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Effect of Roxadustat on the Pharmacokinetics of Simvastatin, Rosuvastatin, and Atorvastatin in Healthy Subjects: Results From 3 Phase 1, Open-Label, 1-Sequence, Crossover Studies

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Abstract

Roxadustat inhibits breast cancer resistance protein and organic anion transporting polypeptide 1B1, which can affect coadministered statin concentrations. Three open-label, 1-sequence crossover phase 1 studies in healthy subjects were conducted to assess effects from steady-state 200-mg roxadustat on pharmacokinetics and tolerability of 40-mg simvastatin (CL-0537 and CL-0541), 40-mg atorvastatin (CL-0538), or 10-mg rosuvastatin (CL-0537). Statins were dosed concomitantly with roxadustat in 28 (CL-0537) and 24 (CL-0538) healthy subjects, resulting in increases of maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from the time of dosing extrapolated to infinity (AUC_{inf}) 1.87- and 1.75-fold for simvastatin, 2.76- and 1.85-fold for simvastatin acid, 4.47- and 2.93-fold for rosuvastatin, and 1.34- and 1.96-fold for atorvastatin, respectively. Additionally, simvastatin dosed 2 hours before, and 4 and 10 hours after roxadustat in 28 (CL-0541) healthy subjects, resulted in increases of C_{max} and AUC_{inf} 2.32- to 3.10-fold and 1.56- to 1.74-fold for simvastatin and 2.34- to 5.98-fold and 1.89- to 3.42-fold for simvastatin acid, respectively. These increases were not attenuated by time-separated statin dosing. No clinically relevant differences were observed for terminal elimination half-life. Concomitant 200-mg roxadustat and a statin was generally well tolerated during the study period. Roxadustat effects on statin C_{max} and AUC_{inf} were statin and administration time dependent. When coadministered with roxadustat, statin-associated adverse reactions and the need for statin dose reduction should be evaluated.

Keywords

chronic kidney disease, prolyl hydroxylase inhibitors, renal anemia, roxadustat, statins

Anemia is a common complication of chronic kidney disease (CKD) and is associated with left ventricular dysfunction, heart failure, poor quality of life, and mortality.[1–3] Anemia of CKD occurs due to impaired oxygen sensing and reduced synthesis of erythropoietin by failing kidneys and therefore worsens with declining kidney function.[4] Iron therapies and erythropoiesis-stimulating agents are currently the standard treatment for anemia of CKD.[5–7] However, studies have highlighted shortcomings related to the mode of administration[8] (eg, injectable), safety[8–10] (eg, increased risk of cardiovascular complications when targeting near-normal hemoglobin levels), and efficacy[11,12] (eg, hyporesponsiveness) of these treatments in some patients with CKD.[8,9,11,12]

Another class of agents, hypoxia-inducible factor prolyl hydroxylase inhibitors, has recently emerged

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as an alternative treatment option for anemia of CKD.[1,13] These agents induce a response similar to the body's natural response to hypoxia (independent of cellular oxygen levels), which results in the activation of erythropoiesis, improved iron transport, and an increase in hemoglobin levels.[14,15] Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor developed for the treatment of anemia with both dialysis-dependent and non–dialysis-dependent CKD.[16–19] When administered orally in healthy subjects, roxadustat is rapidly absorbed, reaches maximum plasma concentration (C_{max}) within 2 hours, and has a terminal elimination half-life ($t_{1/2}$) of ≈12 hours after single-dose administration.[20,21] Roxadustat has demonstrated efficacy and a favorable safety profile in the treatment of anemia of CKD in >15 phase 3 clinical trials with ≈10 000 patients with CKD, encompassing patients who are non–dialysis dependent, hemodialysis dependent, and peritoneal dialysis dependent, as well as newly initiated dialysis patients.[7] Roxadustat has been approved in multiple countries for the treatment of anemia in dialysis-dependent CKD and non–dialysis-dependent CKD at an initial dose of 50, 70, or 100 mg 3 times weekly.[22]

Roxadustat could be coadministered with statins in patients with CKD with dyslipidemia.[23] Absorption and/or elimination of statins involve the breast cancer resistance protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).[24–27] These transporters play an important role in drug disposition due to their ubiquitous presence in the intestine, liver, and kidney.[24–26] In vitro results have indicated an inhibitory potential of roxadustat for the transporters BCRP and OATP1B1 at clinically relevant concentrations, which could result in increased statin exposure (unpublished data). Roxadustat is a lipophilic acid that achieves steady-state plasma concentrations within 1 week (3 doses) with minimal accumulation; its metabolism primarily occurs through phase I oxidation (cytochrome P450 [CYP] 2C8) and phase II conjugation (glucuronidation via uridine diphosphate-glucuronosyltransferases), resulting in maximum plasma concentrations (C_{max}) within 2 hours after dosing in the fasted state and no metabolites with >10% of drug-related material exposure.[28] Following active transport into the liver and metabolism, roxadustat is excreted by the kidney with <2% of a dose recovered in the urine as unchanged roxadustat.[29] Based on in vitro data, at clinically relevant concentrations roxadustat may be an inhibitor of CYP2C8, BCRP, OATP1B1, and organic anion transporting polypeptide 3 but is unlikely to inhibit P-glycoprotein (unpublished data). Roxadustat is an inhibitor of CYP2B6, CYP2C8, and CYP2C9 in vitro, with inhibition constant (K_i) values of 110, 16, and 140 μmol/L, respectively. However, roxadustat did not inhibit bupropion (probe CYP2B6 substrate), rosiglitazone (probe CYP2C8 substrate), or warfarin (S-warfarin probe CYP2C9 substrate), suggesting the clinical implications for these enzymes are minimal. Roxadustat demonstrated little or no inhibition of CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5 in vitro, with K_i or half maximal inhibitory concentration estimates of 370 μM and higher. Roxadustat inhibits the transport activities of BCRP and OATP1B1 in vitro, with half maximal inhibitory concentration values of 3.05 and 2.59 μmol/L, respectively (unpublished data). Drug-drug interactions for roxadustat have been explored, including the reduction in roxadustat concentrations by phosphate binding agents, which was mitigated by separating administration by ≥1 hour. This is in contrast to the minimal or no clinical impact seen with spherical carbon absorbent, a proton pump inhibitor, or warfarin.[28,30–32] Roxadustat may be an inhibitor of intestinal but not hepatic uridine diphosphate-glucuronosyltransferase 1A1 and showed no inhibition of other CYP metabolizing enzymes or transporters, or induction of CYP enzymes at clinically relevant concentrations (unpublished data). The area under the plasma concentration–time curve (AUC) of roxadustat and its metabolites is higher in patients with severely impaired kidney function compared to normal kidney function, and roxadustat and its metabolites are not significantly cleared by hemodialysis or hemofiltration.[29] Roxadustat is highly protein bound (99%) to predominantly albumin.[28]

Because of the association between adverse events (AEs) and statin use, such as rhabdomyolysis, it is important to characterize the behavior of statins and roxadustat.[33] Therefore, the current studies were conducted to determine the effect of roxadustat on the pharmacokinetics of a single oral dose of atorvastatin, simvastatin, and rosuvastatin to assess in vivo inhibitory potential of roxadustat on BCRP and OATP1B1 transporters. Additionally, because the timing of statin dosing in relation to roxadustat dosing could attenuate these effects, time-separated administration was investigated. These studies also evaluated the safety and tolerability of roxadustat alone and in combination with selected statins.

