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Effect of Upadacitinib on the Pharmacokinetics of Rosuvastatin or Atorvastatin in Healthy Subjects

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Abstract

This phase 1, 2-part, 2-period, open-label, drug-drug interaction study evaluated the potential for pharmacokinetic interactions between upadacitinib and rosuvastatin, an organic anion transporting polypeptide (OATP) 1B1 and breast cancer resistance protein substrate, or atorvastatin, a cytochrome P450 3A, OATP1B1, and OATP1B3 substrate, in 36 healthy volunteers. During period 1, a single dose of rosuvastatin (5 mg; part 1) or atorvastatin (10 mg; part 2) was administered on day 1, followed by a washout period of 5 days. During period 2, once-daily doses of upadacitinib extended-release (30 mg) were administered on days 1 to 10, and a single dose of rosuvastatin (5 mg; part 1) or atorvastatin (10 mg; part 2) was administered 1 hour after the upadacitinib dose on day 7. Serial blood samples were collected for assays of drug concentrations. In Part 1, rosuvastatin maximum observed plasma concentration (C_{max}) and area under the plasma concentration–time curve from time 0 to infinity (AUC_{inf}) were 23% and 33% lower, respectively, when administered with upadacitinib relative to when administered alone. In part 2, atorvastatin C_{max} and AUC_{inf} was 11% and 23% lower, respectively, when administered with upadacitinib relative to when administered alone. The C_{max} and AUC_{inf} of the active metabolite ortho-hydroxyatorvastatin remained unchanged. Administration of a single 5-mg dose of rosuvastatin or a single 10-mg dose of atorvastatin had no relevant effect on upadacitinib C_{max} or area under the plasma concentration–time curve. These results demonstrated that upadacitinib has no clinically relevant effect on the pharmacokinetics of rosuvastatin and atorvastatin or on substrates transported by OATP1B or breast cancer resistance protein.

Keywords

ABT-494, atorvastatin, BCRP, OATP1B1, P-gp, rosuvastatin, upadacitinib

Upadacitinib is an oral, selective, and reversible inhibitor of Janus kinase 1, which was approved for the treatment for moderate-to-severe rheumatoid arthritis (RA) by the US Food and Drug Administration, the European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency, and other regulatory agencies. Additionally, upadacitinib is currently being evaluated for the treatment of other autoimmune diseases in several phase 3 clinical trials.[1–6] The approved dose of upadacitinib in subjects with moderate to severe RA is 15 mg once daily using an extended-release formulation based on results from phase 3 clinical trials that evaluated both 15 mg and 30 mg once daily doses and demonstrated that upadacitinib 15 mg once daily maximizes efficacy in RA.[4–11]

Upadacitinib pharmacokinetics have been characterized in healthy subjects and in patient populations for several autoimmune diseases (eg, RA, Crohn disease, ulcerative colitis).[9,12–16] Upadacitinib is a nonsensitive substrate of cytochrome P450 (CYP) 3A.[12,17] In a clinical cocktail drug interaction study, administration of upadacitinib 30 mg once daily (twice the approved dose in RA) in healthy subjects resulted in a decrease in midazolam area under the plasma concentration–

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time curve (AUC) and maximum observed plasma concentration (C_{max}) of 26% when administered with upadacitinib relative to when administered alone.[18] This limited effect on the CYP3A probe substrate midazolam is not expected to be clinically relevant and aligns with the lack of effect of upadacitinib on exposures of levonorgestrel and ethinylestradiol, 2 oral contraceptives that are also CYP3A substrates.[19] No relevant effects on CYP1A2, CYP2C9, CYP2C19, or CYP2D6 activity were observed following upadacitinib dosing in the cocktail drug interaction study.[18] Upadacitinib is a substrate for P-glycoprotein and breast cancer resistance protein (BCRP) based on in vitro assessments; however, modulation of P-glycoprotein and BCRP transporters is not expected to have clinically relevant effects on upadacitinib plasma exposures.[12] Based on in vitro assessments, upadacitinib is not expected to inhibit the transporters BCRP and organic anion transporting polypeptide (OATP) 1B1 at clinically relevant concentrations.[12]

Patients with chronic inflammation are at risk for developing cardiovascular disease,[20] and they may be prescribed statins while taking upadacitinib. Atorvastatin and rosuvastatin, 2 commonly prescribed statins, function as competitive inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes a rate-limiting step in cholesterol biosynthesis and reduces plasma low-density lipoprotein cholesterol concentrations associated with cardiovascular disease.[21] Atorvastatin is extensively metabolized, primarily by CYP3A,[22,23] to a number of metabolites. Approximately 70% of circulating HMG-CoA reductase inhibitory activity can be attributed to the active metabolites of atorvastatin, including the main metabolite ortho-hydroxyatorvastatin.[24] Both atorvastatin and its metabolites are substrates for cellular uptake through OATP1B1 and OATP1B3.[25,26] Rosuvastatin, on the other hand, is not extensively metabolized, and the majority of the active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.[27] The main metabolite of rosuvastatin, N-desmethyl rosuvastatin, is formed principally by CYP2C9 and has minimal inhibitory activity of HMG-CoA reductase compared to rosuvastatin.[27] Rosuvastatin is a substrate for cellular uptake through OATP1B1[25,27] and cellular efflux through BCRP.[25,28]

This study was conducted to evaluate the effect of administration of multiple doses of upadacitinib on the pharmacokinetics of rosuvastatin and atorvastatin and the effect of single doses of these statins on the pharmacokinetics of upadacitinib at steady state. Results from this study informed the prescribing instructions on concomitant administration of upadacitinib with rosuvastatin and atorvastatin.

