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ARTICLE

Evaluation of drug-drug interaction potential between omecamtiv mecarbil and rosuvastatin, a BCRP substrate, with a clinical study in healthy subjects and using a physiologically-based pharmacokinetic model

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Abstract

Omecamtiv mecarbil (OM) is a novel cardiac myosin activator in development for the treatment of heart failure. In vitro, OM is an inhibitor of BCRP. Rosuvastatin, a BCRP substrate, is one of the most commonly prescribed medications in patients with heart failure. The potential for a pharmacokinetic (PK) drug-drug interaction (DDI) was investigated, specifically to determine whether a single 50 mg dose of OM would impact the PKs of a single 10 mg dose of rosuvastatin in an open-label study in 14 healthy subjects. The ratios of the geometric least-square means (90% confidence intervals [CIs]) of rosuvastatin co-administered with OM compared to rosuvastatin alone were 127.1% (90% CI 113.8–141.9), 132.8% (90% CI 120.7–146.1), and 154.2% (90% CI 132.8–179.1) for area under the plasma-concentration time curve from time zero to infinity (AUC_{inf}), area under the plasma-concentration time curve from time zero to time of last quantifiable concentration (AUC_{last}), and maximum observed plasma concentration (C_{max}), respectively. Whereas the DDI study with rosuvastatin was conducted with the co-administration of a single dose of OM, in the clinical setting, patients receive OM at doses of 25, 37.5, or 50 mg twice daily (b.i.d.). Hence, to extrapolate the results of the DDI study to a clinically relevant scenario of continuous b.i.d. dosing with OM, physiologically-based pharmacokinetic (PBPK) modeling was performed to explore the potential of BCRP inhibition following continuous b.i.d. dosing of OM at the highest 50 mg dose. Modeling results indicated that following 50 mg b.i.d. dosing of OM, the predicted ratios of the geometric means (90% CIs) for rosuvastatin AUC_{inf} and C_{max} were 1.18 (90% CI 1.16–1.20) and 2.04 (90% CI 1.99–2.10), respectively. Therefore, these results suggest that OM, following multiple dose administration, is a weak inhibitor of BCRP substrates and is in accordance with that observed in the single dose OM DDI clinical study.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Omecamtiv mecarbil (OM) is a cardiac myosin activator and is currently under investigation for the treatment of heart failure with reduced ejection fraction.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study investigated the drug-drug interaction (DDI) potential of OM on the pharmacokinetics of rosuvastatin, a BCRP substrate, using a clinical study and a physiologically-based pharmacokinetic (PBPK) modeling approach.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The clinical study and PBPK modeling analyses confirm that OM is expected to be a weak inhibitor of BCRP in the clinical setting.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study highlights the DDI potential of single doses of OM for BCRP substrates from a clinical study and demonstrates the importance of the PBPK modeling approach to investigate DDI effects following multiple doses of OM at therapeutic concentrations.

INTRODUCTION

Omecamtiv mecarbil (OM) is a cardiac myosin activator that improves myocardial function by directly enhancing cardiac sarcomere function.[1,2] OM is a myotrope that acts directly on the myofilament without modifying intracellular calcium.[3] OM has demonstrated improvements in cardiac function in healthy subjects and patients with heart failure with reduced ejection fraction (HFrEF).[4–9] OM was assessed in patients with HFrEF with reduced ejection fraction in a recently completed phase III trial GALACTIC-HF. In this trial, the OM dosing schema was individualized using a pharmacokinetic (PK)-based dose titration strategy. Patients received a starting dose of 25 mg twice a day (b.i.d.) with a potential to increase the dose to 37.5 or 50 mg b.i.d. dose based on individually measured OM trough plasma concentrations. The PK-based dosing titration was based on the trough concentrations measured at week 2. Specifically, if the week 2 OM trough concentrations were less than 200 ng/ml, the dose was uptitrated to 50 mg b.i.d. If the week 2 trough OM concentrations were between 200 and 300 ng/ml, then the dose was uptitrated to 37.5 mg b.i.d. If the trough concentrations were greater than 300 ng/ml, subjects remained at the 25 mg b.i.d. Patients who received OM had a lower incidence of a composite of a heart failure event or death from cardiovascular causes than those who received a placebo.[2,10]

OM is administered as a modified release formulation with a median time to maximum concentration (T_{max}) of ~ 2–4 h. The plasma protein binding of OM is ~ 82% and the terminal elimination half-life ($t_{1/2}$) is ~ 20 h. OM is extensively metabolized by multiple CYP450 enzymes (CYP3A4, CYP2D6, CYP4A11, CYP4F2, CYP4F3B, and CYP4F12) with ~ 11% of a single dose recovered as parent drug in urine and feces.[11–13] Patients with HFrEF are more likely to have coronary artery disease and it is well-established that statins (HMG-CoA reductase inhibitors) reduce coronary artery disease events in this patient population.[14] Rosuvastatin, a well-known lipid-lowering agent, is also commonly prescribed to patients with HFrEF to lower the risk of heart attack and stroke. In addition, rosuvastatin is a prototypical substrate of the efflux transporter BCRP, and in vitro findings suggested that OM is a weak inhibitor of BCRP (half-maximal inhibitory concentration [IC_{50}] = 2.9 μM [1428 ng/ml]). Therefore, it was deemed critical to assess the potential for drug-drug interaction (DDI) of the novel small molecule, OM, with commonly co-administered drugs, such as rosuvastatin, as well as to assess the impact of OM administration on the PKs of BCRP substrates.