Material and Methods

Study Design

All 3 studies, CL-0537, CL-0538, and CL-0541, were phase 1 open-label, 1-sequence crossover studies in healthy subjects. These studies assessed the effect of 200-mg roxadustat on the pharmacokinetics, safety, and tolerability of single oral doses of simvastatin (CL-0537 and CL-0541), rosuvastatin (CL-0537), and atorvastatin (CL-0538). These statins were chosen on the

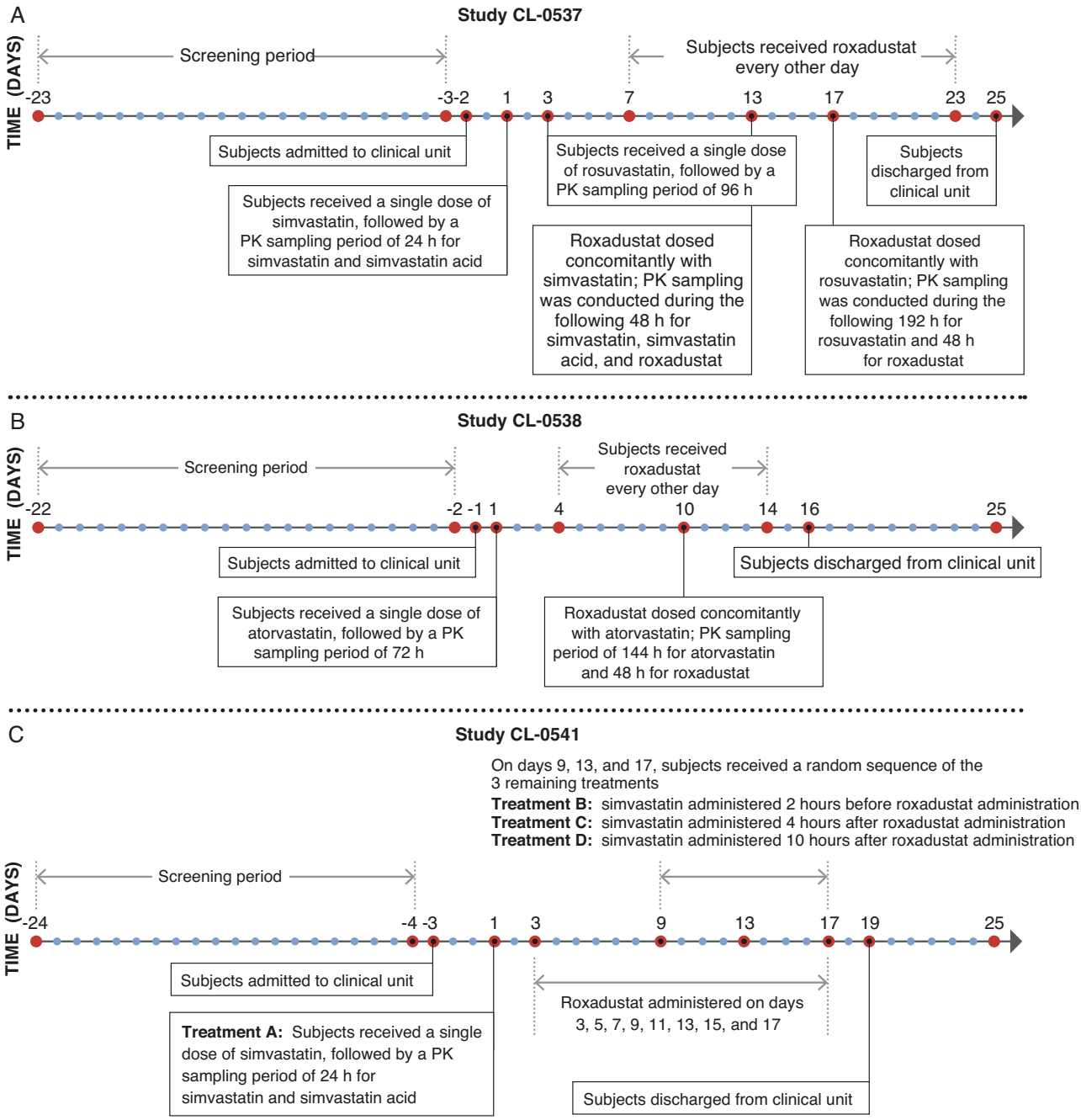

Figure 1. Timeline for administration of study medication in studies CL-0537 (A), CL-0538 (B), and CL-0541 (C). PK, pharmacokinetic.

basis of clinical use and expected interaction potential with roxadustat. Per regulatory guidelines, a therapeutic dose of roxadustat expected to be at the high end of the likely clinical dosing range was chosen to maximize the chance of potential interactions, if any, while still avoiding safety concerns based on existing safety and tolerability data with roxadustat. Following the screening period, subjects were admitted to the clinical unit and received the study medications as shown in Figure 1. Simvastatin and simvastatin acid plasma concentrations were evaluated before dosing and then after dosing at 30 minutes, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours as well as at 36 and 48 hours with roxadustat coadministration. Atorvastatin plasma concentrations were evaluated similarly to simvastatin and simvastatin acid as well as at 48 and 72 hours without roxadustat coadministration and at 96, 120, and 144 hours with roxadustat coadministration. Rosuvastatin plasma concentrations were evaluated before dosing; at 30 minutes and 4, 24, 48, and 96 hours initially; then every 24 hours

up to 192 hours with roxadustat coadministration. All treatments were administered orally with 240 mL of water. Roxadustat was administered as 2 × 100-mg tablets per dose every other day, simvastatin as 1 × 40-mg tablet per dose (CL-0537 and CL-0541), rosuvastatin as 1 × 10-mg tablet per dose (CL-0537), and atorvastatin as 1 × 40-mg tablet per dose (CL-0538). In studies CL-0537 and CL-0538, statins were dosed concomitantly with roxadustat. In study CL-0541, simvastatin was dosed 2 hours before and 4 and 10 hours after roxadustat. All study drug administrations occurred after an overnight fast of at least 10 hours. Water intake (except for the water to be given to swallow the tablet) was not allowed from at least 2 hours before dosing until 2 hours after dosing. When simvastatin, rosuvastatin, or atorvastatin were administered alone or concomitantly with roxadustat, the first meal was provided 4 hours after dosing; when roxadustat was administered alone, the first meal was provided 2 hours after dosing.

At the end of the pharmacokinetic sampling period, subjects were discharged from the clinical unit on the condition that all required assessments had been performed and no medical reasons were cited that required a prolonged stay. The clinical study was completed with an end-of-study visit, which took place after the last treatment or after early withdrawal. Safety assessments were performed throughout the clinical study as per a predefined assessment schedule. The clinical study was conducted in accordance with the clinical study protocol, Good Clinical Practice, International Conference on Harmonization guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

Study Population

These studies included healthy male or female subjects aged 18 to 55 years, with a body mass index of 18.5 to 29.9 kg/m^2. Subjects were excluded if they had results from liver chemistry tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin) that were >1.5 times the upper limit of normal or if they used any prescribed or nonprescribed drugs before study drug administration (except for occasional use of paracetamol) or used any drugs of abuse or inducer of metabolism within 3 months before admission to the clinical unit.

These studies were approved by the Ethics Committee of the Land Berlin and conducted at Parexel Berlin. A total of 76 subjects were enrolled in studies CL-0537, CL-0538, and CL-0541. All subjects completed the respective studies. The demographics and baseline characteristics were comparable across both studies (Table 1). There were no deviations in treatment compliance or deviations in relationship to dates/times of meals in any study. Subjects were categorized based on BCRP and OATP1B1 mutations. Most subjects (≈60%-80%) in all studies were BCRP wild type/wild type, and at least 75% were OATP1B1 G11187A wild type/wild type.