Methods

The study was conducted at the AbbVie Clinical Pharmacology Research Unit (Grayslake, Illinois) in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocol and informed consent form were approved by the institutional review board (Vista Medical Center East Institutional Review Board, Vista Health System, Waukegan, Illinois), and participants provided written informed consent before any study-related procedures were performed.

Study Subjects

Healthy men and women (postmenopausal or surgically sterile) aged 18 to 55 years with a body mass index between 18 and 29 kg/m^2 were enrolled on the basis of screening results of a medical history, physical examination, vital signs assessments, laboratory profile, and a 12-lead electrocardiogram (ECG). Subjects with any history or evidence of active tuberculosis (TB) disease, latent TB infection, or a history of a positive TB skin test; any active or recurrent viral infection; significant illness/infection/major febrile illness; hospitalization; or who had any surgical procedure within 30 days before the first dose of the study drug were excluded from this study. Use of tobacco or nicotine-containing products, a history of clinically significant drug or alcohol use within 180 days before the first dose of study drug administration, or a positive screen for drugs of abuse/alcohol/nicotine resulted in those subjects being excluded from this study. Subjects were also excluded if they had received an organ transplant or used any over-the-counter or prescription medication, vitamins, or herbal supplements on a regular basis. Use of any known inhibitors or inducers of drug-metabolizing enzymes within 30 days before the study start and through the course of the study was prohibited. Subjects with prior exposure to upadacitinib or any other Janus kinase inhibitor within the 3 months before the first dose of the study drug administration were also excluded from participation in the study.

Study Design

This was a phase 1, single-center, open-label study to evaluate the effects of coadministration of upadacitinib on the pharmacokinetics of rosuvastatin and atorvastatin as well as the effect of single doses of these statins on upadacitinib steady-state pharmacokinetics (Figure 1). The study consisted of 2 parts, with 2 treatment periods in each study part. A single dose of rosuvastatin (5 mg) or atorvastatin (10 mg) was administered on day 1 of period 1 for part 1 and part 2, respectively. During period 2 of both parts of this study, upadacitinib 30 mg was dosed alone once daily for

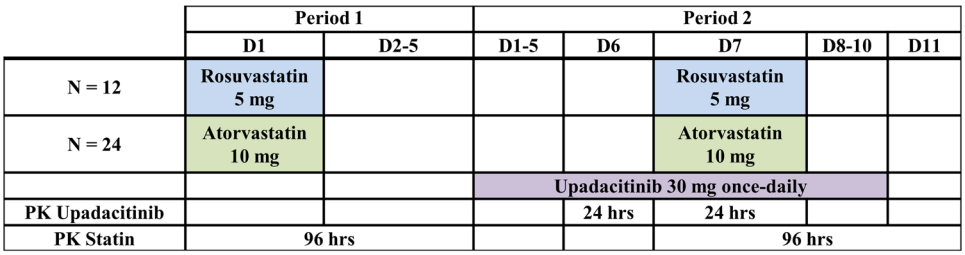

Figure 1. Study design schematic.

10 days and rosuvastatin (in part 1) or atorvastatin (in part 2) was administered 1 hour following upadacitinib dosing on day 7. Part 1 was conducted in 12 healthy subjects, and part 2 was conducted in 24 healthy subjects, given the higher within-subject variability in atorvastatin pharmacokinetics compared to rosuvastatin.[29,30] All study drugs were administered orally with ≈240 mL of water under nonfasting conditions. Rosuvastatin and atorvastatin were administered in period 2 one hour after administration of upadacitinib extended-release formulation to account for the delay in upadacitinib absorption from the extended-release formulation under nonfasting conditions.

Pharmacokinetic Sampling and Bioanalysis

Serial blood samples were collected in dipotassium ethylenediaminetetraacetic acid–containing collection tubes to determine plasma concentrations of upadacitinib and rosuvastatin and sodium heparin-containing collection tubes to determine the plasma concentrations of atorvastatin and ortho-hydroxyatorvastatin. For rosuvastatin, samples were collected starting on day 1 of period 1 and day 7 of period 2 at 0 (before dosing), 0.5, 1, 2, 3, 4, 5, 6, 8, 11, 15, 23, 36, 48, 72, and 96 hours after dosing rosuvastatin. For the atorvastatin and ortho-hydroxyatorvastatin, samples were collected starting on day 1 of period 1 and day 7 of period 2 at 0 (before dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11, 15, 23, 36, 48, 72, and 96 hours after dosing atorvastatin. For upadacitinib, samples were collected on day 6 of period 2 at 0 (before dosing), 0.5, 1, 2, 3, 4, 7, 9, 12, and 16 hours after upadacitinib dosing. Additional samples were collected on day 7 of period 2 before upadacitinib dosing (0 hour; 24 hours after day 6 upadacitinib dose); at 0.5 and 1 hour before the statin dose; and at 2, 3, 4, 7, 9, 12, 16, and 24 hours after upadacitinib dosing.

