

Effect of Cobicistat on Glomerular Filtration Rate in Subjects With Normal and Impaired Renal Function

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Objective: This study evaluated the effect of cobicistat (COBI) on glomerular filtration rate in subjects with normal renal function (RF) or with mild/moderate renal impairment, by comparing creatinine clearance [estimated glomerular filtration rate (eGFR)] with actual GFR (aGFR) using iohexol, a probe drug excreted by glomerular filtration. COBI is a potent CYP3A inhibitor (pharmacoenhancer) currently in phase 3 testing with elvitegravir, atazanavir, and darunavir.

Methods: Normal RF subjects received COBI 150 mg QD, ritonavir (RTV) 100 mg QD, or placebo for 7 days; subjects with mild/moderate renal impairment received COBI 150 mg QD. The eGFR and aGFR were measured on days 0, 7, and 14 and within-subject changes calculated relative to day 0. COBI and RTV pharmacokinetics were analyzed on day 7.

Results: All 36 subjects in cohort 1 and 17 of 18 subjects in cohort 2 completed all study treatments. Study treatments were well tolerated. Small increases in serum creatinine with corresponding mean decreases in eGFR (~ 10 mL/min or mL/min per 1.73 m²) were observed on day 7 relative to day 0 in subjects receiving COBI ($P < 0.05$). The decreases were reversible on COBI discontinuation; mean eGFR values returned to baseline on day 14 ($P > 0.05$). No statistically significant changes in aGFR on days 7 or 14 relative to day 0 were seen with COBI ($P > 0.05$). No statistically significant decreases in aGFR or eGFR were observed with RTV or placebo.

Conclusions: COBI affects eGFR but not the actual GFR. The time to onset, magnitude, and time to resolution of changes in eGFR are consistent with altered proximal tubular secretion of creatinine through inhibition of drug transporters.

Key Words: COBI, GFR, transporters, iohexol, renal dysfunction

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INTRODUCTION

Estimation of glomerular filtration rate (GFR) based on serum creatinine (SCr) is routinely used to assess kidney

function. A number of SCr-based equations, including variables such as age, sex, race, and body size have been developed to provide a relatively accurate and simple calculation of creatinine clearance as an index of estimated GFR (eGFR) over the use of SCr alone.^{1,2} However, eGFR overestimates actual GFR (aGFR) because approximately 10%–20% of creatinine eliminated by the kidneys is actively secreted by the renal tubules.^{3–6} As such, inhibition of creatinine secretion and resultant increases in plasma creatinine are reflected as a reduction in GFR, suggestive of impaired renal function (RF).^{1,7} Drugs known to interfere with creatinine tubular secretion leading to its plasma/serum increases include cimetidine, trimethoprim, pyrimethamine, rilpivirine, ranolazine, and dolutegravir.^{8–13} The effect of these drugs on creatinine secretion is due to reversible inhibition of renal transporters, an interaction that neither affects actual GFR nor warrants drug discontinuation for toxicity concerns.¹⁴ In fact, administration of high doses of cimetidine provides a more accurate estimation of true GFR when calculated by the Cockcroft–Gault (CG) method because creatinine concentrations are no longer influenced by tubular secretion.^{14–17}

Cobicistat (COBI) is a potent cytochrome P450 3A (CYP3A) inhibitor in phase 3 testing in a single-tablet regimen of elvitegravir/COBI/emtricitabine/tenofovir (EVG/COBI/FTC/TDF) and as a pharmacoenhancer (“booster”) with human immunodeficiency virus–1 (HIV-1) protease inhibitors atazanavir (ATV) and darunavir for treatment of HIV-1 infection in treatment-naïve patients.^{18,19} In phase 1 and 2 studies, small SCr increases (0.10–0.15 mg/dL) with corresponding eGFR (CG and Modification of Diet in Renal Disease [MDRD]), decreases (10–15 mL/min or mL/min per 1.73 m²) have been observed. In phase 1 studies, in which healthy subjects received COBI or ritonavir (RTV; another pharmacoenhancer), these changes occurred within 2–5 days of dosing and returned to baseline upon study drug discontinuation (data on file). The onset, magnitude and resolution of these changes were consistent with a “drug-interaction” effect of COBI altering creatinine secretion. In phase 2 studies in HIV-infected patients who received either EVG/COBI/FTC/TDF or COBI-boosted ATV plus FTC/TDF or RTV-boosted ATV plus FTC/TDF, small mean increases in SCr and corresponding mean decreases in eGFR ($\sim 15\%$) were observed in all treatment groups. Changes were seen as early as in the first study visit at week 2 of dosing; values were stable after week 24 or 48 and remained within the normal range in all treatment groups.^{20,21} In these studies, no subjects discontinued study drug due to changes in SCr or eGFR.