This clinical study evaluated the DDI potential of a single dose of 50 mg OM on the PK of a single dose of 10 mg rosuvastatin. A single dose regimen of OM was evaluated because it was considered more sensitive in measuring PK changes than a multiple-dose regimen in accordance with the US Food and Drug Administration (FDA) issued 2014 Guidance for Industry Bioavailability and Bioequivalence Studies. In the clinical setting, OM was administered b.i.d., with 50 mg b.i.d. as the highest possible dose following a PK-based dosing titration. The mean (SD) maximum observed plasma concentration (C_{max}) following a single dose of 50 mg OM was 113 (30.4) ng/ml. The mean (SD) C_{max} at steady-state after 50 mg b.i.d. dosing following PK-based titration was 360 (137) ng/ml. The mean accumulation ratio of OM was approximately fourfold

at a steady-state with b.i.d. dosing. Thus, to evaluate the BCRP inhibition potential of OM following continuous 50 mg OM b.i.d. dosing, we utilized physiologically-based pharmacokinetic modeling (PBPK) modeling approach. This was accomplished by developing and verifying PBPK models for OM and rosuvastatin using data obtained from the clinical study described in this paper. This was subsequently followed by performing simulations to investigate the drug interaction potential when rosuvastatin was co-administered as a victim drug and with OM as the perpetrator at these simulated higher exposures.

In this paper, we describe and discuss the results from an open-label study conducted in healthy subjects and the supportive PBPK modeling work conducted to investigate the PK DDI potential of OM when co-administered with rosuvastatin.

METHODS

Study design

This clinical study was conducted as a single-center, open-label, fixed-sequence study in healthy subjects. Subjects were kept in-house throughout the duration of the study to collect samples required for PK and laboratory assessments. Safety assessments throughout the study included adverse event monitoring, electrocardiograms (ECGs), clinical examination, vital signs, and clinical laboratory evaluations. After screening for 21 days to assess eligibility, ~ 14 subjects were planned for enrollment so that at least 12 subjects would complete the study. On day 1, subjects received a 10 mg oral tablet of rosuvastatin with 8 ounces of water after an overnight fast of at least 10 h. On day 6, subjects received a 10 mg oral tablet of rosuvastatin and a 50 mg oral OM tablet with 8 ounces of water after an overnight fast of at least 10 h. Blood was collected at predose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 h postdose following administration of rosuvastatin on days 1 and 6 to characterize plasma concentrations of rosuvastatin. The study schema is presented in Figure S1. Safety and tolerability monitoring were performed throughout the study.

The study was conducted at the Covance Clinical Research Unit in Daytona Beach, Florida, USA, in accordance with ethical guidelines from the Declaration of Helsinki and Council for International Organizations of Medical Sciences, applicable Good Clinical Practice guidelines of the International Council for Harmonization, and applicable local laws and regulations. Salus institutional review board (Austin, TX) approved the research protocol and study conduct. All study subjects provided written informed consent before enrollment into the study and could withdraw from the study at any time. Qualified researchers may request data from Amgen clinical studies; complete details are available at http://www.amgen.com/datasharing.

Study subjects

Eligibility was determined by medical history, physical examination, vital signs, laboratory values, and cardiac monitoring at screening and check-in. Eligible subjects were men or women aged 18 to 55 years (inclusive) with a body mass index (BMI) between 18.0 and 30.0 kg/m^2 (inclusive).

Exclusion criteria were related to medical history (e.g., history of uncontrolled or unstable cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematopoietic, psychiatric, or neurological disease) and laboratory screening tests, including aspartate aminotransferase or alanine aminotransferase levels above the upper limit of normal (ULN). Exclusion criteria also included elevated levels of biomarkers associated with coronary events: creatine kinase or creatine kinase muscle/brain levels greater than the ULN, and troponin I levels greater than the ULN at screening or check-in. Subjects were excluded if they had previous exposure to the study drug (OM) or if they had prior or concomitant use of over-the-counter or prescription drugs that could affect the PKs of the study drugs. In addition, users of tobacco- or nicotine-containing products within 6 months at screening, any subjects testing positive for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use, and female and male subjects of reproductive potential who were unwilling to practice the protocol-specified contraception requirements were excluded from the study.

Bioanalytical method

A 300-μl matrix aliquot was fortified with 30 μl of 100 ng/ml rosuvastatin-d6/100 ng/ml N-desmethylrosuvastatin-d6 internal standard working solution. Analytes were isolated through liquid/liquid extraction. The eluate was evaporated to dryness under a nitrogen stream at ~ 50°C. Following reconstitution with 250 μl of water/acetonitrile/acetic acid (80:20:0.0625, v/v/v), the extract was washed with 1.0 ml of hexanes, and the organic was aspirated to waste.