Plasma samples for upadacitinib were stored frozen at ≈–20°C and plasma samples for rosuvastatin, atorvastatin, and ortho-hydroxyatorvastatin were stored at –70°C until analyzed. Plasma concentrations of upadacitinib were determined using a validated salt-assisted liquid/liquid extraction with liquid chromatography method with tandem mass spectrometry detection by the Drug Analysis Department at AbbVie (North Chicago, Illinois) as described previously.[31] Plasma concentrations of rosuvastatin, atorvastatin, and ortho-hydroxyatorvastatin were determined using a validated liquid chromatography method with tandem mass spectrometry detection (PPD Inc, Middleton, Wisconsin).

For the atorvastatin/ortho-hydroxyatorvastatin, the analytes of interest were extracted by liquid/liquid extraction from 100-μL sample volume combined with 50 μL of the internal standards (atorvastatin-d_5, ortho-hydroxyatorvastatin-d_5) . Chromatographic separation for atorvastatin/ortho-hydroxyatorvastatin was achieved using a Betasil C18 column (5 μm, 2.1 × 50 mm; Thermo Fisher Scientific, Waltham, Massachusetts) and gradient mobile phase. Mobile phase A consisted of 1000/1 water:formic acid (v/v), mobile phase B consisted of 500:500:1 acetonitrile:methanol:formic acid (v/v/v), and mobile phase C consisted of 90/10 acetone:water (v/v). Chromatographic separation for rosuvastatin was achieved using a Gemini C18 column (5 μm, 2 × 50 mm; Phenomenex, Torrance, California) and gradient mobile phase. Mobile phase A consisted of 40/60/0.05 methonal:water:1.0 M ammonium acetate, 2% acetic acid to pH 6 (v/v/v); and mobile phase B consisted of 100% methanol. An API 3000 mass spectrometer (AB Sciex, Framingham, Massachusetts) employing electrospray ionization in positive ion mode was used to monitor the analyte for atorvastatin/ortho-hydroxyatorvastatin. Multiple reaction monitoring transitions were m/z 559.2 → 440.3 for atorvastatin and 575.3 → 440.3 for ortho-hydroxyatorvastatin. For atorvastatin, the lower limit of quantification was 0.100 ng/mL, and intraday precision and accuracy/bias as demonstrated by the performance of the quality control samples were between 1.98% and 5.97% and between −7.91% and 6.41%, respectively. Interday precision and accuracy/bias for atorvastatin were between 4.40% and 7.51% and between −1.58% and 0.334%, respectively. For ortho-hydroxyatorvastatin, the lower limit of quantification was 0.100 ng/mL, and intraday precision and accuracy/bias as demonstrated by the performance of the quality control samples were between 2.43% and 6.36% and between −2.61% and 9.64%, respectively. Interday precision and accuracy/bias for

ortho-hydroxyatorvastatin were between 4.38% and 5.95% and between 2.39% and 5.89%, respectively.

For the rosuvastatin assay, the analyte of interest was extracted by liquid/liquid extraction from 300-μL sample volume combined with 30 μL of the internal standard (rosuvastatin-d_6). Chromatographic separation for rosuvastatin was achieved using a Gemini C18 column (5 μm, 2 × 50 mm; Phenomenex) and gradient mobile phase. Mobile phase A consisted of 40/60/0.05 methonal:water:1.0M ammonium acetate, 2% acetic acid to pH 6 (v/v/v); and mobile phase B consisted of 100% methanol. An API 3000 mass spectrometer (AB Sciex) employing electrospray ionization in negative ion mode was used to monitor the analyte for rosuvastatin. Multiple reaction monitoring transitions were m/z 480.4 → 418.2 for rosuvastatin. The lower limit of quantification was 0.100 ng/mL. Intraday assay precision and accuracy/bias for rosuvastatin, as demonstrated by the performance of the quality control samples, were between 1.01% and 16.2% and between −9.80% and 3.41%, respectively. Interday precision and accuracy/bias for rosuvastatin were between 1.95% and 11.7% and between –2.41% and 1.34%, respectively.

Pharmacokinetic Analyses

Pharmacokinetic parameters for upadacitinib, rosuvastatin, atorvastatin and ortho-hydroxyatorvastatin were estimated using noncompartmental methods in Phoenix WinNonlin version 6.4 (Pharsight, A Certara Company, St. Louis, Missouri). Pharmacokinetic parameters included the C_{max}, time to reach C_{max}, the area under the plasma concentration–time curve (AUC) from time 0 to the last measurable time point (AUC_t) and from time 0 to infinity (AUC_{inf}), and the terminal-phase elimination half-life. Upadacitinib pharmacokinetic parameters included C_{max}, time to reach C_{max}, observed concentration 24 hours after dosing, apparent oral clearance, and AUC from time 0 to 24 hours after dosing ($AUC_{0\text{-}24}$).