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To obtain a better understanding of the effect of COBI on RF, we evaluated the effect of COBI (and RTV) on eGFR and aGFR in subjects with normal and mild/moderately impaired RF. eGFR was calculated using SCr by CG (eGFR_{CG}) and MDRD (eGFR_{MDRD}) methods because both equations are routinely used. Although measured GFR (mGFR) using 24-hour urinary output and SCr was assessed for completeness, this metric may not be more reliable than eGFR with SCr-based equations.²² aGFR was determined via the calculation of iohexol plasma clearance (CL_{iohexol}), a non-radioactive contrast agent that is nearly 100% filtered through the glomeruli.²³ Numerous studies of iohexol-measured GFR show excellent agreement with the clearance over a wide range of kidney function.^{24–27}

The data from this study aimed to provide an understanding of an effect of COBI on RF and to provide evidence for a putative drug-transporter interaction that affects SCr via its handling by the kidney.

METHODS

The study protocol and informed consent documents were reviewed and approved by a duly constituted Independent Ethics Committee or Institutional Review Board (Western IRB, Olympia, WA; Independent IRB, Plantation, FL; Quorum Review, Inc, Seattle, WA; Ethikkommission der Bayerischen Landesärztekammer, München, Germany) before study initiation. All the subjects provided written informed consent before participation in the study.

Subjects and Study Treatment

The study proceeded in 2 cohorts. Cohort 1 was randomized, double-blinded, and placebo-controlled, and it aimed to assess the effects of COBI and RTV on eGFR and aGFR in subjects with normal RF (screening eGFR_{CG} ≥80 mL/min). Cohort 2 was single treatment and open label and aimed to investigate the effects of COBI on eGFR and aGFR in subjects with mild or moderate renal impairment (RI, screening eGFR_{CG} 50–79 mL/min). In cohort 1, 36 healthy male and female subjects were randomized evenly to 1 of 3 treatments (N = 12 per treatment) and received active COBI 150-mg tablet and RTV 100-mg placebo soft-gelatin capsule (treatment 1), active RTV 100 mg and COBI 150-mg placebo (treatment 2) or placebo for COBI and RTV (treatment 3). In cohort 2, 18 subjects with stable mild or moderate RI received active COBI 150 mg.

All study procedures were standardized. The doses of study drugs were administered every morning on days 1–7, within 5 minutes of standardized breakfast completion (~400 kcal). Because the pharmacokinetic profiles of COBI and RTV are well characterized, a 7-day treatment was deemed sufficient to enable evaluation under steady-state conditions. All the subjects were required to drink 240 mL of water upon waking and every 6 hours while awake to facilitate urine production. The subjects were confined to the study center from day 1 through completion of assessments on day 15. The subjects returned for safety assessments on day 21.

Renal Function and Pharmacokinetic Evaluations

The subjects underwent renal assessments the day before treatment (day 0), the last day of treatment (day 7), and 7 days after treatment cessation (day 14). All the subjects received iohexol as an intravenous bolus (over 1–2 minutes) (Omnipaque 300; 1500 mg as 5 mL of a 300 mg of iodine per milliliter of solution), immediately after the administration of the study drug.

A blood sample for analysis of SCr, blood urea nitrogen (BUN), sodium, and phosphate was obtained on days 0, 7, and 14 at the midpoint of the 24-hour dosing interval. Urine collection was performed at 0–4, 4–8, 8–12, and 12–24 intervals. Urine creatinine was determined from a pooled 24-hour urine collection. eGFR was determined from SCr; mGFR was measured using SCr and urine creatinine. Serial blood samples were collected at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours after iohexol administration. These samples were analyzed for COBI (both cohorts) and RTV (cohort 1) on day 7, and on days 0, 7, and 14, for iohexol for the calculation of CL_{iohexol}, as a surrogate marker of RF.

Safety Assessments

Clinical safety laboratory tests, vital signs, and physical examinations were performed at Screening and throughout the study. Weight was measured at Screening, daily through the end of confinement, and on day 21. Twelve-lead safety electrocardiogram was performed at Screening. At the study center in Germany (cohort 2), electrocardiograms were also performed on days 6 and 15. Assessment of adverse events (AEs) and concomitant medications continued throughout the study. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.1). AEs and abnormal laboratory values were graded according to National Institute of Allergy and Infectious Disease Common Toxicity Grading Scale.²⁸

Bioanalysis

Iohexol, COBI, and RTV plasma concentrations were determined using validated high-performance liquid chromatography tandem mass spectrometry (LC/MS/MS) methods. Iohexol analysis was performed at Covance (Madison, WI); COBI and RTV analyses were performed at QPS, Inc (Newark, DE). The lower limits of quantitation were 5 ng/mL for COBI and RTV, and 1000 ng/mL for iohexol. For all analytes, interassay precision was <10%; intraassay accuracy was within ±10%. COBI and RTV bioanalytical methods have been described previously.²⁹ For iohexol, 50 µL of human plasma was spiked with a deuterated internal standard and extracted using protein precipitation. The compounds were detected by MS/MS in the selected reaction monitoring mode using electrospray ionization with positive polarity; the following ion transitions were monitored: *m/z* 822 → 603 for iohexol and 706 → 615 for internal standard.