Table 1. Demographics and Baseline Characteristics

Category	Study CL-0537 n = 28	Study CL-0538 n = 24	Study CL-0541 n = 24
Age, y	40.1 (11.5)	43.5 (10.2)	45.0 (9.9)
Sex, n (%)			
Male	16 (57.1)	15 (62.5)	12 (50.0)
Female	12 (42.9)	9 (37.5)	12 (50.0)
Race, n (%)			
White	27 (96.4)	24 (100.0)	23 (95.8)
Other	1 (3.6)	0 (0.0)	1 (4.2)
Height, cm	173.2 (11.5)	174.2 (6.8)	170.58 (7.72)
Weight, kg	77.3 (13.4)	76.8 (8.6)	73.3 (8.8)
BMI, kg/m^2	25.7 (2.8)	25.3 (2.5)	25.2 (2.2)

BMI, body mass index; SD, standard deviation.
Data are expressed as mean (SD), unless otherwise indicated. All variables were assessed using the safety analysis set.

Study Objectives and Parameters

The pharmacokinetic parameters included the AUC from the time of dosing extrapolated to infinity (AUC_{inf}) and C_{max} for simvastatin, rosuvastatin, and atorvastatin. Additional pharmacokinetic parameters for simvastatin, rosuvastatin, and atorvastatin included the AUC from the time of dosing to the last measurable concentration (AUC_{last}), apparent total systemic clearance after extravascular dosing (CL/F), time before the time corresponding to the first measurable concentration (t_{lag}), time of maximum concentration (t_{max}), and $t_{1/2}$.

Additional parameters for simvastatin acid included AUC_{last}, t_{lag}, t_{max}, $t_{1/2}$, and the metabolite-parent ratio in plasma, as well as the AUC from the time of dosing to 24 hours after dosing, AUC from the time of dosing to the start of the next dosing interval, C_{max}, concentration immediately before dosing at multiple dosing, CL/F, t_{max}, and $t_{1/2}$ for roxadustat. Additionally, the urinary 6β-hydroxycortisol/cortisol ratios were calculated from a 24-hour urine collection for each subject on days −1, 13, and 23 in study CL-0537.

Safety was assessed by monitoring nature, frequency, and severity of AEs, vital signs, laboratory tests, and routine 12-lead electrocardiogram. An AE was considered a treatment-emergent AE (TEAE) if it was not present before the first dose of study drug or if

it was present before the first dose of the study drug but increased in severity during the treatment period. An AE was considered serious by either the investigator or sponsor if it resulted in death or was life threatening, resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, resulted in congenital anomaly or birth defect, required inpatient hospitalization or led to prolongation of hospitalization, or resulted in any other medically important event.

Analytic Assay Methods

Blood samples were obtained via a peripherally placed intravenous cannula or by direct venipuncture in a forearm vein. Roxadustat plasma samples (CL-0537 and CL-0538) were collected in 3-mL tubes containing sodium heparin, shipped to the Bioanalysis section of Astellas Pharma Europe B.V., and measured using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. Roxadustat and the stable isotope label ([$^{13}C_2$, D_3]-roxadustat) as the internal standard (IS) were extracted by solid phase extraction (SPE) using an Oasis HLB 30 μm 96 well-plate (Waters Corp., Milford, Massachusetts), and separated by a column of Gemini C18, 3 μm, 50 $\times$ 2.1 mm (Phenomenex, Torrance, California). Detection was performed via a 4000 QTrap mass spectrometer (AB Sciex, Framingham, Massachusetts) using positive Turbo ion spray ionization with mass transitions of m/z 353.1 $\rightarrow$ 278.1 for roxadustat and m/z 358.1 $\rightarrow$ 281.1 for IS. The calibration range was 1–1000 ng/mL with the lower limit of quantification (LLOQ) of 1 ng/mL using 100 μL plasma. The interrun accuracy of roxadustat varied between -9.5% and -4.2% in study CL-0537 or -8.4% and -4.9% in study CL-0538, while the interrun precision ranged between 2.5% and 7.3% in study CL-0537 or 2.6% and 4.3% in study CL-0538.

The samples of simvastatin, simvastatin acid, and atorvastatin were collected in 4-mL tubes containing lithium heparin, and samples of rosuvastatin were collected in 4-mL tubes containing dipotassium-ethylenediaminetetraacetic acid. All plasma samples of simvastatin, simvastatin acid, rosuvastatin, and atorvastatin in studies CL-0537, CL-0538, and CL-0541 were shipped to SGS Cephac Europe (St. Benoit, France) and measured using validated LC-MS/MS methods.

Simvastatin, simvastatin acid, and the stable isotope labels ([D_6]-simvastatin and [D_6]-simvastatin acid) as the ISs were extracted by liquid-liquid extraction using tert-butylmethylether and separated by a column of Kromasil C18, 5 μm, 150 $\times$ 4.6 mm (Interchim, Montluçon, France) in study CL-0537 or a column of Kinetex, 2.6 μm, 50 $\times$ 2.1 mm (Phenomenex, Le Pecq, France) in study CL-0541. Detections were performed on a Sciex API3000 mass spectrometer (AB Sciex, Les Ulis, France) using positive and negative Turbo ion spray ionization with mass transitions of m/z 419.4 $\rightarrow$ 199.1 for simvastatin, m/z 435.2 $\rightarrow$ 319.2 for simvastatin acid, m/z 425.4 $\rightarrow$ 199.2 for IS of simvastatin, and m/z 441.2 $\rightarrow$ 319.2 for IS of simvastatin acid in study CL-0537 or a Sciex API4000 mass spectrometer (AB Sciex) using positive Turbo ion spray ionization with mass transitions of m/z 419.3 $\rightarrow$ 199.2 for simvastatin, m/z 437.3 $\rightarrow$ 303.2 for simvastatin acid, m/z 425.3 $\rightarrow$ 199.3 for IS of simvastatin, and m/z 443.4 $\rightarrow$ 303.2 for IS of simvastatin acid in study CL-0541. The calibration range of both simvastatin and simvastatin acid was 250–50,000 pg/mL with the LLOQ of 250 pg/mL using 250 μL plasma in study CL-0537 or 100–50,000 pg/mL with the LLOQ of 100 pg/mL using 200 μL plasma in study CL-0541. The interrun accuracy of simvastatin and simvastatin acid varied between -7.3% and 6.2% in study CL-0537 or -5.9% and 6.7% in study CL-0541, while the interrun precision ranged between 3.1% and 6.8% in study CL-0537 or 3.7% and 6.5% in study CL-0541.

Rosuvastatin and the stable isotope label ([^{13}C, D_4]-rosuvastatin) as the IS were extracted by protein precipitation using acetonitrile and separated by a column of Kinetex, 2.6 μm, 50 $\times$ 2.1 mm. Detection was performed on a Sciex API4000 mass spectrometer using positive Turbo ion spray ionization with mass transitions of m/z 482.1 $\rightarrow$ 258.1 for rosuvastatin and m/z 487.2 $\rightarrow$ 263.1 for IS. The calibration range was 100–60,000 pg/mL with the LLOQ of 100 pg/mL using 250 μL plasma. The interrun accuracy of rosuvastatin varied between -6.2% and 5.6%, while the interrun precision ranged between 2.1% and 4.1% in study CL-0537.