Statistical Analyses

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina). The effect of upadacitinib on pharmacokinetics of rosuvastatin and atorvastatin was assessed through a repeated measures analysis for the natural logarithms of C_{max} and AUC using data from day 1 of period 1 and day 7 of period 2. A separate analysis was performed for each part, and the model had study period as a fixed effect.

The bioavailability of the rosuvastatin or atorvastatin when administered concomitantly with upadacitinib (day 7 of period 2) relative to that of the rosuvastatin or atorvastatin alone (day 1 of period 1) was assessed by calculating the difference of the least squares means obtained from the repeated measures analyses of the natural logarithms of C_{max} and AUC. The 90% confidence intervals (CIs) were obtained for those ratio estimates by taking the antilogarithm of the upper and lower limits of CIs for the difference of the least squares means on the logarithmic scale. Similar analyses were performed to assess the change in ratio of ortho-hydroxyatorvastatin to atorvastatin AUC when atorvastatin was administered with upadacitinib relative to when administered alone (part 2; day 7 of period 2 relative to day 1 of period 1) and to assess the effect of a single doses of rosuvastatin and atorvastatin on the steady-state plasma exposures of upadacitinib (day 7 of period 2 relative to day 6 of period 2 in each part).

Safety Monitoring

Routine safety evaluations, which included adverse event monitoring, physical examinations, vital sign measurements, ECG assessments, and clinical laboratory tests (hematology, chemistry, and urinalysis) were performed throughout the course of the study.

Results

Subject Disposition

A total of 36 healthy subjects (3 women and 33 men) were enrolled in the study (12 subjects in part 1 and 24 subjects in part 2). The mean age of the 12 subjects in part 1 was 36 years (range, 24-53), and the mean weight was 79.2 kg (range, 58.8-112.1). In part 1, 4 subjects were White (33%), 7 subjects were Black (58%), and 1 subject was an American Indian/Alaska Native (8%). The mean age of the 24 subjects in part 2 was 35 years (range, 23-54), and the mean weight was 76.7 kg (range, 59.8-101.0). In part 2, 12 subjects were White (50%), 10 subjects were Black (42%), and 2 were multiracial (8.3%). All subjects completed the study and were included in the analyses.

Pharmacokinetics of Rosuvastatin and Atorvastatin

The mean plasma concentration–time profiles for rosuvastatin and atorvastatin administered alone and with upadacitinib are shown on a linear and log-linear scale in Figures 2 and 3A, respectively, and the mean plasma concentration–time profiles for the active metabolite ortho-hydroxyatorvastatin following administration of atorvastatin alone and with upadacitinib are shown in Figure 3B. The pharmacokinetic parameters for rosuvastatin, atorvastatin, and ortho-hydroxyatorvastatin following the administration of atorvastatin with and without upadacitinib are presented in Table 1.

The ratios of central values and 90%CIs for the effect of upadacitinib on the $C_{max,}$ $AUC_{t,}$ and AUC_{inf} for rosuvastatin, atorvastatin, and ortho-hydroxyatorvastatin are shown in Figure 4. Following the administration of multiple doses of upadacitinib

Table 1. Mean ± SD Pharmacokinetic Parameters of Statins Following Administration of a Single Dose of Rosuvastatin and Atorvastatin Alone and With Multiple Upadacitinib 30 mg Once Daily Doses

Pharmacokinetic Parameters (Units)	Period 1, Day 1: Rosuvastatin 5 mg Alone (N = 12)	Period 2, Day 7: Upadacitinib 30 mg Once Daily + Rosuvastatin 5 mg (N = 12)
C_{max}, ng/mL	1.91 ± 0.699	1.43 ± 0.404
T_{max}[a], h	4.0 (1.0-4.0)	4.0 (1.0-4.0)
AUC_t, ng · h/mL	17.5 ± 6.53	12.8 ± 5.73
AUC_{inf}, ng · h/mL	22.8 ± 6.69	15.9 ± 6.62
$t_{1/2}$[b] (h)	18.8 ± 9.89[b]	10.2 ± 5.14[b]
	27.5 ± 23.6[c]	15.1 ± 11.5[c]
Pharmacokinetic Parameters (Units)	**Period 1, Day 1: Atorvastatin 10 mg Alone (N = 24)**	**Period 2, Day 7: Upadacitinib 30 mg Once Daily + Atorvastatin 10 mg (N = 24)**
	Atorvastatin	Atorvastatin
C_{max}, ng/mL	1.67 ± 0.828	1.50 ± 0.813
t_{max}[a], h	3.5 (0.5-4.0)	1.5 (0.5-4.0)
AUC_t, ng · h/mL	15.6 ± 8.43	11.9 ± 6.72
AUC_∞, ng · h/mL	17.8 ± 8.72	13.6 ± 6.98
$t_{1/2}$, h	8.15 ± 3.42[b]	7.28 ± 2.00[b]
	9.90 ± 5.14[c]	7.85 ± 2.35[c]
	Ortho-hydroxyatorvastatin	Ortho-hydroxyatorvastatin
C_{max}, ng/mL	1.58 ± 0.716	1.54 ± 0.610
t_{max}[a], h	4.0 (2.0-8.0)	4.0 (2.0-8.0)
AUC_t, ng · h/mL	19.4 ± 9.50	19.0 ± 7.61
AUC_{inf}, ng · h/mL)	22.8 ± 9.68	22.1 ± 7.66
$t_{1/2}$, h	11.1 ± 3.92[b]	10.0 ± 2.60[b]
	12.9 ± 5.76[c]	10.7 ± 2.76[c]
Ortho-hydroxyatorvastatin to atorvastatin AUC_t ratio[d]	1.33 ± 0.492	1.73 ± 0.517
Ortho-hydroxyatorvastatin to atorvastatin AUC_{inf} ratio[e]	1.39 ± 0.499	1.74 ± 0.440