Pharmacokinetic Analyses

Pharmacokinetic parameters were estimated by non-compartmental methods, using linear up/log down method for

area under the plasma concentration–time curve (AUC) estimation (WinNonlin software, version 6.1; Pharsight, Mountain View, CA). Pharmacokinetic parameters calculated for COBI and RTV were AUC over the dosing interval (AUC_{τ}), maximum concentration (C_{\max}), time of C_{\max} (T_{\max}), concentration at the end of the dosing interval (C_{τ}), and half-life ($T_{1/2}$). Plasma CL_{iohexol} was calculated as $\text{dose}/AUC_{\text{inf}}$ (AUC extrapolated to infinity).

Statistical Analyses

In cohort 1, the sample size was determined using the pooled mean change from baseline and intersubject SD in $eGFR_{CG}$ from prior phase 1 studies. With 12 subjects per treatment, the study had at least 83% power to reject the null hypothesis of no difference between COBI and placebo with respect to $eGFR_{CG}$ change and to accept an alternative hypothesis of a 15-mL/min difference between groups. Given a larger percent coefficient of variation (CV) associated with a pooled mean change from baseline with RTV, the study had at least 64% power to reject the null hypothesis of no difference between RTV and placebo and to accept an alternative hypothesis of a 12-mL/min difference between groups. It was assumed that a common SD would be 12 mL/min, the placebo subjects would experience no $eGFR_{CG}$ decrease from baseline, and 2 independent group t tests would be conducted at a 2-sided alpha level of 0.05. In cohort 2, a sample size was determined using data from cohort 1. Sixteen evaluable subjects provided 90% power to detect an 8% decrease from baseline in $eGFR_{CG}$ on day 7. It was assumed that the SD of change from baseline in $eGFR$ would be 9%, and a 1-sample t test would be conducted at a 2-sided alpha level of 0.05. Eighteen subjects were enrolled to ensure 16 evaluable subjects for analysis.

SCr, aGFR, $eGFR_{CG}$, $eGFR_{MDRD}$, and mGFR were summarized descriptively by cohort, treatment, and visit (days 0, 7, and 14). Within-subject and mean (SD) and median (Q1; Q3) changes in these endpoints were calculated on days 7 and 14 relative to day 0. A paired t test was used to evaluate if the changes from day 0 were significantly different from 0 at a 2-sided alpha level of 0.05 for within-treatment comparisons. Differences in least-squares means (LSM) between treatments (COBI or RTV

vs. placebo), associated 95% confidence intervals (CI) for the observed differences and P values were computed using analysis of variance. The relationship between changes from day 0 in $eGFR_{CG}$ and aGFR on day 7 and day 0 $eGFR_{CG}$ was explored using a regression model.

Pharmacokinetic parameters were summarized descriptively. A parametric analysis of variance using a mixed-effect model, including treatment as fixed and subject within-treatment group as random effects, was fitted to the natural-log transformed parameters of COBI in cohorts 2 vs. 1. The 90% CI for the ratio of the geometric LSM of COBI in cohorts 2 and 1 was calculated.

RESULTS

Subject Demographics

In cohort 1, the subjects were balanced for gender, age, weight, race, and ethnicity across treatments (Table 1). Cohort 2 subjects were older than subjects in cohort 1, consistent with the presence of baseline renal dysfunction and balanced in terms of sex; they were predominantly white and almost exclusively non-Hispanic/Latino (Table 1). One subject in cohort 2 experienced an AE that occurred 2 days after COBI cessation and did not receive iohexol on day 14. This subject completed other study procedures on day 14. All the remaining subjects in cohort 2 and all the subjects in cohort 1 completed all study treatments.

Safety

Study treatments were well tolerated. In cohort 1, treatment-emergent AEs were reported for 4 of 12 subjects (33.3%) receiving COBI, 5 of 12 subjects (41.7%) receiving RTV, and 6 of 12 subjects (50.0%) receiving placebo. Adverse events were predominantly grade 1 (mild) or grade 2 (moderate) in severity. No AE occurred with greater than single subject incidence in any treatment. The most frequent treatment-emergent AEs were diarrhea (3 subjects: 1 subject in each treatment group), headache (2 subjects: 1 subject on COBI and 1 subject on placebo), and food intolerance (2 subjects: 1 subject on COBI and 1 subject on placebo). There were no grade 3 or grade 4, or serious AEs (SAEs), and no subject in this cohort prematurely discontinued study drug because of an