The final extract was analyzed via high-performance liquid chromatography and tandem mass spectrometry detection using negative ion electrospray. Mobile phase A was methanol/water/1.0 M ammonium acetate/2.00% acetic acid, pH 6.00 (40:60:0.05, v/v/v) and mobile phase B

was 100% methanol. The m/z values for rosuvastatin were 480.4 → 418.2, and for internal standard were 486.4 → 424.2. The interassay accuracy ranged from −7.06% to 5.70% and the interassay accuracy was less than or equal to 4.45%. A linear, 1/concentration^2 weighted, least-squares regression algorithm was used to quantitate unknown samples.

Pharmacokinetics parameters

The estimated PK parameters were C_{max}, T_{max}, apparent plasma $t_{1/2}$, area under the plasma-concentration time curve from time zero to time of last quantifiable concentration (AUC_{last}), and area under the plasma-concentration time curve from time zero to infinity (AUC_{inf}). All PK parameters for rosuvastatin were estimated using noncompartmental analysis (Phoenix WinNonlin version 8.1, Certara).

Safety evaluation

Safety and tolerability assessments included the monitoring of adverse events (AEs), clinical laboratory tests, 12-lead ECGs, and vital signs. Monitoring of AEs occurred throughout the study. Clinical chemistry and hematology evaluations were conducted. Blood pressure and pulse rate, 12-lead ECGs, and oral body temperature were recorded at screening, check-in, protocol scheduled timepoints predose and postdose, and at the end of the study visit.

Statistical analysis

A linear mixed-effects model was used to analyze log-transformed primary PK parameters (C_{max}, AUC_{last}, and AUC_{inf}). The model assumed a fixed effect for treatment and a random effect for the subject. The ratios of geometric least square means (GLSMs) for C_{max} and AUC values and associated 90% confidence intervals (CIs; test/reference) were estimated. The "reference" treatment for PK analysis was rosuvastatin administered alone, whereas the "test" treatment was rosuvastatin administered in combination with OM. Safety outcomes were summarized using descriptive statistics. The statistical analyses were performed using SAS Enterprise Guide Version 7.13 (SAS Institute).

Physiologically-based pharmacokinetic modeling

Simcyp Simulator (Simcyp, version 17.1) was used for PBPK modeling. The characteristics of the PBPK model, including the differential equations and the physiological parameters used as inputs by the Simcyp Simulator for PBPK modeling, have been published.[15] The development and verification of the OM model compound file were performed using clinical PK data available from a single dose study with intravenous administration, single and multiple dosing from four earlier clinical studies with oral administration, and the current study, as shown in Table 1. The OM compound file was further refined for use to simulate inhibition of BCRP for single-dose administration and then applied for predictions of inhibitory effect on BCRP following multiple doses of OM, where no clinical data are available. The graphical presentation of the PBPK model building is presented in Figure S2. The details of the overview of the PBPK modeling strategy are provided in Supplementary Materials.

OM model development

The clinical PK data from a study conducted in healthy subjects following 35 mg i.v. OM administration demonstrated a biexponential decline. Therefore, a two-compartment model was fit to this PK data using SAAM II (version 1.0.001, The Epsilon Group) to characterize the distribution of OM in humans. The distribution rate constant for mass transfer from the central to the peripheral compartment (k_{12}), the peripheral

TABLE 1 Study design of OM clinical trials in healthy subjects used for PBPK simulations

Study	OM dose	Route of administration	Number of subjects for each trial	Number of virtual trials	Proportion of women	Age range (years)	
						Min	Max
Study 1	50 mg single dose	Oral	14	10	0.43	22	54
Study 2	25 mg b.i.d.	Oral	20	10	0.30	22	45
Study 3	50 mg b.i.d.	Oral	13	10	0.08	20	35
Study 4	25 mg b.i.d.	Oral	13	10	0.5	22	54
Study 5	35 mg single dose	Intravenous	7	NA	0.0	21	45
OM-Rosuvastatin DDI study	50 mg single dose	Oral	14	5	0.57	18	50

Abbreviations: DDI, drug-drug interaction; NA, not applicable; OM, omecamtiv mecarbil; PBPK, physiologically-based pharmacokinetic.

to the central compartment (k_{21}), the first-order elimination rate constant describing elimination from the central compartment (k_{10}), and the central compartment volume (V_c) were obtained by parameter estimation. The volume of the peripheral compartment (V_{sac}; single adjusting compartment volume of distribution) and the steady-state distribution volume (V_{ss}) were calculated by the following equation:

$$V_{sac} = \frac{k_{12}}{k_{21}} \cdot V_c$$

$$V_{ss} = V_c + \frac{k_{12}}{k_{21}} \cdot V_c$$

In the next step, the population estimates of CL_{po} and k_a upon oral administration of OM were used to simulate the oral PK of OM in healthy subjects using Simcyp. Absorption from the gastrointestinal tract was assumed to follow first-order kinetics. A minimal PBPK model was utilized and the distribution-related parameters (k_{12}, k_{21}, V_{sac}, and V_{ss}) were fixed based on the compartmental analysis of intravenous data. The CL_{po} and k_a were estimated from clinical PK data following oral administration of OM to healthy subjects. Clinical PK data following administration of a single 50 mg dose of OM (study 1; Table 1) in addition to 25 mg OM b.i.d. for 7 days (study 2; Table 1) were used to obtain parameter estimates of CL_{po} and k_a that could reasonably predict plasma concentration-time profiles of OM for both single and multiple oral dosing. The "maximum likelihood" objective function was used along with the "expectation maximization" minimization method.