AUC_{inf}, area under the plasma concentration–time curve from time 0 to infinity; AUC_t, area under the plasma concentration–time curve from time 0 to the last measurable time point; C_{max}, maximum observed plasma concentration; $t_{1/2}$, terminal-phase elimination half-life; t_{max}, time to maximum observed plasma concentration.

[a] Median (minimum-maximum)

[b] Harmonic mean ± pseudo-standard deviation.

[c] Arithmetic mean ± standard deviation.

[d] Ratio of metabolite (ortho-hydroxyatorvastatin) AUC_t to parent drug (atorvastatin) AUC_t.

[e] Ratio of metabolite (ortho-hydroxyatorvastatin) AUC_{inf} to parent drug (atorvastatin) AUC_{inf}.

30 mg once daily in part 1, the central values for rosuvastatin C_{max}, AUC_t, and AUC_{inf} ratios were 0.77, 0.71, and 0.67 compared to administration of rosuvastatin alone. In part 2, the ratios of atorvastatin C_{max}, AUC_t, AUC_{inf} central values were 0.88, 0.77, and 0.77 with no change in ortho-hydroxyatorvastatin C_{max} and AUC (with 90%CI within the 0.8-1.25 equivalence boundaries) when atorvastatin was administered with upadacitinib 30 mg once daily relative to when administered alone. The ratios reflecting the change in ortho-hydroxyatorvastatin to atorvastatin AUC_t and AUC_{inf} ratios were 1.32 and 1.28, respectively, when atorvastatin was administered with upadacitinib 30 mg once daily relative to when administered alone (Figure 4).

Pharmacokinetics of Upadacitinib

The mean plasma concentration–time profiles for upadacitinib when it was administered alone (day 6 of period 2) and with rosuvastatin or atorvastatin (day 7 of period 2) are shown in Figure 5A and 5B respectively. The pharmacokinetic parameters of upadacitinib in the presence of either rosuvastatin or atorvastatin are presented in Table 2.

The ratios of central values and 90%CIs for upadacitinib C_{max} and $AUC_{0\text{-}24}$ when upadacitinib was administered with rosuvastatin and atorvastatin relative to when adminsitered alone are presented in Figure 6. There was no relevant effect of rosuvastatin or atorvastatin on upadacitinib C_{max} and $AUC_{0\text{-}24}$.

Table 2. Mean ± SD Pharmacokinetic Parameters of Upadacitinib Following the Administration of Upadacitinib 30 mg Once Daily Doses Alone and With Single Doses of Rosuvastatin and Atorvastatin

	Part 1		Part 2	
Pharmacokinetic Parameters (Units)	Period 2, Day 6 Upadacitinib 30 mg Once Daily (N = 12)	Period 2, Day 7 Upadacitinib 30 mg Once Daily + Rosuvastatin 5 mg Single Dose (N = 12)	Period 2, Day 6 Upadacitinib 30 mg Once Daily (N = 24)	Period 2, Day 7 Upadacitinib 30 mg Once Daily + Atorvastatin 10 mg Single Dose (N = 24)
C_{max}, ng/mL	73.0 ± 23.6	80.9 ± 21.2	76.5 ± 16.1	73.2 ± 17.1
t_{max}[a], h	3.0 (1.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-7.0)
AUC_{0-24}, ng · h/mL	585 ± 153	567 ± 131	547 ± 112	533 ± 103
C_{24}, ng/mL	5.17 ± 1.56	5.56 ± 1.52	4.30 ± 1.74	4.61 ± 1.67
CL/F, L/h	54.6 ± 14.4	55.9 ± 14.7	57.2 ± 12.3	58.4 ± 11.7

AUC_{0-24}, area under the plasma concentration–time curve from time 0 to 24 hours after dosing; C_{24}, observed concentration 24 hours after dosing; C_{max}, maximum observed plasma concentration; CL/F, apparent oral clearance; t_{max}, time to maximum observed plasma concentration.
[a]Median (minimum-maximum).