TABLE 1. Subject Enrollment and Demographics

Subjects	Cohort 1			Cohort 2 COBI
	COBI	RTV	Placebo	
Enrolled/completed	12/12	12/12	12/12	18/17
Gender (male/female)	6/6	6/6	6/6	8/10
Mean age (yrs, range)	32 (22, 39)	34 (24, 43)	32 (19, 43)	58 (46, 65)
Mean weight (kg, range)	73 (51, 88)	71 (53, 86)	70 (55, 90)	69 (50, 100)
Race				
White (%)	50	50	42	78
Nonwhite (%)	50	50	58	22
Ethnicity				
Hispanic/Latino (%)	83	67	67	6
Non-Hispanic/Latino (%)	17	33	33	94

AE. Study drug-related AEs (nausea, abdominal distension, and asthenia) were reported for 1 subject, in the RTV group on day 1 and resolved the same day without treatment.

In cohort 2, treatment-emergent AEs were reported for 7 of 18 subjects (38.9%) receiving COBI. AEs were predominantly grade 1 or grade 2; there were no grade 3 or grade 4 AEs or SAEs. The most common treatment-emergent AE was headache (4 subjects). Study drug-related AEs were reported for 6 of 18 subjects (33.3%) in this cohort, among which only headache (in all 4 subjects reporting it) occurred with greater than single subject incidence. One subject discontinued study treatment on day 9, having received all planned doses of COBI, because of a moderate maculopapular rash, considered by the investigator as related to study drug; the rash was treated and resolved on day 15.

In both cohorts, treatment-emergent laboratory abnormalities were almost exclusively grade 1 (mild) or grade 2 (moderate), predominantly the former. In cohort 1, grade 3 hematuria, as assessed by dipstick analysis (grade 2 by microscopy) was reported for 1 male placebo subject on day 6. Decreased grade 1 hemoglobin was observed in a subject on COBI in cohort 1, reported as grade 2 anemia starting on study day 13 and considered by the investigator as related to study procedures (but not the study drug), was the only treatment-emergent laboratory abnormality reported as an AE. This event remained ongoing at study completion.

In cohort 2, grade 4 elevated serum lipase, a reflex test triggered by grade 2 [$>1.5 \times \text{ULN}$ (upper limit of normal)] serum amylase, was reported for 1 subject on day 6 of COBI administration. Serum amylase remained $<1.5 \times \text{ULN}$ at subsequent assessments and serum lipase testing was not repeated. Grade 4 glycosuria was reported for 1 subject in cohort 2 (COBI) on day 21. None of these laboratory abnormalities were reported as an AE.

There was little variation from baseline in mean BUN, urine sodium (FENa) or phosphate (FEPO₄) fractional excretion (percent) in cohort 1 or in mean BUN or FENa in cohort 2 during treatment. In cohort 2, during treatment, mean FEPO₄ slightly increased from baseline but remained within normal limits and returned to baseline by day 14 (data not shown).

Pharmacodynamics/Renal Effects

Values for SCr, aGFR, eGFR_{CG}, eGFR_{MDRD}, and mGFR, and within-treatment changes (absolute and percent) in these values on days 7 and 14 relative to day 0 are shown in Table 2. The comparisons of changes in these endpoints on days 7 and 14 relative to day 0 between cohort 1 subjects who received COBI or RTV and subjects who received placebo are given in Table 3.

Administration of COBI to subjects with normal RF or mild/moderate RI resulted in statistically significant ($P < 0.05$) SCr increases, as assessed on day 7 relative to day 0. Correspondingly, SCr-based GFR estimations (eGFR_{CG}, eGFR_{MDRD}, and mGFR) demonstrated statistically significant ($P < 0.05$) decreases in both cohorts. After administration of COBI to subjects with normal RF in cohort 1, a mean eGFR decrease of 9.9 mL/min (or mL/min per 1.73 m²), representing

mean decreases of 8.1% and 9.9% in eGFR_{CG} and eGFR_{MDRD}, respectively, and a mean mGFR decrease of 18.4 mL/min (mean decrease of 14.4%) were observed at day 7 relative to day 0. In subjects with mild/moderate RI in cohort 2, mean decreases of 11.9 mL/min (17.5%), 13.9 mL/min per 1.73 m² (20%) and 11.2 mL/min (8.8%) were calculated using eGFR_{CG}, eGFR_{MDRD}, and mGFR equations, respectively. The changes were reversible with eGFR (both cohorts) and mGFR (cohort 1) values being not different from baseline levels ($P > 0.05$) by day 14.

Comparison of eGFR changes on days 7 and 14 relative to day 0 between cohort 1 subjects who had received COBI and subjects who had received placebo confirmed a statistically significant difference at day 7 (12.1 mL/min or mL/min per 1.73 m², $P < 0.05$, Table 3). No differences relative to day 0 were observed at day 14 in eGFR or at day 7 or day 14 in mGFR ($P > 0.05$). Because placebo was not administered to cohort 2 subjects, the comparisons of changes from day 0 were not performed.

