	15.8

Treatment: single dose of 10 mg rosuvastatin (noninvestigational medicinal product) on Day 1; 100 mg mavodelpar (investigational medicinal product) once daily from Day 6 to Day 15, coadministered with a single dose of 10 mg rosuvastatin on Day 12. Results obtained using a fixed-effects analysis of variance (ANOVA) with fixed effects of treatment and subject.
Abbreviations: AUC_{inf}, area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{0-t}, area under the plasma concentration-time profile from time zero to the time of the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-square mean.

DISCUSSION AND CONCLUSIONS

- Mavodelpar coadministration with the described statins is unlikely to change the risk to benefit ratio in patients with PMM based on altered statin PK
- From the clinical study results, mavodelpar appears to be a weak inhibitor of BCRP with minimal impact on OATP1B1/OATP1B3 (area under the plasma concentration-time profile from time zero extrapolated to infinite time [AUC_{inf}] ratio >1.3 and <2.0)
- The PBPK model tends to under-predict the rosuvastatin C_{max} alone, but in the presence of mavodelpar and when Ki_{-BCRP} is reduced by 15-fold, the impact on C_{max} is predicted well, and the predicted C_{max} GMR is within 1.25-fold of observed values
- The PBPK model tends to over-predict the rosuvastatin AUC alone, but in the presence of mavodelpar and when Ki_{-BCRP} is reduced by 15-fold, the AUC prediction is improved. The magnitude of the predicted interaction on the rosuvastatin AUC was lower than observed, but the predicted GMR is within 2-fold of the observed values
- It is also possible that the inclusion of other transporters involved in rosuvastatin disposition such as organic anion transporting polypeptide 2B1 (OATP2B1), may have improved the prediction

CONFLICT OF INTEREST

Maurice Emery is a paid consultant for Reneo Pharmaceuticals, Inc. and Certara UK Ltd.

Helen Bridger, Helen Barker, and Lynn Purkins are employees of Reneo Pharma Ltd, a subsidiary of Reneo Pharmaceuticals, Inc., and hold stock in Reneo Pharmaceuticals, Inc.

Hannah M. Jones and Ludwig Vincent are employees of Certara UK Ltd and hold stock in the company.

Annelize Koch and Danielle Webb are employees of Simbec-Orion Group Ltd and have no other conflicts of interest regarding the poster.

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REFERENCES

1. Davies M, et al. *J Clin Trials*. 2022;12(2):1–8.
2. Feng Q, et al. *Pharmacogenomics*. 2012;13(5):579–594.
3. Turner RM, Pirmohamed M. *J Clin Med*. 2019;9(1):22.
4. Shen H, et al. *Drug Metab Dispos*. 2018;46(8):1075–1082.
5. Lai Y, et al. *J Pharmacol Exp Ther*. 2016;358(3):397–404.

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