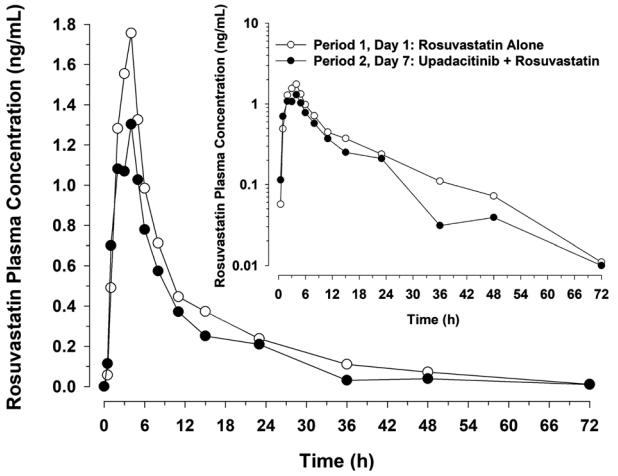

Figure 2. Mean rosuvastatin plasma concentration–time profiles following administration of a single dose of 5 mg rosuvastatin alone (open circles) and with multiple once-daily doses of 30 mg upadacitinib (filled circles). Plots are on linear-linear and log-linear scales (inset).

Safety and Tolerability

There was no pattern to the adverse events reported, and no new safety findings for upadacitinib, alone or with the statins, were identified in this study. The regimens were well tolerated by the healthy subjects in this study. No subject had a severe or serious adverse event; discontinued from the study due to an adverse event; or had a clinically relevant change in vital signs, laboratory values, or ECGs. Three subjects reported the occurrence of a treatment-emergent adverse events of headaches (grade 1 or grade 2) during treatment with upadacitinib and atorvastatin. During treatment with rosuvastatin and upadacitinib, 1 patient reported constipation (grade 1).

Discussion

This study characterized the effect of coadministration of upadacitinib 30 mg once daily using the extended-release formulation on the pharmacokinetics of rosuvastatin (a substrate for OATP1B1 and BCRP) and atorvastatin (a substrate for CYP3A, OATP1B1, and OATP1B3) in healthy subjects. The study results showed no increase in rosuvastatin and atorvastatin plasma exposures, which is consistent with expected lack of clinically relevant inhibition of the hepatic uptake transporter OATP1B1 and efflux transporter BCRP based on in vitro assessments and upadacitinib clinically relevant concentrations. Following the administration of upadacitinib 30 mg once daily, rosuvastatin and atorvastatin C_{max} and AUC were slightly (11%-33%) lower when the statins were administered alone. This relatively small effect is within the reported intrasubject variability in rosuvastatin and atorvastatin plasma exposures (≈25% and 45%, respectively)[29,32]; therefore, it is not expected to be of clinical relevance. Additionally, the approved doses of rosuvastatin (5-40 mg) and atorvastatin (10-80 mg) are at 5- to 40-fold the estimated dose that results in 50% of the maximum effect and the pharmacologic effect of the statins is estimated to be near the plateau at this therapeutic dose range.[33] Therefore, this relatively apparent small decrease in rosuvastatin and atorvastatin plasma exposures is not expected to result in clinically relevant effect on the efficacy of the statins or to require dose adjustment. The lack of change in the plasma levels of the atorvastatin active metabolite (ortho-hydroxyatorvastatin) further supports the lack of clinically relevant effect of upadacitinib on atorvastatin. The mechanism for the slight decrease in rosuvastatin plasma exposures is not clear. Upadacitinib

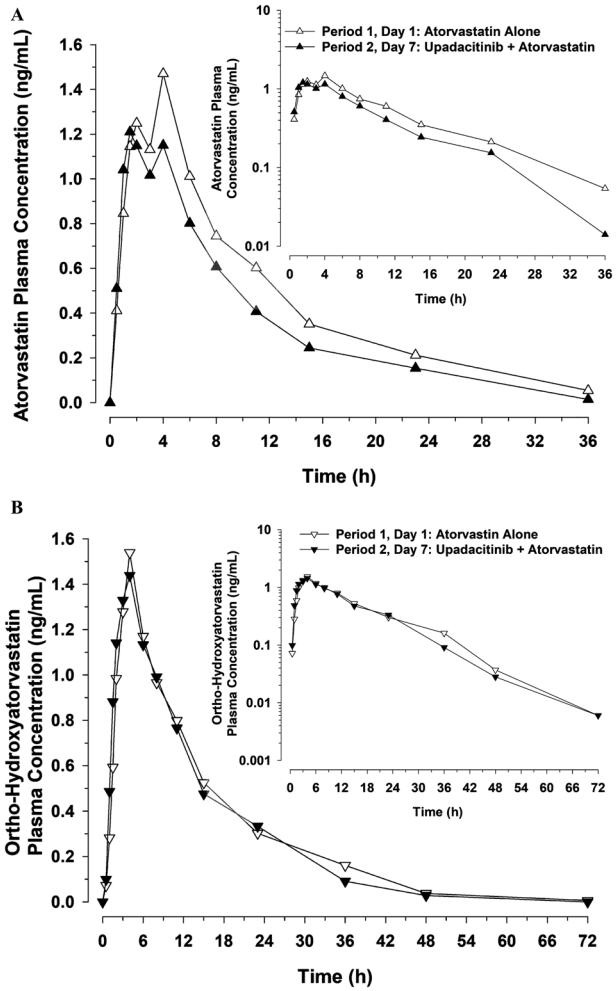

Figure 3. Mean atorvastatin (up triangles) and ortho-hydroxyatorvastatin (down triangles) plasma concentration–time profiles following the administration to healthy subjects of a single dose of 10 mg atorvastatin alone (open triangles) and with multiple once-daily doses of 30 mg upadacitinib (closed triangles). Plots are on linear-linear and log-linear scales (inset).