OM model verification

The optimized parameters were used to simulate plasma concentration-time profiles in virtual populations mimicking the respective designs of studies 3 and 4 (Table 1) with respect to the administered dose, dosing regimen, age range, number of subjects in the study, and the proportion of women in each study. Table 1 summarizes the virtual study design for each clinical study. The simulated C_{max}, T_{max}, and AUC values were compared with the observed values and deemed acceptable if they fell within twofold of observations, which is a commonly accepted criterion.[16]

Model application-prediction of the perpetrator potential of OM toward BCRP inhibition

The BCRP inhibition potential of OM was assessed by using rosuvastatin as the BCRP clinical probe substrate. OM was found to be an inhibitor of BCRP (IC_{50} 2.9 μM) based on in vitro studies. According to the Cheng-Prussof equation, the relationship between IC_{50} and K_i can be described as follows[17]:

$$K_i = \frac{IC_{50}}{1 + \frac{S}{K_m}}$$

The K_i obtained from IC_{50} by the above equation in cellular systems overexpressing efflux transporters is an "apparent K_i" because the concentrations from the in vitro assays used to calculate the IC_{50} are incubation concentrations, whereas the actual driving concentrations for the efflux reaction are the intracellular unbound concentrations. Efflux transporter IC_{50} and the K_i values obtained from in vitro cellular assays are quite variable and can depend on the transporter expression level.[18] Therefore, the utility of the BCRP IC_{50} obtained for OM, in this case, was limited to indicate that OM is a BCRP inhibitor. However, the K_i obtained from this IC_{50} was not considered to be representative of the quantitative inhibition potential of OM in vivo. Hence, sensitivity analysis was conducted to approximate the value of K_i that described the BCRP inhibition potential of OM in vivo. The plasma concentration-time profiles of rosuvastatin upon administration of a single 50 mg dose of OM were simulated at a range of BCRP K_i values ranging from 0.0001 μM to 0.1 μM in virtual populations mimicking the population characteristics from the clinical study with rosuvastatin with respect to the age range, the number of subjects in the study, the proportion of women, dose, and dosing regimen (a single 10 mg dose of rosuvastatin administered with or without a 50 mg single dose of OM). The simulated C_{max}, T_{max}, and AUC values were compared with the observed values and deemed acceptable if they fell within twofold of observations. Following the determination of acceptable DDI predictions for single-dose administration of 50 mg OM, DDI predictions were performed assuming twice daily dosing of 50 mg OM for 14 days and administration of 10 mg rosuvastatin with or without OM on day 10.

RESULTS

Participant demographics and baseline characteristics

The demographics and baseline characteristics of all subjects are summarized in Table S1. Overall, six subjects (42.9%) were men and eight subjects (57.1%) were women, the mean age was 34.1 years, and the mean BMI was 25.1 kg/m^2. The proportion of Black, White, and multiple race subjects was 21.4%, 71.4%, and 7.1%, respectively. There were no Asian subjects that enrolled in the study.

Pharmacokinetic analyses

Rosuvastatin was rapidly absorbed, with detectable concentrations observed by the first measured time point (0.5 h) in all subjects, following oral doses of 10 mg rosuvastatin alone or in combination with 50 mg OM. Median rosuvastatin T_{max} appeared to be similar after dosing of rosuvastatin alone (3 h [range: 0.5 to 6 h]) or in combination with OM (4 h [range: 1 to 6.1 h]; Table 2). The plasma concentration-time profile for rosuvastatin is shown in Figure 1.

Based on AUC (AUC_{inf} and AUC_{last}) and C_{max} parameter values, systemic rosuvastatin exposures were higher when rosuvastatin was co-administered with OM, as shown in Table 2. Statistical analysis to evaluate the effect of OM on the PK of rosuvastatin showed that systemic rosuvastatin exposures increased when rosuvastatin was administered in combination with OM. The ratios of the GLSM of rosuvastatin co-administered with OM compared to rosuvastatin alone were 127.1%, 132.8%, and 154.2% for AUC_{inf}, AUC_{last}, and C_{max}, respectively (Table 2).

The arithmetic mean half-life ($t_{1/2}$) appeared to be slightly longer when rosuvastatin was administered alone at 13.6 h (10.2 h), compared to 9.72 h (3.68 h) when rosuvastatin was administered with OM.

Safety evaluation

Single oral doses of rosuvastatin 10 mg alone or in combination with OM 50 mg were safe and well-tolerated. Two treatment-emergent AEs were reported by two subjects (14.3%) following administration of OM in combination with rosuvastatin. No treatment-emergent AEs were reported following administration of rosuvastatin alone. All events were mild in severity and considered by the investigator to be not related to study treatments. There were no serious AEs or treatment-emergent AEs leading to discontinuation from the study.