In contrast, aGFR (CL_{iohexol}) was unchanged on day 7 or day 14 relative to day 0 in the subjects receiving COBI. Consistent with these data, no statistically significant differences were observed when the changes on days 7 and 14 were compared between the subjects who received COBI and those subjects who received placebo.

An exploratory regression analysis assessed the relationship between the changes on day 7 relative to day 0 in eGFR_{CG} or aGFR vs. day 0 eGFR_{CG} in subjects who received COBI (Fig. 1). No linear relationship was observed between day 0 eGFR_{CG} and the change in eGFR_{CG} or aGFR on day 7 ($r^2 \sim 0$; slope ~ 0); the differences in the regression lines were attributed to the differences in the intercepts (-2.84 mL/min for aGFR change and -13.2 mL/min for eGFR_{CG} change). Described by these regression equations, a decrease of approximately 12 mL/min in eGFR_{CG} is expected for a subject with a baseline eGFR_{CG} of 50 mL/min. In contrast, aGFR is unaffected with a predicted decrease of only 3 mL/min in the same subject. Cumulatively, these results demonstrate that COBI can cause an increase in SCr that results in a decrease in estimated/measured GFR but does not affect actual GFR. This disconnect is illustrative of the proposed drug-transporter interaction indicating that the increase in SCr is due to COBI effect on tubular secretion of creatinine, not the integrity of the glomeruli responsible for the filtration of creatinine and other organic drugs.

No statistically significant decreases in any of the measures of estimated or actual GFR were observed in subjects on RTV or placebo in cohort 1. In subjects who received RTV, statistically significant increases in eGFR were noted on day 14 visit relative to day 0. As such, no differences were seen on comparison of RTV and placebo treatments.

Pharmacokinetics

COBI exposure was modestly higher in subjects with mild/moderate RI than in subjects with normal RF (Table 4; Fig. 2). The mechanism for higher COBI exposures in cohorts 2 vs. 1 is unknown as renal excretion is a minor pathway of COBI elimination³⁰ and similar exposures were seen in a

TABLE 2. SCr, eGFR, and aGFR by Visit and Change From Baseline in Cohorts 1 and 2

PD Endpoint		Placebo: Cohort 1			COBI: Cohort 1		
		Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
SCr (mg/dL)	Mean (SD)	0.88 (0.19)	0.87 (0.17)	0.80 (0.26)	0.85 (0.19)	0.94 (0.26)	0.86 (0.24)
	Mean Δ from day 0 (SD)		-0.02 (0.08)	-0.08 (0.17)		0.10 (0.09)*	0.01 (0.06)
	Median Δ from day 0 (Q1, Q3)		-0.01 (-0.03, 0.03)	-0.05 (-0.09, 0.01)		0.11 (0.03, 0.15)	0.02 (-0.04, 0.06)
	Mean % Δ from day 0 (SD)		-1.19 (7.73)	-8.86 (20.2)		10.49 (10.4)*	0.40 (7.63)
aGFR (mL/min)	Mean (SD)	130 (24.2)	135 (26.7)	130 (23.5)	134 (14.3)	131 (16.2)	131 (16.0)
	Mean Δ from day 0 (SD)		4.7 (15.1)	0 (12.0)		-2.7 (8.71)	-2.5 (5.50)
	Median Δ from day 0 (Q1, Q3)		5.3 (-1.0, 13.7)	-1.6 (-5.5, 10.6)		-3.6 (-4.2, 5.4)	-1.4 (-5.3, 1.5)
	Mean % Δ from day 0 (SD)		4.0 (9.95)	0.5 (8.60)		-2.0 (6.58)	-1.9 (4.19)
eGFR _{CG} (mL/min)	Mean (SD)	114 (26.7)	116 (23.9)	137 (59.0)	121 (22.9)	111 (26.6)	123 (28.0)
	Mean Δ from day 0 (SD)		2.2 (9.10)	22.8 (59.9)		-9.9 (13.1)*	1.4 (11.5)
	Median Δ from day 0 (Q1, Q3)		2.9 (-4.0, 5.2)	7.1 (-2.0, 14.8)		-12.7 (-18.0, -1.6)	-0.3 (-7.0, 6.3)
	Mean % Δ from day 0 (SD)		3.0 (9.61)	24.0 (66.5)		-8.1 (9.27)*	1.0 (8.08)
eGFR _{MDRD} (mL/min/1.73 m ²)	Mean (SD)	108 (24.0)	111 (25.3)	132 (60.0)	109 (18.6)	98.8 (25.8)	110 (26.7)
	Mean Δ from day 0 (SD)		2.2 (11.3)	23.7 (65.0)		-9.9 (12.2)*	1.1 (11.3)
	Median Δ from day 0 (Q1, Q3)		1.3 (-3.8, 5.1)	7.1 (-1.8, 13.0)		-14.0 (-19.9, -3.9)	-2.3 (-6.3, 7.9)
	Mean % Δ from day 0 (SD)		2.2 (10.3)	28.9 (85.0)		-9.9 (10.5)*	0.2 (9.22)
mGFR (mL/min)	Mean (SD)	112 (33.5)	112 (22.3)	137 (59.9)	98.3 (38.9)	79.8 (29.4)	93.1 (35.7)
	Mean Δ from day 0 (SD)		-0.2 (31.1)	25.5 (72.7)		-18.4 (23.9)*	-5.1 (31.5)
	Median Δ from day 0 (Q1, Q3)		0.0 (-15.9, 10.4)	1.1 (-8.3, 22.5)		-18.4 (-26.3, -7.9)	-7.7 (-25.8, 6.5)
	Mean % Δ from day 0 (SD)		10.0 (54.1)	43.9 (113)		-14.4 (26.3)	0 (41.6)