Atorvastatin and the stable isotope label ([D_5]-atorvastatin) as the IS were extracted by SPE using Oasis HLB cartridges 30 mg (Waters Corp.) and separated by a column of Atlantis dC18, 5 μm, 150 $\times$ 2.1 mm (Waters Corp.). Detection was performed on a Sciex API3000 mass spectrometer using positive Turbo ion spray ionization with mass transitions of m/z 559.3 $\rightarrow$ 440.2 for atorvastatin and m/z 564.3 $\rightarrow$ 445.2 for IS. The calibration range was 100–50,000 pg/mL with the LLOQ of 100 pg/mL using 250 μL plasma. The interrun accuracy of rosuvastatin varied between -4.4% and 1.0%, while the interrun precision ranged between 1.8% and 2.2% in study CL-0538.

Urine samples were collected in study CL-0537 for measurements of cortisol and 6β-hydroxycortisol. Volume of urine samples, date, and time of collection interval were recorded. Then urine samples were shipped to SGS Cephac Europe and were measured using a validated LC-MS/MS method.

Cortisol and 6β-hydroxycortisol, the stable isotope labels ([D_4]-cortisol and [D_4]-6β-hydroxycortisol) as the ISs, were extracted by SPE using Oasis HLB cartridges 30 mg (Waters Corp.) and separated by a column of Chromolith RP18e, 100 × 4.6 mm (Merck, Molsheim, France). Detection was performed on a Sciex API4000 mass spectrometer using positive Turbo ion spray ionization with mass transitions of m/z 363.3 → 121.1 for cortisol, m/z 379.3 → 343.3 for 6β-hydroxycortisol, m/z 367.3 → 121.0 for IS of cortisol, and m/z 383.2 → 347.2 for IS of 6β-hydroxycortisol. The calibration range was 1–100 ng/mL for cortisol with the LLOQ of 1 ng/mL using 500 μL urine, and 10–3000 ng/mL for 6β-hydroxycortisol with the LLOQ of 10 ng/mL using 500 μL urine. The interrun accuracy of cortisol and 6β-hydroxycortisol varied between −4.4% and 7.9%, while the interrun precision ranged between 2.2% and 5.1% in study CL-0537.

Pharmacokinetic Analysis

The pharmacokinetic parameters were calculated using traditional, noncompartmental methods in Phoenix software (Pharsight Corp., Mountain View, California) version 6.2.1.

Statistical Analysis

In study CL-0537, the within-subject coefficient of variation (CV) for pharmacokinetic parameters AUC_{inf} and C_{max} of simvastatin, simvastatin acid, and rosuvastatin were estimated to be between 14% (AUC_{inf} for rosuvastatin) and 47% (C_{max} for simvastatin) based on previous data.[34] A total of 28 subjects were to be enrolled in the clinical study. Subjects who discontinued early could be replaced at the discretion of the sponsor.

In study CL-0538, the within-subject CV for pharmacokinetic parameters AUC_{inf} and C_{max} of atorvastatin were estimated to be between 12.2% (AUC_{inf}) and 32.4% (C_{max}) based on data from a previous clinical study (NCT01635946). A total of 24 subjects were to be enrolled in the clinical study.

In study CL-0541, the within-subject CV for pharmacokinetic parameters AUC_{inf} and C_{max} of simvastatin, simvastatin acid was estimated to be ≈43%. A total of 24 subjects were to be enrolled in the clinical study. Subjects who discontinued early could be replaced at the discretion of the sponsor.

Baseline characteristics, concentrations, and pharmacokinetic parameters were summarized using descriptive statistics. For C_{max} and AUC, the geometric mean was also calculated as described by Martinez and Bartholomew.[35] Pharmacokinetic parameters, AUC_{inf} and C_{max} for simvastatin, simvastatin acid, rosuvastatin, and atorvastatin were analyzed using a mixed-effects model. The effect of roxadustat on the pharmacokinetics of a single oral dose of simvastatin, rosuvastatin, and atorvastatin was assessed by evaluating the differences between combination treatment and treatment with each drug alone with 90%CIs. These were back transformed to the natural scale to provide estimates for the ratio of the magnitude of the interaction. As a secondary analysis, AUC_{last} was analyzed using the same methodology as described for AUC_{inf}.

In study CL-0537, 6β-hydroxycortisol/cortisol ratios were analyzed using a mixed-effects model applied to the log-transformed ratios with clinical study day (day −1, 13, or 23).

Results

Pharmacokinetic Parameters

Administration of simvastatin in the presence of roxadustat resulted in consistently higher mean simvastatin (Figure 2A and 2B) and simvastatin acid concentrations (Figure 2C and 2D) compared with simvastatin alone. Administration of rosuvastatin in the presence of roxadustat resulted in consistently higher mean rosuvastatin concentration compared with rosuvastatin alone (Figure 3A), and atorvastatin in the presence of roxadustat resulted in consistently higher mean atorvastatin concentration compared with atorvastatin alone (Figure 3B). Pharmacokinetic parameters of simvastatin, rosuvastatin, and atorvastatin after administration of each statin alone and in the presence of roxadustat are summarized in Tables 2 to 4. Based on the geometric least squares mean ratio, the presence of roxadustat resulted in higher C_{max} for simvastatin, simvastatin acid, rosuvastatin, and atorvastatin, compared with administration of each statin alone (Tables 5 and 6). In CL-0537 and CL-0538, increases of C_{max} and AUC_{inf} 1.87- and 1.75-fold for simvastatin, 2.76- and 1.85-fold for simvastatin acid, 4.47- and 2.93-fold for rosuvastatin, and 1.34- and 1.96-fold for atorvastatin, respectively, were observed. In study CL-0541, simvastatin was dosed 2 hours before, and 4 and 10 hours after roxadustat, resulting in increases of C_{max} and AUC_{inf} 2.32- to 3.10-fold and 1.56- to 1.74-fold for simvastatin and 2.34- to 5.98-fold and 1.89- to 3.42-fold for simvastatin acid, respectively (Table 3).

In studies CL-0537 and CL-0541, the geometric least squares mean ratio of metabolite-parent ratio (ie, the ratio of metabolite, simvastatin acid to parent, simvastatin) indicated that the metabolism of simvastatin was not affected by the presence of roxadustat. The intersubject variability in C_{max} and AUC_{inf} was comparable in the presence of roxadustat and when the statins were administered alone.