PBPK modeling

Development and verification of the OM model

The PBPK model development and verification was a three-step process: estimation of distribution parameters, estimation of absorption parameters, and verification of the model through comparison of simulations to existing PK data. In order to estimate distribution parameters, a two compartment model was fit to clinical PK data following 35 mg i.v. OM dose using SAAM II software. The estimates (95% CI) for k_{12}, k_{21}, k_{10}, and V_c were 0.319 (0.186 to 0.452) h^{-1}, 0.200 (0.136 to 0.265) h^{-1}, 0.098 (0.079 to 0.116) h^{-1}, and 124.7 (102.18 to 147.2) L, respectively. The corresponding V_{sac} and V_{ss} values were 198.5 L and 323.3 L, respectively. The final parameters used in the OM model development in addition to the source of each parameter are listed in Table 3.

In order to estimate absorption parameters (CL_{po} and k_a), the minimal PBPK model with first order absorption was fit to plasma concentration-time profiles of oral OM administration following a single 50 mg dose and twice daily doses of 25 mg using the Simcyp simulator. The results are presented in Figure S3. The estimates (95% CI) for CL_{po} and k_a were 10.8 (95% CI

TABLE 2 Summary of PK parameters and statistical analysis of PK parameters for OM-rosuvastatin clinical drug interaction study

Parameter, unit	10 mg Rosuvastatin ($N = 14$)	10 mg Rosuvastatin + 50 mg OM ($N = 14$)
C_{max}, ng/ml	5.31 (2.50)	8.30 (3.88)
T_{max}, h	3.0 (0.50–6.0)	4.0 (1.0–6.1)
AUC_{inf}, h*ng/ml	58.6 (28.2)	76.8 (27.7)
AUC_{last}, h*ng/ml	55.5 (25.4)	72.8 (28.2)
$t_{1/2}$, h	13.6 (10.2)	9.72 (3.68)
	Statistical analysis	
Treatment	**PK parameter**	**GLSM (90% CI)**
10 mg Rosuvastatin (reference), 10 mg Rosuvastatin +50 mg OM (test)	C_{max}, ng/ml	154.2 (132.8, 179.1)
	AUC_{last}, h*ng/ml	132.8 (120.7, 146.1)
	AUC_{inf}, h*ng/ml	127.1 (113.8, 141.9)

Abbreviations: $AUC_{inf,}$ area under the plasma concentration-time curve (AUC) from time zero to infinity; AUC_{last}, AUC from time zero to time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed concentration; GLSM, geometric least-squares mean ratio; OM, omecamtiv mecarbil; PK, pharmacokinetics (PK data presented as mean [SD] and reported to 3 significant figures, except for T_{max} which is presented as median (range) and two significant figures); $t_{1/2}$, apparent plasma terminal elimination half-life; T_{max}, time to reach C_{max}.

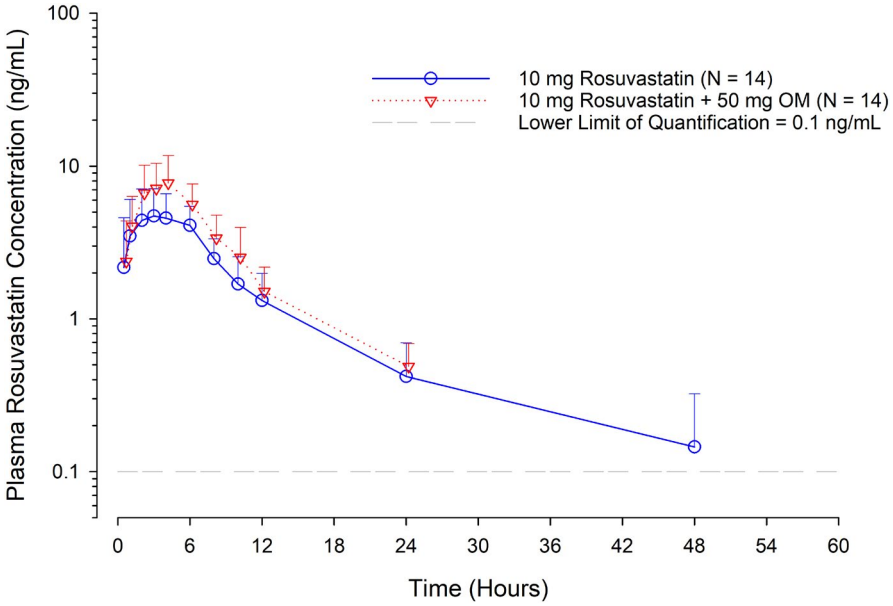

FIGURE 1 Arithmetic mean plasma concentration-time profiles of 10 mg single dose oral tablet of rosuvastatin administered alone and in combination with 50 mg single oral dose of omecamtiv mecarbil (OM) in healthy subjects. The dashed gray line represents the lower limit of quantitation. Error bars represent SD

10.3 to 11.3) L/h and 0.22 (95% CI 0.18 to 0.26) h^{-1}, respectively. The simulated C_{max}, T_{max}, and AUC were within twofold of the observed values, indicating an adequate model fit and a reasonable prediction of the observed data (Table 4).