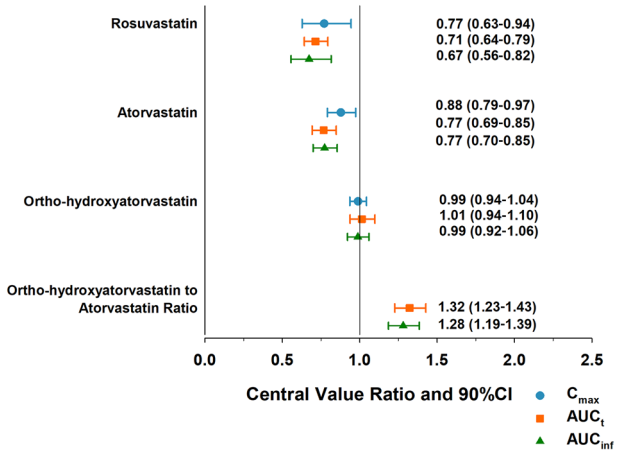

Figure 4. Effect of upadacitinib on the exposures of rosuvastatin, atorvastatin, and ortho-hydroxyatorvastatin. Symbols and lines represent ratio of central values and 90% confidence intervals for maximum observed plasma concentration (C_{max}; blue circles), area under the plasma concentration–time curve from time 0 to the last measurable time point (AUC_t; orange squares), and area under the plasma concentration–time curve from time 0 to infinity (AUC_{inf}; green triangles) following the coadministration of the statins with upadacitinib versus administration of the statins alone.

is not known to induce BCRP or OATP1B, which could have been a potential reason for a decrease in rosuvastatin exposures, and there is no clear evidence supporting that OATP1B transporters can be induced in vivo.[34] The relatively small decrease in atorvastatin plasma exposures can potentially be due to a weak and non–clinically relevant induction of CYP3A with multiple doses of upadacitinib, which was observed also with midazolam in a cocktail drug-drug interaction study.[18] In another clinical drug interaction study, upadacitinib had no effect on the plasma exposures of the oral contraceptives ethinylestradiol and levonorgestrel, which are partially metabolized by CYP3A.[19] Interoccasion variability in the statin exposures could have also contributed to the relatively small change observed in exposures, particularly given the fixed-sequence design of the study. Results from this study supported that upadacitinib has no clinically relevant effect on rosuvastatin and atorvastatin and can be administered concomitantly with these drugs.

At the time of conducting this study, upadacitinib was being evaluated in phase 3 clinical trials in subjects with RA at doses of 15 mg and 30 mg once daily using the extended-release formulation.[4–7] Therefore, the dose of upadacitinib evaluated for potential effects on rosuvastatin and atorvastatin was the 30 mg (the higher of the 2 potential clinical dose levels). For rosuvastatin and atorvastatin, the dose used in the study corresponds to the recommended starting daily doses of each of the 2 drugs for the treatment of dyslipidemia (5 mg and 10 mg, respectively). The main objective of the study was to evaluate the effects of upadacitinib on rosuvastatin and atorvastatin, particularly to confirm the lack of clinically relevant inhibition of OATP1B transporters in vivo at clinically relevant exposures. Therefore, the doses evaluated of rosuvastatin and atorvastatin were the starting, rather than the maximum, therapeutic doses to ensure that atorvastatin and rosuvastatin exposures stay within safe and acceptable ranges in case of increased exposures due to OATP1B inhibition. For the effects of rosuvastatin and atorvastatin on upadacitinib pharmacokinetics, there is no mechanistic reason to expect that higher doses of rosuvastatin or atorvastatin will have a relevant effect on upadacitinib plasma exposures, as neither rosuvastatin nor atorvastatin is