In studies CL-0537 and CL-0538, mean $t_{1/2}$ for simvastatin and simvastatin acid, rosuvastatin, and atorvastatin were not affected by roxadustat coadministration. In study CL-0541, the mean $t_{1/2}$ of

Table 2. Summary of Plasma Pharmacokinetic Parameters of Simvastatin and Simvastatin Acid, Rosuvastatin, and Atorvastatin After Single-Dose Administration of Simvastatin Alone, Rosuvastatin Alone, Atorvastatin Alone, and in the Presence of Roxadustat (CL-0537 and CL-0538 Pharmacokinetic Analysis Set)

	Simvastatin – CL-0537		Simvastatin acid – CL-0537		Rosuvastatin – CL-0537		Atorvastatin – CL-0538	
Parameter	Simvastatin Alone	Roxadustat + Simvastatin	Simvastatin Alone	Roxadustat + Simvastatin	Rosuvastatin Alone	Roxadustat + Rosuvastatin	Atorvastatin Alone	Roxadustat + Atorvastatin
C_{max}, pg/mL								
N	28	28	28	28	28	28	24	24
Mean (SD)	6185 (4891)	11 987 (7830)	2168 (1500)	5913 (3512)	4939 (2991)	22 980 (12 787)	16 181 (7145)	23 441 (17 153)
Median (min-max)	4775 (0–25 043)	10 512 (2602–32 968)	2060 (0–6198)	4671 (1807–14 448)	4062 (0–13 775)	19 811 (4059–58 463)	13 787 (4086–32 858)	17 585 (7047–89 554)
AUC_{inf}, pg • h/mL								
N	24	26	19	28	27	28	24	24
Mean (SD)	38 703 (23 827)	71 234 (49 695)	31 628 (17 858)	53 322 (33 539)	67 613 (33 727)	196 187 (95 367)	103 254 (63 441)	200 146 (119 078)
Median (min-max)	31 682 (14 278–89 921)	53 151 (18 539–216,950	28 578 (5720–71 340)	43 931 (13 567–146 986)	57 187 (21 336–165 242)	177 873 (48 036–503 953)	89 352 (34 764–334 245)	166 618 (75 351–622 976)
AUC_{last}, pg • h/mL								
N	28	28	28	28	28	28	24	24
Mean (SD)	30 587 (23 659)	63 356 (48 889)	21 897 (16 393)	48 870 (31 225)	61 459 (34 796)	192 156 (95 253)	100 074 (62 420)	196 935 (118 588)
Median (min-max)	23 849 (0–82 146)	47 728 (13 224–212 919)	16 214 (0–62 181)	40 497 (10 992–128 877)	54 017 (0–159 223)	173 565 (43 917–498 457)	86 772 (33 229–326 168)	163 717 (73 568–616 962)
t_{max}, h								
N	27	28	27	28	27	28	24	24
Mean (SD)	1.47 (1.14)	1.79 (1.29)	5.70 (2.77)	4.05 (1.11)	3.90 (0.75)	3.43 (0.69)	0.90 (0.63)	1.69 (1.65)
Median (min-max)	1.02 (0.50–6.03)	1.51 (0.50–6.00)	4.02 (2.00–12.00)	4.02 (2.07–8.07)	4.00 (3.00–6.02)	4.00 (2.00–4.03)	0.50 (0.50–3.00)	1.00 (0.50–8.00)
$t_{1/2}$, h								
N	24	26	19	28	27	28	24	24
Mean (SD)	6.06 (2.67)	7.12 (2.80)	6.28 (2.13)	5.98 (3.22)	15.48 (5.07)	16.81 (4.96)	10.67 (2.76)	10.93 (3.22)
Median (min-max)	5.68 (2.05–12.40)	6.40 (3.08–13.00)	5.78 (3.08–12.10)	5.266 (2.59–18.6)	15.18 (6.70–27.3)	16.11 (10.40–35.20)	10.18 (7.05–17.40)	11.09 (6.34–17.90)

(*Continued*)

Table 2. Continued

Parameter	Simvastatin – CL-0537		Simvastatin acid – CL-0537		Rosuvastatin – CL-0537		Atorvastatin – CL-0538	
	Simvastatin Alone	Roxadustat + Simvastatin	Simvastatin Alone	Roxadustat + Simvastatin	Rosuvastatin Alone	Roxadustat + Rosuvastatin	Atorvastatin Alone	Roxadustat + Atorvastatin
t_{lag}, h								
N	27	28	27	28	27	28	24	24
Mean (SD)	0 (0.0)	0 (0.0)	0.47 (0.31)	0.29 (0.35)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Median (min-max)	0 (0–0)	0 (0–0)	0.50 (0–1.00)	0 (0–1.02)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
CL/F, L/h								
N	24	26	…	…	27	28	24	24
Mean (SD)	1407 (719.7)	838.9 (520.2)	…	…	185.3 (91.3)	63.4 (35.8)	505.9 (253.4)	253.6 (114.5)
Median (min-max)	1263 (445–2802)	752.9 (184–2158)	…	…	174.9 (60.5–469)	56.22 (19.8–208)	447.7 (120–1151)	240.1 (64.2–531)

AUC_{inf}, area under the plasma concentration–time curve from the time of dosing extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from the time of dosing to the last measurable concentration; CL/F, apparent total systemic clearance after extravascular dosing; C_{max}, maximum plasma concentration; max, maximum recorded values; min, minimum recorded values; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; time before the time corresponding to the first measurable (non-0) concentration; t_{max}, time to maximum concentration.

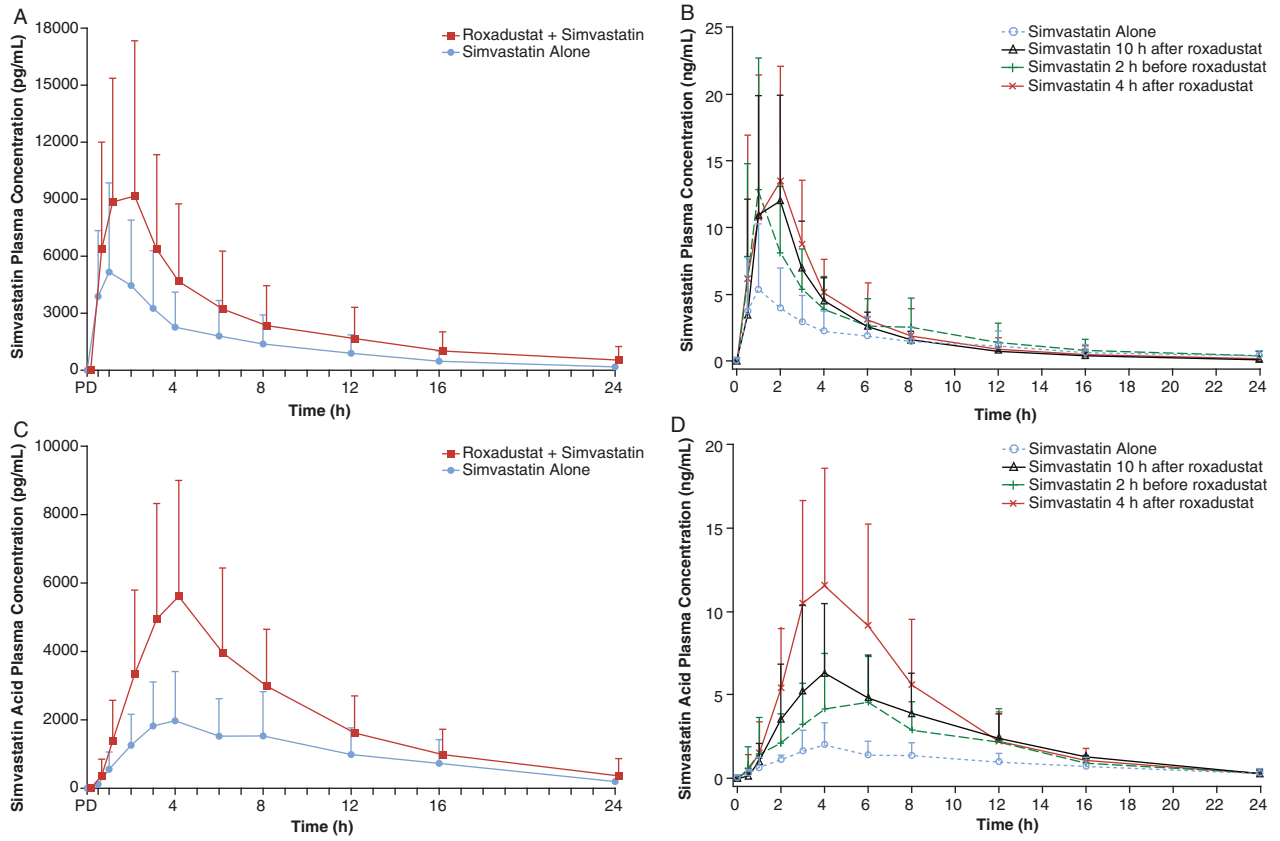

Figure 2. Mean concentration-time profiles of simvastatin (A, B) and simvastatin acid (C, D) after single-dose administration alone and in the presence of roxadustat (linear scale; CL-0537 and CL-0541 pharmacokinetic analysis set). Error bars represent the upper limit of the standard deviation. PD, predose.

simvastatin was 5.8 hours when administered 2 hours before roxadustat. Administration 4 and 10 hours after roxadustat reduced the $t_{1/2}$ of simvastatin from ≈6.9 hours to 4.2 and 4.4 hours, respectively.