Table 5 and Figure S4 summarize the results from the verification of the developed OM compound file. The details of the development of the OM compound file in healthy subjects are provided in Supplementary Materials. The simulated C_{max}, T_{max}, and AUC values were within a twofold range of the observed values. Thus, the developed OM PBPK compound file was considered verified.

Prediction of the perpetrator potential of OM toward BCRP inhibition

The parameters of the rosuvastatin compound file and validation of the rosuvastatin PBPK model are shown in Tables S3 and S4, respectively; and are visualized in Figure S5. The experimental methodology is provided in the Supplementary Material. The simulated and observed rosuvastatin plasma concentration-time profiles in the presence and absence of OM are presented in Figure S6. The BCRP K_i was identified to be 0.05 μM based on a sensitivity analysis. As shown in Table 6, the simulated C_{max}, T_{max}, and AUC values of rosuvastatin were within twofold of the observed values, indicating a reasonable prediction of the observed data. The predicted geometric mean (90% CI) ratios for rosuvastatin AUC and Cmax upon multiple 50 mg b.i.d. dosing of OM at steady-state for 14 days and rosuvastatin administration on the 10th day were 1.18 (90% CI 1.16, 1.20) and 2.04 (90% CI 1.99, 2.10), respectively.

DISCUSSION

BCRP is an efflux transporter that serves two major drug transport functions. First, it restricts the circulation and absorption of its substrates across the gastrointestinal tract. Second, it eliminates its substrates from excretory organs, facilitating both biliary and renal excretion, and infrequently direct gut secretion. Rosuvastatin represents a class of lipid-lowering medications commonly administered in patients with heart failure, which are commonly known to be substrates for the BCRP efflux pump transporter. The results from the in vitro studies demonstrate that OM is a weak inhibitor of BCRP, inhibiting BCRP with an IC_{50} of 2.9 μM. Basic models to estimate the magnitude of DDI expected in the gut as presented in FDA guidance use drug dose and in vitro inhibition potency as key inputs.[19] Based on either a 25 or 50 mg dose of OM and the measured BCRP IC_{50} (2.9 μM), a clinical BCRP DDI study was recommended due to the expected magnitude of interaction using the basic models. Therefore, a DDI study was conducted using rosuvastatin as a prototypical BCRP substrate to evaluate the potential effect of OM on rosuvastatin PK, due to known inhibition of BCRP by OM.

In this study, OM was administered as a single 50 mg oral tablet, which was the highest dose strength evaluated in the phase III study. Statistical analysis of the rosuvastatin PK parameters AUC_{inf}, AUC_{last}, and C_{max} showed that systemic exposure to rosuvastatin increased by ~ 27%, 33%, and 54%, respectively, when rosuvastatin was administered in combination with OM. Although there is no current standard classification for transporter inhibitors, the increase in rosuvastatin AUC (27%–33%) is analogous to a weak inhibition, with a magnitude of an interaction

TABLE 3 Parameters for OM PBPK model building

Parameter	Value	Source
Physiochemical properties		
Molecular weight (Da)	401.4	In-house data
LogP	3.71	In-house data
pK_a	5.10,6.10	In-house data
f_u in plasma	0.815	In-house data
Red blood cell partitioning	0.970	In-house data
P_{app} ($\times 10^{-6}$ cm/s, LLC-PK1 cell line)	31.1	In-house data
Absorption – first order model		
k_a (h^{-1})	0.220	Parameterized
$f_{u,gut}$	1.00	Assumed
Distribution – minimal PBPK model		
k_{12} (h^{-1})	0.319	Parameterized
k_{21} (h^{-1})	0.200	Parameterized
V_c (L/kg)	1.49	Parameterized
V_{sac} (L/Kg)	2.37	Calculated (V_{sac} = 198.5 L; mean weight 83.79 kg)
V_{ss} (L/kg)	3.86	Calculated (V_{ss} = 323.3 L; mean weight 83.79 kg)
Elimination		
CL_{po} (L/h)	10.8	Parameterized
Interaction parameters		
BCRP K_i (μM)	0.05	Estimated by sensitivity analysis

Abbreviations: CL_{po}, apparent oral clearance; f_u, unbound fraction in plasma; $f_{u,gut}$, unbound fraction in gut enterocytes; k_{12}, distribution rate constant from central to peripheral compartment; k_{21}, distribution rate constant from peripheral to central compartment; k_a, first order absorption rate constant; OM, omecamtiv mecarbil; PK, pharmacokinetics; V_c, volume of distribution in central compartment; V_{sac}, volume of peripheral compartment; V_{ss}, volume of distribution at steady-state.

that may be defined as minor (>1.25–<2.00) in the scenario of CYP inhibition with a sensitive substrate.[20] Based on these findings, OM appears to be a weak inhibitor of BCRP substrates.