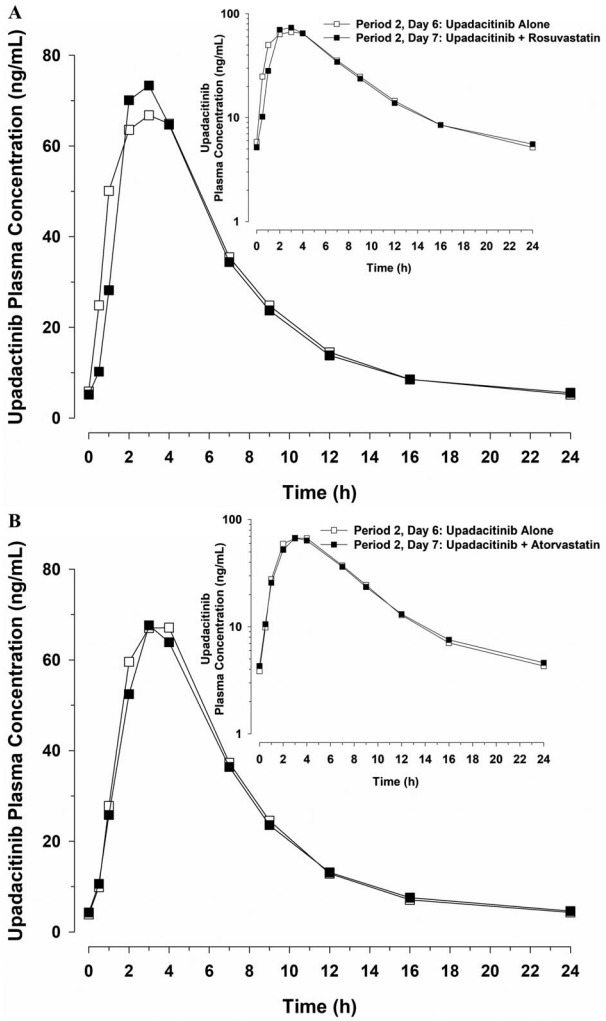

Figure 5. Mean upadacitinib plasma concentration versus time profiles at steady state following the administration of multiple once-daily doses of 30 mg upadacitinib alone (open squares) and with single doses of (A) rosuvastatin and (B) atorvastatin (closed squares). Plots are on linear-linear and log-linear scales (inset).

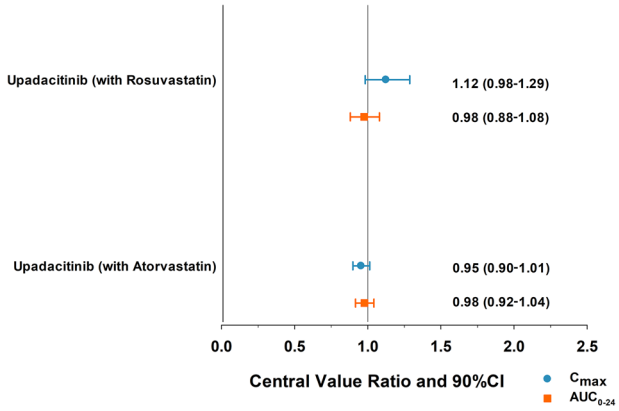

Figure 6. Effect of rosuvastatin or atorvastatin on the exposures of upadacitinib. Symbols and lines represent ratio of central values and 90%CIs for maximum observed plasma concentration (C_{max}; blue circles) and area under the plasma concentration–time curve from time 0 to 24 hours after dosing ($AUC_{0\text{-}24}$; orange squares) following the coadministration of upadacitinib with either statin versus administration of upadacitinib alone.

known to be an inhibitor of CYP3A, which is the main enzyme involved in upadacitinib metabolism.[12,17]

In this study, upadacitinib was administered for 6 days before being administered concomitantly with rosuvastatin and atorvastatin. Upadacitinib demonstrates no significant accumulation in plasma with repeated once-daily dosing of the extended-release formulation, and steady state is achieved within 4 days of once-daily dosing.[9] Therefore, it is expected that steady-state upadacitinib exposures were achieved by the day of coadministration with rosuvastatin and atorvastatin (day 7 of period 2). Daily administration of the upadacitinib alone continued for 3 additional days (days 8-10 of period 2) after the statin administration to ensure that any potential effect of upadacitinib on statin clearance was sustained during statin washout. Therefore, the trial design ensured characterization of the maximum potential effect of upadacitinib 30 mg once daily on rosuvastatin and atorvastatin pharmacokinetics. Doses of the statins were administered 1 hour after administration of upadacitinib extended release to ensure assessment of maximum inhibition potential between the agents.

The doses of rosuvastatin, atorvastatin, and upadacitinib that were administered alone or in combination were generally well tolerated by the subjects in this study. No clinically significant changes in vital signs or laboratory measurements were observed during the course of the study, and no new safety findings were identified from this study. Mild or moderate headaches were the most common adverse events and there was no pattern for time dependency for the incidence of this adverse event. These findings are consistent with previous phase 1 studies.[16]

Conclusions

Following multiple upadacitinib 30 mg once daily dose administrations, there was no increase in rosuvastatin or atorvastatin exposures, indicating lack of inhibition of OATP1B or BCRP in vivo by upadacitinib. Rosuvastatin C_{max} and AUC_{inf} were 23% and 33% lower, respectively, and atorvastatin C_{max} and AUC_{inf} was lower by 11% and 23%, respectively, when they were coadministered with upadacitinib relative to when administered alone. AUC and C_{max} for ortho-hydroxyatorvastatin (the major active metabolite for atorvastatin) remained unchanged for atorvastatin concomitant administration with upadacitinib relative to atorvastatin administration alone. This apparent small

decrease in rosuvastatin and atorvastatin exposures after multiple 30 mg once daily dose administration of upadacitinib is within the intrasubject variability in plasma exposures of these drugs and is not expected to be clinically relevant. The findings of this study indicate that upadacitinib may be administered concomitantly with rosuvastatin or atorvastatin to manage low-density lipoprotein cholesterol when applicable.

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Conflicts of Interest

Drs Mohamed-Eslam F. Mohamed, Sheryl Coppola, Tian Feng, Heidi S. Camp, and Elaine Kim are employees of AbbVie and may hold AbbVie stock. Dr Ahmed A. Othman is a former AbbVie employee and may hold AbbVie stock. This study was sponsored by AbbVie, Inc. AbbVie contributed to the study design, research, and interpretation of data, and the writing, reviewing, and approving of the publication.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data-sharing agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

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