The CL/F of simvastatin, rosuvastatin, and atorvastatin were 40%, 66%, and 50% lower, respectively, in the presence of roxadustat compared with administration of rosuvastatin alone. In study CL-0541, time-separated administration of simvastatin 2 hours before, 4 hours after, and 10 hours after roxadustat resulted in 42%, 51%, and 46% lower mean CL/F of simvastatin, respectively.

In studies CL-0537 and CL-0538, with respect to the pharmacokinetics of roxadustat, assessment of predose trough plasma concentrations of roxadustat indicated that steady-state levels were reached before assessment of the pharmacokinetics of concomitant simvastatin (day 13), rosuvastatin (day 17), and atorvastatin (day 10). This was maintained until day 25 for simvastatin and rosuvastatin and until day 16 for atorvastatin. Similarly, in study CL-0541, assessment of predose trough plasma concentrations of roxadustat indicated that steady-state levels were reached before and maintained during assessment of pharmacokinetics of simvastatin and simvastatin acid in combination with roxadustat, time-separately administered on days 9, 13, and 17. Across all 3 studies, there was no apparent effect of a single dose of simvastatin, rosuvastatin, or atorvastatin on mean roxadustat trough concentrations. In addition, across all 3 studies, all of the observed pharmacokinetic parameters (C_{max}, t_{max}, AUC from the time of dosing to the start of the next dosing interval, $t_{1/2}$, and CL/F) of roxadustat were similar when administered with simvastatin, rosuvastatin, or atorvastatin (data not shown).

In study CL-0537, compared with baseline (day −1), after 4 (day 13), and 9 (day 23) doses of 200-mg roxadustat once every other day, the urinary 6β-hydroxycortisol/cortisol ratios as a measure of CYP3A4 activity were increased by 1.3- and 1.2-fold, respectively. Additionally, the intrasubject variability was ≈40%, suggesting that roxadustat exerted a minimal effect (1.3-fold) on the activity of CYP3A4 in vivo.

Safety

Overall, no deaths, serious AEs, or TEAEs leading to permanent discontinuation of the study drug or from the study occurred during any study.

Table 3. Summary of Plasma Pharmacokinetic Parameters of Simvastatin After Single-Dose Administration of Simvastatin Alone, 2 Hours Before, 4 Hours After, and 10 Hours After Administration of Roxadustat (CL-0541 Pharmacokinetic Analysis Set)

	C_{max}, ng/mL	t_{max}, h	AUC_{last}, ng • h/mL	AUC_{inf}, ng • h/mL	$t_{1/2}$, h	CL/F, L/h
Simvastatin alone						
N	24	24	24	24	24	24
Mean (SD)	6.52 (4.45)	1.815 (1.58)	33.21 (22.21)	37.74 (26.11)	6.928 (2.40)	1775 (1627)
Median (min-max)	5.53 (1.80–20.10)	1.01 (0.500–6.00)	27.43 (4.01–91.40)	29.79 (4.98–100)	6.573 (2.08–14.30)	1343 (399–8028)
Simvastatin administered 2 hours before roxadustat						
N	24	24	24	24	24	24
Mean (SD)	14.62 (9.12)	1.09 (0.60)	57.16 (35.76)	60.99 (37.07)	5.83 (1.91)	1038 (950.50)
Min-max	3.01–46.40	0.50–3.02	8.23–150	9.07–154	3.34–10.90	260–4408
Median (min-max)	13.88 (3.01–46.40)	1.00 (0.50–3.02)	51.87 (8.23–150)	59.15 (9.07–154)	5.30 (3.34–10.90)	676 (260–4408)
Simvastatin administered 4 hours after roxadustat						
N	24	24	24	24	24	24
Mean (SD)	18.59 (8.99)	1.54 (0.77)	57.57 (32.98)	58.92 (33.88)	4.17 (0.74)	870.90 (474.30)
Median (min-max)	17.28 (6.25–41.80)	2.00 (0.50–3.00)	55.34 (16.10–174)	56.54 (16.60–181)	4.08 (2.79–5.88)	707 (221–2410)
Simvastatin administered 10 hours after roxadustat						
N	24	24	24	24	24	24
Mean (SD)	15.16 (9.51)	1.74 (0.76)	49.66 (22.05)	50.99 (22.15)	4.42 (0.83)	959 (511)
Median (min-max)	13.03 (3.79–41.00)	2.00 (0.52–4.00)	47.41 (13.70–113)	48.83 (14.40–114)	4.25 (2.93–6.04)	819 (351–2773)

AUC_{inf}, area under the plasma concentration–time curve from the time of dosing extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from the time of dosing to the last measurable concentration; CL/F, apparent total systemic clearance after extravascular dosing; C_{max}, maximum plasma concentration; max, maximum recorded values; min, minimum recorded values; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time to maximum concentration.

In CL-0537, the investigator considered 2 TEAEs reported for 2 (7.1%) subjects after receiving rosuvastatin alone, 4 TEAEs reported for 4 (14.3%) subjects after receiving roxadustat alone, 5 TEAEs reported for 3 (10.7%) subjects after receiving roxadustat in combination with simvastatin, and 1 TEAE reported for 1 (3.6%) subject after receiving roxadustat in combination with rosuvastatin to be related to the study drug.

In CL-0538, the investigator considered 2 TEAEs reported for 2 (8.3%) subjects after receiving atorvastatin alone, 3 TEAEs reported for 2 (8.3%) subjects after receiving roxadustat alone, and 7 TEAEs reported for 5 (20.8%) subjects after receiving roxadustat in combination with atorvastatin to be possibly related to the study drug.

In CL-0541, a total of 6 TEAEs were reported for 5 (20.8%) subjects after receiving simvastatin alone, 12 TEAEs were reported for 9 (37.5%) subjects after receiving simvastatin administered 2 hours before roxadustat, 8 TEAEs were reported for 6 (25.0%) subjects after receiving simvastatin administered 4 hours after roxadustat and 9 TEAEs were reported for 4 (16.7%) subjects after receiving simvastatin administered 10 hours after roxadustat. The investigator considered 1 TEAE of dizziness reported for 1 (4.2%) subject after receiving simvastatin administered 4 hours after roxadustat and 2 TEAEs of dizziness reported for 1 (4.2%) subject after receiving simvastatin administered 10 hours after roxadustat, to be possibly related to the study drug; no TEAEs were considered by the investigator to be probably related to the study drug.