The results and interpretation of data from the clinical study herein were based on the evaluation of a single 50 mg OM dose and a single 10 mg rosuvastatin dose. OM was administered as 25, 37.5, or 50 mg b.i.d. doses in patients with heart failure in the phase III study. For safety considerations, a clinical study with multiple doses of OM was not conducted in healthy subjects. Therefore, the inhibitory effect of OM following multiple 50 mg b.i.d. doses, which represents the highest possible dose and systemic exposures that can be achieved in patients with heart failure, was also evaluated on a BCRP substrate using a PBPK modeling approach. Although multiple dosing of 10 mg rosuvastatin is also a clinically relevant scenario, DDI simulations evaluating the administration of a single dose of 10 mg rosuvastatin is expected to result in a degree of OM-mediated BCRP inhibition that is similar or slightly less than that compared to multiple rosuvastatin dosing under the assumptions of linear PK. If multiple dosing results in the accumulation of rosuvastatin, higher circulating concentrations of rosuvastatin would compete for binding to BCRP and likely reduce the magnitude of OM-mediated DDI effects. Thus, a DDI assessment based on a single dose of rosuvastatin is expected to provide a more conservative estimate of the drug interaction.

To further investigate the DDI effect of OM on rosuvastatin, a PBPK model was constructed. Based on in vitro experimental data, the BCRP IC_{50} of OM was estimated to be 2.9 μM. Literature evidence suggests that the IC_{50} calculated by conventional approaches (and in turn, the K_i calculated therefrom) is a highly variable parameter and for transporters, depends on the transporter expression level of the cell system being used for the study.[18] Hence, in this case, although an experimental BCRP IC_{50} was available, sensitivity analysis was conducted to estimate the BCRP K_i of OM in a top-down manner by using the clinical DDI study data with rosuvastatin. A K_i value of

TABLE 4 Development of OM PBPK model - Simulated and observed OM PK parameters in healthy subjects after oral administration of a single 50 mg dose ($N = 14$) or 25 mg b.i.d. dose for 7 days

Study		Study 1[b] (Control group, $N = 14$)	Study 2[c] (Day 1, $N = 20$)	Study 2[d] (Day 8, $N = 20$)
OM dose		50 mg, single dose	25 mg, b.i.d.	25 mg, b.i.d.
T_{max}[a]	Observed	9.0 (3.0–12.0)	4.0 (0.5 −8.0)	2.0 (0.5–4.0)
(h)	Simulated	4.6 (0.8–15.5)	4.6 (0.9–12.1)	3.1 (0.8–4.4)
	Ratio[e]	0.51	1.15	1.55
C_{max}[a]	Observed	112 ± 19.1	77.4 ± 21.6	256 ± 71.2
(ng/ml)	Simulated	218 ± 229	114 ± 118	256 ± 108
	Ratio[e]	1.95	1.47	1.00
AUC_t[a]	Observed	4430 ± 1040	687 ± 210	2570 ± 739
(h*ng/ml)	Simulated	4956 ± 1627	930 ± 693	2512 ± 837
	Ratio[e]	1.12	1.35	0.98
AUC_{inf}[a]	Observed	4490 ± 1050	–	–
(h*ng/ml)	Simulated	5227 ± 1835		
	Ratio[e]	1.16		
$C_{predose}$	Observed	Not applicable	Not applicable	190 ± 58.5
(ng/ml)	Simulated			162 ± 70.9
	Ratio[e]			0.85

Abbreviations: $AUC_{inf,}$ area under the plasma concentration-time curve (AUC) from time zero to infinity; C_{max}, maximum observed concentration; OM, omecamtiv mecarbil; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetics; T_{max}, time to reach C_{max}.

[a]C_{max} and AUC are reported as mean values ± SD; T_{max} is reported as a median (range).

[b]$AUC_t = AUC_{144}$.

[c]C_{max} = day 1 C_{max}; T_{max}= day 1 T_{max}; AUC_t = day 1 AUC_{12}.

[d]C_{max} = day 8 C_{max}; T_{max}= day 8 T_{max}; AUC_t = day 8 AUC_{12}; $C_{predose}$ = $C_{predose}$ day 8.

[e]Ratio = ratio of simulated/observed results.

TABLE 5 Verification of OM PBPK model - Simulated and observed OM PK parameters in healthy subjects after 25 mg b.i.d. or 50 mg b.i.d. for 7 days

Study		Study 4[b] (Control group, $N = 13$)	Study 3[c] (Day 1, $N = 13$)	Study 3[d] (Day 8, $N = 13$)
OM dose		25 mg, b.i.d.	50 mg, b.i.d.	50 mg, b.i.d.
T_{max}[a]	Observed	2.0 (1.0, 11.8)	3.0 (0.5–6.0)	3.0 (0.5–4.0)
(h)	Simulated	3.1 (0.7–3.9)	4.6 (0.9–12.0)	3.1 (0.8–4.4)
	Ratio[e]	1.55	1.54	1.03
C_{max}[a]	Observed	229 ± 15	154 ± 22	537 ± 91.7
(ng/ml)	Simulated	266 ± 111	216 ± 223	506 ± 199
	Ratio[e]	1.16	1.4	0.94
AUC_t[a]	Observed	2520 ± 15	1330 ± 217	5490 ± 1000
(h*ng/ml)	Simulated	2624 ± 935	1768 ± 1243	5026 ± 1609
	Ratio[e]	1.04	1.33	0.92
$C_{predose}$	Observed	Not available	Not applicable	401 ± 77.8
(ng/ml)	Simulated			326 ± 146
	Ratio[e]			0.81

Abbreviations: $AUC_{,}$ area under the plasma concentration-time curve; C_{max}, maximum observed concentration; OM, omecamtiv mecarbil; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetics; T_{max}, time to reach C_{max}.