PD Endpoint		RTV: Cohort 1			COBI: Cohort 2		
		Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
SCr (mg/dL)	Mean (SD)	0.85 (0.18)	0.86 (0.22)	0.82 (0.20)	1.08 (0.26)	1.31 (0.29)	1.13 (0.31)
	Mean Δ from day 0 (SD)		0.01 (0.06)	-0.03 (0.06)		0.24 (0.13)*	0.05 (0.08)*
	Median Δ from day 0 (Q1, Q3)		-0.01 (-0.04, 0.06)	-0.03 (-0.07, 0.01)		0.28 (0.11, 0.33)	0.04 (0.0, 0.08)
	Mean % Δ from day 0 (SD)		-0.11 (6.58)	-3.76 (6.40)		23.0 (14.8)*	4.11 (7.27)*

TABLE 2. (Continued) SCr, eGFR, and aGFR by Visit and Change From Baseline in Cohorts 1 and 2

PD Endpoint		RTV: Cohort 1			COBI: Cohort 2		
		Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
aGFR (mL/min)	Mean (SD)	142 (22.4)	144 (23.8)	141 (20.1)	76.8 (15.4)	73.2 (16.6)	70.8 (21.7)
	Mean Δ from day 0 (SD)		2.2 (9.69)	-0.8 (6.28)		-3.6 (7.63)	-5.8 (13.2)
	Median Δ from day 0 (Q1, Q3)		1.9 (-5.3, 9.4)	-1.7 (-5.4, 4.7)		-2.6 (-9.5, 1.7)	-4.3 (-9.3, -0.1)
	Mean % Δ from day 0 (SD)		1.8 (6.92)	-0.1 (5.30)		-5.0 (10.3)	-8.5 (18.2)
eGFR _{CG} (mL/min)	Mean (SD)	117 (17.5)	118 (18.5)	123 (21.2)	68.7 (9.67)	56.8 (11.0)	66.5 (10.6)
	Mean Δ from day 0 (SD)		1.0 (8.62)	5.7 (8.21)*		-11.9 (6.97)*	-2.2 (5.61)
	Median Δ from day 0 (Q1, Q3)		0.3 (-7.3, 10.2)	6.4 (-0.1, 7.8)		-12.0 (-17.0, -8.5)	-1.6 (-6.4, 0.7)
	Mean % Δ from day 0 (SD)		1.0 (7.19)	4.7 (7.74)		-17.5 (9.99)*	-3.2 (7.72)
eGFR _{MDRD} (mL/min/1.73 m ²)	Mean (SD)	109 (19.1)	109 (20.5)	114 (21.2)	68.9 (13.0)	55.1 (12.8)	66.4 (14.5)
	Mean Δ from day 0 (SD)		0.4 (8.68)	5.3 (7.99)*		-13.9 (8.22)*	-2.6 (5.24)
	Median Δ from day 0 (Q1, Q3)		0.9 (-7.8, 7.9)	6.2 (-1.1, 8.8)		-13.9 (-18.3, -9.5)	-2.3 (-5.2, 0.0)
	Mean % Δ from day 0 (SD)		0.6 (7.60)	5.0 (8.41)		-20.0 (10.7)*	-4.0 (7.74)*
mGFR (mL/min)	Mean (SD)	107 (43.1)	109 (31.7)	111 (40.2)	76.7 (24.9)	65.4 (19.4)	70.5 (22.3)
	Mean Δ from day 0 (SD)		2.8 (35.0)	4.6 (22.8)		-11.2 (18.0)*	-6.1 (12.0)*
	Median Δ from day 0 (Q1, Q3)		0.9 (-17.5, 26.5)	4.4 (-10.2, 8.8)		-14.9 (-17.6, -4.5)	-4.6 (-17.2, 3.6)
	Mean % Δ from day 0 (SD)		28.5 (81.3)	18.3 (63.0)		-8.8 (30.7)	-4.3 (24.2)

*P within-treatment group < 0.05.

previous phase 1 study comparing COBI pharmacokinetics in subjects with severe RI and matched controls with normal RF.³¹ RTV exposures, as a stand-alone agent, were generally similar to historical data (data on file).