The most commonly reported TEAEs were nasopharyngitis (roxadustat, 0.0%; simvastatin, 0.0%; rosuvastatin, 0.0%; roxadustat + simvastatin, 3.6%;

Table 4. Summary of Plasma Pharmacokinetic Parameters of Simvastatin Acid After Single-Dose Administration of Simvastatin Alone, 2 Hours Before, 4 Hours After, and 10 Hours After Administration of Roxadustat (CL-0541 Pharmacokinetic Analysis Set)

	C_{max}, ng/mL	t_{max}, h	AUC_{last}, ng • h/mL	AUC_{inf}, ng • h/mL	$t_{1/2}$, h	MPR
Simvastatin alone						
N	24	24	24	22	22	22
Mean (SD)	2.12 (1.31)	5.38 (3.09)	22.17 (11.98)	24.31 (13.36)	7.00 (2.72)	0.78 (0.28)
Median (min-max)	1.72 (0.36–5.56)	4.00 (3.00–16.00)	19.70 (4.83–48.90)	21.20 (5.68–54.30)	6.36 (4.18–15.10)	0.80 (0.34–1.40)
Simvastatin administered 2 hours before roxadustat						
N	24	24	24	23	23	23
Mean (SD)	4.99 (3.36)	5.55 (1.39)	44.71 (32.70)	48.67 (33.95)	4.60 (1.60)	0.81 (0.34)
Median (min-max)	4.50 (1.27–14.90)	6.00 (3.00–8.03)	38.17 (11.30–163)	41.01 (12.10–170)	4.27 (3.09–10.10)	0.76 (0.38–1.83)
Simvastatin administered 4 hours after roxadustat						
N	24	24	24	24	24	24
Mean (SD)	12.77 (7.67)	4.01 (1.10)	82.81 (47.99)	84.69 (48.71)	3.75 (0.97)	1.52 (0.78)
Median (min-max)	11.60 (2.64–27.40)	4.00 (2.02–6.00)	68.90 (19.10–183)	70.35 (19.90–188)	3.45 (2.53–5.76)	1.56 (0.44–3.33)
Simvastatin administered 10 hours after roxadustat						
N	24	24	24	24	24	24
Mean (SD)	7.13 (5.11)	4.40 (1.40)	57.41 (31.29)	59.43 (31.78)	4.16 (0.90)	1.23 (0.54)
Median (min-max)	6.10 (1.85–26.40)	4.01 (2.05–7.98)	49.83 (16.40–138)	50.54 (18.40–139)	3.87 (3.10–6.40)	1.21 (0.21–2.25)

AUC_{inf}, area under the plasma concentration–time curve from the time of dosing extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from the time of dosing to the last measurable concentration; C_{max}, maximum plasma concentration; max, maximum recorded values; min, minimum recorded values; MPR, metabolite-to-parent ratio; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time to maximum concentration.

roxadustat + rosuvastatin, 14.3%) and headache (roxadustat, 7.1%; simvastatin, 0.0%; rosuvastatin, 0.0%; roxadustat + simvastatin, 3.6%; roxadustat + rosuvastatin, 3.6%) in the CL-0537 study (Table S1) and dry mouth (roxadustat, 8.3%; atorvastatin, 0.0%; roxadustat + atorvastatin, 0.0%) and headache (roxadustat, 4.2%; atorvastatin, 4.2%; roxadustat + atorvastatin, 8.3%) in the CL-0538 study (Table S2). In CL-0541, the most common TEAE was headache reported in 8.3% of subjects when simvastatin was administered alone, 16.7% of subjects when simvastatin was administered 2 hours before roxadustat, 4.2% of subjects when simvastatin was administered 4 hours after roxadustat, and 8.3% of subjects when simvastatin was administered 10 hours after roxadustat (Table S3).

The majority of the TEAEs reported for subjects across all 3 studies were ascertained to be mild in severity by the investigator. No clinically significant changes were observed in any of the clinical laboratory values, vital signs, or 12-lead electrocardiogram assessments.

Discussion

Statins, the most common therapy for dyslipidemia, are expected to be administered with roxadustat in patients with dyslipidemia and anemia of CKD. The current drug-drug interaction studies help to estimate the increase in statin exposure in healthy subjects based on 3 selected statins with distinct pharmacokinetic profiles and relatively large predicted effects with roxadustat, when administered concomitantly with roxadustat. These studies determined the effect of roxadustat, dosed at 200 mg every other day, on the pharmacokinetics of single doses of simvastatin 40 mg, rosuvastatin 10 mg, and atorvastatin 40 mg. A dose of 200-mg roxadustat was selected, as this was in line with a high-range therapeutic dose, which maximized the chance of potential interactions through an inhibition of enzyme activity, if any, in line with regulatory guidelines and without any safety concerns based on existing safety and tolerability data with roxadustat.[36] Single doses of low- to moderate-to-high-dose statins were deemed

Table 5. Statistical Analysis of the Effect of Roxadustat on the Primary Pharmacokinetic Variables of Simvastatin, Simvastatin Acid, Rosuvastatin, and Atorvastatin (CL-0537 and CL-0538 Pharmacokinetic Analysis Set)

Comparison	Parameter	GLS Mean for Statin Alone[a]	GLS Mean for Roxadustat + Statin[a]	GLS Mean Ratio (%)[b]	90%CI of Ratio[b]
Simvastatin					
Simvastatin + roxadustat/simvastatin alone	C_{max}, pg/mL	5469	10 218	186.84	156.45–223.12
	AUC_{inf}, pg • h/mL	33 433	58 493	174.95	146.60–208.80
Simvastatin acid					
Simvastatin + roxadustat/simvastatin alone	C_{max}, pg/mL	1862	5133	275.70	234.49–324.16
	AUC_{inf}, pg • h/mL	24 621	45 668	185.48	154.04–223.34
Rosuvastatin					
Rosuvastatin + roxadustat/rosuvastatin alone	C_{max}, pg/mL	4652	20 810	447.33	386.18–518.16
	AUC_{inf}, pg • h/mL	62 878	183 951	292.55	263.18–325.20
Atorvastatin					
Atorvastatin + roxadustat/atorvastatin alone	C_{max}, pg/mL	15 328	20 562	134.15	110.75–162.50
	AUC_{inf}, pg • h/mL	94 068	184 510	196.14	170.50–225.65

AUC_{inf}, area under the concentration–time curve from the time of dosing extrapolated to infinity; C_{max}, maximum concentration; GLS, geometric least squares.

Data are based on a linear mixed-effects model of natural log-transformed parameters with treatment and sex as fixed effects and subject as a random effect.

[a]The exponentiated value of the least squares mean based on natural log-transformed data.

[b]Ratios and their confidence limits are transformed back to raw scale and values are expressed as percentages.

appropriate for this assessment considering their linear pharmacokinetics.

Concomitant administration of roxadustat with simvastatin, rosuvastatin, or atorvastatin resulted in changes in the pharmacokinetics of all 3 statins compared with administration of each statin alone. In addition, when the time of statin administration was varied between 2 hours before and 10 hours after roxadustat administration, the effects on C_{max} and AUC_{inf} were not attenuated. However, while roxadustat increased the C_{max} and AUC_{inf} of all 3 statins, the $t_{1/2}$ values were not affected by roxadustat, suggesting the potential for a more nuanced drug-drug interaction. In particular, the C_{max} and AUC_{inf} were most affected for rosuvastatin, likely because of rosuvastatin being a sensitive substrate of OATP1B1 and BCRP.[24,26] There was no apparent effect of a single dose of simvastatin, rosuvastatin, or atorvastatin on mean roxadustat trough concentrations.