[a]C_{max} and AUC are reported as mean values ± SD; T_{max} is reported as a median (range).

[b]C_{max} = day 15 C_{max}; T_{max} = day 15 T_{max}; AUC = day 15 AUC_{tau}; $n = 13$.

[c]C_{max} = day 1 C_{max}; T_{max} = day 1 T_{max}; AUC = day 1 AUC_{12}; $n = 13$.

[d]C_{max} = day 8 C_{max}; T_{max} = day 8 T_{max}; AUC = AUC_{12}; $C_{predose}$ = $C_{predose}$ day 8; $n = 13$.

[e]Ratio = ratio of simulated/observed results.

TABLE 6 Simulated and observed rosuvastatin PK parameters in the presence and absence of a 50 mg single dose of OM

Study group		Rosuvastatin ($N = 14$)	Rosuvastatin + OM ($N = 14$)
T_{max}[a]	Observed	3.0 (0.5–6.0)	4.0 (1.0–6.1)
(h)	Simulated	4.2 (2.1–7.8)	2.1 (0.9–3.7)
	Ratio[b]	1.40	0.52
C_{max}[a]	Observed	5.3 ± 2.5	8.3 ± 3.9
(ng/ml)	Simulated	4.2 ± 1.4	7.8 ± 2.2
	Ratio[b]	0.79	0.94
AUC_{inf}[a]	Observed	58.6 ± 28.2	76.8 ± 27.7
(h*ng/ml)	Simulated	50.9 ± 15.9	58.8 ± 16.5
	Ratio[b]	0.87	0.76
AUC ratio	Observed	1.31	-
	Simulated	1.15	–
	Ratio[b]	1.14	–
C_{max} ratio	Observed	1.56	–
	Simulated	1.85	–
	Ratio[b]	1.19	–

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve (AUC) from time zero to infinity; C_{max}, maximum observed concentration; OM, omecamtiv mecarbil; PK, pharmacokinetics; T_{max}, time to reach C_{max}.

[a]C_{max} and AUC are reported as mean values ± SD; T_{max} is reported as a median (range).

[b]Ratio = ratio of simulated/observed results.

0.05 μM reasonably captured the observed C_{max}, T_{max}, and AUC values of rosuvastatin upon coadministration with a single dose of OM. Sensitivity analysis indicated that both the rosuvastatin AUC ratio as well as the C_{max} ratio were relatively insensitive to BCRP inhibition by OM for K_i values within the range of 0.0001 to 0.1 μM, and was increasingly sensitive for K_i values greater than 0.1 μM (Figure S7).

Without optimization of the K_i value from the single dose clinical DDI study, the PBPK model would not be able to successfully predict the magnitude of BCRP inhibition for the multiple doses DDI study. Alternate possibilities exist for the failure of the PBPK model to successfully predict the magnitude of BCRP inhibition. A simple, first order model was used to simulate OM absorption that may be insufficient to fully represent the inhibition processes involved; more complex absorption models may simulate BCRP inhibition in the gut more accurately. Additionally, interpretation of in vitro experimental results for efflux transporters is confounded by varying levels of transporter expression and the determination of the unbound drug fraction in the specific in vitro system; advancements in developing and modeling system-independent inhibition parameters offer promise for more effective translation of in vitro inhibition to the prediction of DDI magnitude in the clinical situation.[21]

The predicted geometric mean (90% CI) rosuvastatin AUC and C_{max} ratios upon multiple b.i.d. dosing of 50 mg OM were 1.18 (90% CI 1.16, 1.20) and 2.04 (90% CI 1.99, 2.10), respectively. The predicted rosuvastatin AUC ratio upon b.i.d. dosing of OM to steady-state was higher than that predicted based upon single dosing. The summary of the results from the clinical study and PBPK modeling analyses confirm that OM is expected to be a weak inhibitor of BCRP in the clinical setting.

CONCLUSIONS

The results of the clinical drug interaction study showed that systemic exposure to rosuvastatin increased when rosuvastatin was administered in combination with a single dose of OM. The PBPK modeling analysis predicted a similarly mild DDI effect of multiple doses of OM on rosuvastatin PKs as expected based on the single dose clinical study results. Overall, rosuvastatin administered alone or in combination with OM was found to be safe and well-tolerated when administered to healthy male and female subjects in this study.

CONFLICT OF INTEREST

A.T., W.S., P.K., P.J., H.Z., M.S., S.A., J.W., E.L., and S.D. are employees and shareholders of Amgen, Inc. P.K. was a full-time employee of Amgen and worked on this assignment and is a current shareholder in Amgen. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.T., P.K., and J.W. wrote the manuscript. A.T., W.S., P.K., P.J., H.Z., S.F., J.W., E.L., and S.D. designed and performed the research. All authors analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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