DISCUSSION

These results show that COBI does not affect actual GFR, as assessed by the absence of changes in CL_{iohexol}. In contrast, COBI affects tubular secretion of creatinine,

TABLE 3. SCr, eGFR, and aGFR Change From Baseline in Cohort 1 Vs. Placebo

PD Endpoint	COBI Vs. Placebo: Cohort 1		RTV Vs. Placebo: Cohort 1		
	Δ From Day 0		Δ From Day 0		
	Day 7	Day 14	Day 7	Day 14	
SCr (mg/dL)	0.1 (0.0, 0.2)*	0.1 (0.0, 0.2)	0.0 (0.0, 0.1)	0.0 (-0.1, 0.2)	
aGFR (mL/min)	-7.5 (-17.7, 2.8)	-2.5 (-10.2, 5.3)	-2.5 (-13.1, 8.0)	-0.7 (-8.7, 7.2)	
eGFR _{CG} (mL/min)	Diff (95% CI)	-12.1 (-21.5, -2.7)*	-21.4 (-57.2, 14.4)	-1.2 (-8.6, 6.1)	-17.1 (-52.5, 18.4)
eGFR _{MDRD} (mL/min/1.73 m ²)		-12.1 (-21.9, -2.3)*	-22.6 (-61.3, 16.1)	-1.8 (-10.2, 6.6)	-18.4 (-56.8, 20.1)
mGFR (mL/min)		-18.2 (-41.2, 4.8)	-30.6 (-77.1, 16.0)	3.0 (-24.5, 30.4)	-20.9 (-65.7, 23.9)

*P between treatment groups < 0.05.

COBI vs. placebo differences (95% CI) on day 14 in eGFR_{CG} and eGFR_{MDRD} of -21.4 mL/min (-57.2, 14.4) and -22.6 mL/min per 1.73 m² (-61.3, 16.1), respectively, were driven by an outlier subject in the placebo group. Excluding this subject results in COBI vs. placebo differences in eGFR_{CG} and eGFR_{MDRD} at day 14 of -4.3 mL/min (-13.3, 4.6) and -4.1 mL/min per 1.73 m² (-13.1, 5.0), respectively.

TABLE 4. Summary of COBI and RTV Pharmacokinetic Parameter Values and Statistical Comparisons of Primary COBI Parameters Between Cohort 1 and Cohort 2 on Day 7

Parameter	COBI Cohort 1 (n = 12)	COBI Cohort 2 (n = 18)	RTV Cohort 1 (n = 12)
AUC ₀₋₂₄ (ng·hr/mL)	14,500 (28.2)	20,800 (38.5)	8750 (42.8)
GMR % (90% CI)	137 (108, 174)		
C _{max} (ng/mL)	1720 (19.8)	2030 (31.6)	1560 (39.3)
GMR % (90% CI)	113 (93.9, 136)		
T _{max} (hr)	2.83 (2.58, 3.83)	3.07 (2.08, 4.03)	4.58 (4.33, 4.58)
C _{1au} (ng/mL)	99.8 (59.2)	303 (70.6)	75.2 (75.3)
GMR% (90% CI)	276 (172, 444)		
T _{1/2} (hr)	4.97 (3.54, 5.74)	7.78 (6.58, 9.11)	5.91 (5.16, 6.24)

Data are presented as mean (%CV), except for T_{max} and T_{1/2}, which are presented as median (Q1; Q3). Data presented in 3 significant figures. GMR, geometric LSM.

manifested as small increases in SCr with corresponding mean decreases in eGFR of approximately 10 mL/min (or mL/min per 1.73 m²) in cohort 1 and approximately 12 mL/min (~14 mL/min per 1.73 m²) in cohort 2. A mean mGFR decrease of approximately 18 mL/min was observed in cohort 1. Although we have used this method for completeness, mGFR has been shown to be no more reliable than SCr-based equations due to collection errors, diurnal variation in GFR and day-to-day variation in creatinine excretion.^{22,32} The decreases were reversible upon COBI discontinuation with mean eGFR returning to baseline on day 14, 7 days post COBI discontinuation. A similar magnitude of change in eGFR was observed in phase 2 studies in HIV-infected patients.^{20,21} No statistically significant decreases in eGFR, mGFR or aGFR were observed in subjects who received RTV or placebo on day 7 (Table 2).