With respect to safety, multiple oral doses of 200-mg roxadustat administered concomitantly with single oral doses of simvastatin, rosuvastatin, and atorvastatin in healthy male and female subjects was generally considered safe and well tolerated in these studies. In the current studies, roxadustat 200 mg did not result in any deaths, serious TEAEs, or AEs leading to discontinuation of study drug or discontinuation from the study during the observation periods.

The current data of the effects of roxadustat on simvastatin, rosuvastatin, and atorvastatin exposure are consistent with an inhibition of both OATP1B1 and BCRP transporters. An interaction between statins and substrates of OATP1B1 or BCRP has been reported to change the pharmacokinetics of pitavastatin and rosuvastatin, though inhibition of OATP1B1 is more likely to have affected the volume of distribution and CL/F to a similar extent such that the $t_{1/2}$ is likely to be minimally affected or unaffected.[37,38] Additionally, many statins are metabolized via the CYP3A4 isoenzyme. Measurement of the urinary hydroxycortisol/cortisol as well as the similar ratio of simvastatin acid to simvastatin before and after roxadustat administration appears to suggest that roxadustat exerted minimal to no effect on

Table 6. Statistical Analysis of the Effect of Time-Separated Administration of Simvastatin and Roxadustat on the Pharmacokinetics of Simvastatin and Simvastatin Acid (CL-0541 Pharmacokinetic Analysis Set)

Comparison	Parameter	Time Separation	GLS Mean for Simvastatin Alone[a]	GLS Mean for Simvastatin + Roxadustat[a]	GLS Mean Ratio, %[b]	90%CI of Ratio, %[b]
Simvastatin						
Simvastatin + roxadustat/simvastatin alone	C_{max}, ng/mL	Simvastatin 2 h before	5.357	12.41	231.64	192.23–279.13
		Simvastatin 4 h after		16.62	310.24	257.45–373.84
		Simvastatin 10 h after		12.78	238.54	197.95–287.44
	AUC_{inf}, ng • h/mL	Simvastatin 2 h before	29.79	50.11	168.22	144.41–195.97
		Simvastatin 4 h after		51.93	174.32	149.64–203.07
		Simvastatin 10 h after		46.43	155.86	133.79–181.56
Simvastatin acid						
Simvastatin + roxadustat/simvastatin alone	C_{max}, ng/mL	Simvastatin 2 h before	1.759	4.115	234.02	198.72–275.60
		Simvastatin 4 h after		10.52	598.05	507.83–704.30
		Simvastatin 10 h after		5.922	336.75	285.95–396.58
	AUC_{inf}, ng • h/mL	Simvastatin 2 h before	20.97	39.59	188.82	161.56–220.67
		Simvastatin 4 h after		71.81	342.47	293.65–399.39
		Simvastatin 10 h after		52.72	251.43	215.60–293.22

AUC_{inf}, area under the plasma concentration–time curve from the time of dosing extrapolated to infinity; C_{max}, maximum concentration; GLS, geometric least squares.

Data are based on a linear mixed-effects model of natural log-transformed parameters with treatment and sex as fixed effects and subject as a random effect.

[a]The exponentiated value of the least squares mean based on natural log-transformed data.

[b]Ratios and their confidence limits are transformed back to raw scale and values are expressed as percentages.

the activity of CYP3A4 in vivo, which is consistent with a lack of in vitro inhibition of roxadustat on CYP3A4, though extensive inter- and intraindividual variability may limit the interpretation of these results.[39]

These drug-drug interaction studies in healthy subjects informed the design of phase 3 studies, during which it was advised that the statin doses not exceed the maximum recommended dose. Concomitant use of statins at this dose was considered generally safe in the CKD population with no reports of myositis or other statin-related side effects.[40,41]

A limitation of this study is that the study population consisted of healthy subjects and therefore may not represent the real-world CKD population. The pharmacokinetics of non–renally cleared drugs in patients with CKD are difficult to predict due to alterations in the expression and activity of extrarenal drug-metabolizing enzymes and transporters localized in the liver and intestine; however, the effect of roxadustat-induced organic anion transporting polypeptide inhibition on statin pharmacokinetics may be less in patients with CKD compared to healthy subjects as OATP activity is already somewhat reduced in CKD.[42–44] Another limitation is a small sample size; however, 3 commonly prescribed statins as well as the pharmacologically active simvastatin acid were tested, including variations in the timing of dose, which improve the generalizability of these data.[45]

In conclusion, when statins were dosed concomitantly with roxadustat in healthy subjects, C_{max} and

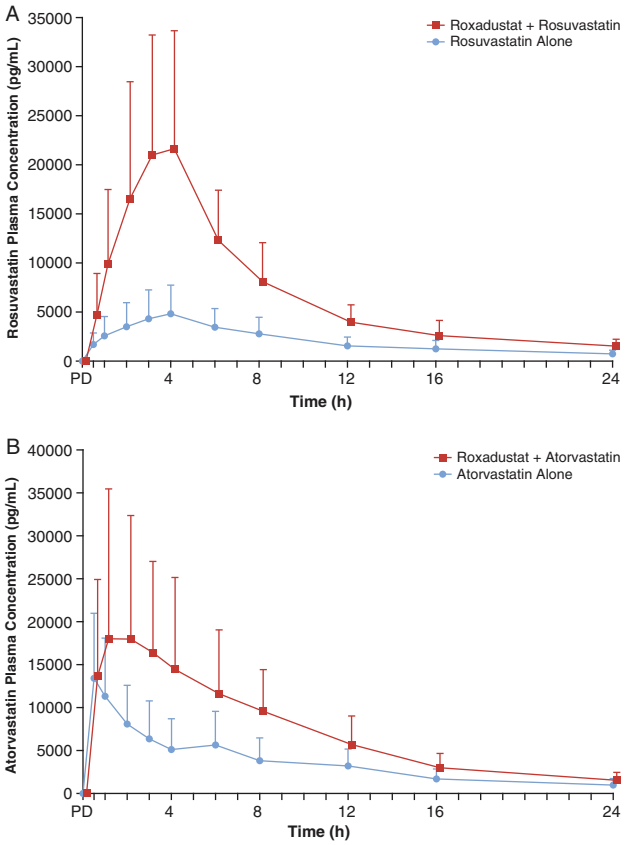

Figure 3. Mean concentration-time profiles of rosuvastatin (A) and atorvastatin (B) after single-dose administration alone and in the presence of roxadustat (linear scale; pharmacokinetic analysis set). Error bars represent the upper limit of the standard deviation. PD, predose.

AUC_{inf} increased 1.87- and 1.75-fold for simvastatin, 2.76- and 1.85-fold for simvastatin acid, 4.47- and 2.93-fold for rosuvastatin, and 1.34- and 1.96-fold for atorvastatin, respectively. When the timing of the simvastatin dose in relation to roxadustat was varied, these increases were not attenuated. The intersubject variability in C_{max} and AUC_{inf} was comparable in the presence of roxadustat and when the statins were administered alone. When coadministered with roxadustat, statin-associated adverse reactions and the need for statin dose reduction should be evaluated.

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Conflicts of Interest

V.K. reported personal fees from Astellas Pharma, Inc. during the conduct of the study and outside the submitted work. D.G.-vdM., J.vD., T.S., K.K., and M.S. are employees of Astellas Pharma, Inc. M.dA. was an employee of Astellas Pharma, Inc. during the conduct of the study

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