Inhibition of creatinine renal tubular secretion of a similar magnitude has been observed with established drugs, such as cimetidine, pyrimethamine, and trimethoprim,

and newer or investigational agents (ie, rilpivirine, ranolazine, and dolutegravir). Administration of these agents results in 15%–30% increases in plasma or SCr and corresponding 10%–30% decreases in eGFR.¹⁴ Alteration of SCr and eGFR by these drugs is nonpathologic and attributed to competitive inhibition of uptake and/or efflux transporters in the renal tubules that mediate secretion of many ionic drugs.^{33–36} However, clinically relevant renal interactions resulting in toxicity due to inhibition of these transporters seem to be rare.^{37,38} For a renally cleared drug, a limited plasma exposure increase is usually observed because active secretion accounts for only a fraction of renal clearance that is mediated by both active tubular secretion and passive glomerular filtration³⁸; hence, renal drug interactions may be primarily important for narrow therapeutic index drugs, such as some antiarrhythmics and antineoplastics.^{39–42}

Creatinine has been reported to be an endogenous substrate of hOCT2, an organic cation transporter expressed in the basolateral membrane of the renal proximal tubules that plays a role in the tubular uptake of organic cations.^{43,44} More recently, creatinine has been found to be a substrate of multidrug and toxin extrusion (MATE) efflux proteins MATE1 and MATE2-K, which mediate secretion of organic cations.^{42,45} In vitro data demonstrated that COBI is a weak

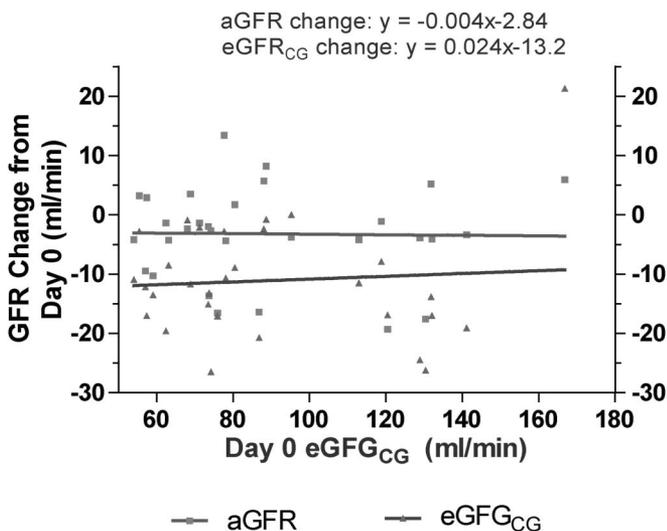


FIGURE 1. eGFR_{CG} and aGFR change from baseline (milliliters per minute) on day 7 vs. day 0 eGFR_{CG} in subjects receiving COBI.

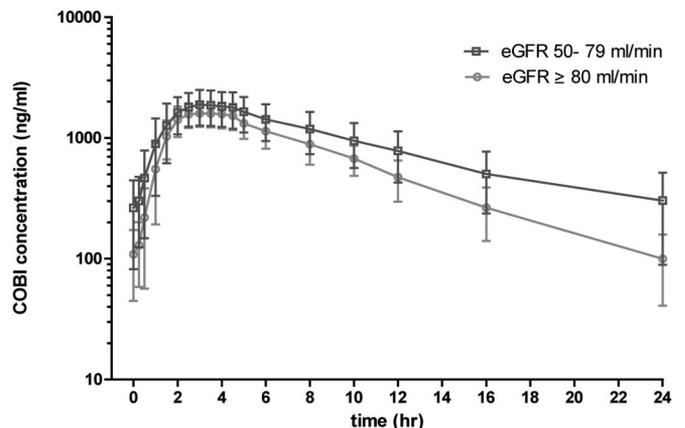


FIGURE 2. COBI plasma time-concentration profiles in subjects with eGFR ≥ 80ml/min or eGFR 50–79 ml/min.

inhibitor of human renal transporters OCT2 and MATE2-K and is a more potent inhibitor of OCTN1 and MATE1.⁴⁶ Inhibition of MATE1 may provide an insight into the biological mechanisms responsible for SCr increases observed in previous studies. These data are important, especially in the context of coadministration with tenofovir DF, a nucleotide analogue for which eGFR monitoring is recommended for patients at risk of RI.⁴⁷ The modulation of MATE1 by COBI would not affect elimination of tenofovir (TFV), an organic anion and thus a substrate of different renal transporters (i.e. OAT1/3 and MRP4).⁴⁸ As such, COBI is not expected to exacerbate renal toxicity of TFV.

Modestly higher COBI exposures were observed in subjects with mild/moderate RI as compared with that in subjects with normal RF. The mechanism for this observation is unknown because COBI is extensively metabolized via CYP3A (major)- and CYP2D6 (minor)- mediated oxidation and is primarily eliminated in the feces with renal excretion playing a minor role in COBI elimination (<10% of the administered dose present in urine as parent drug plus metabolites).³⁰ No clinically relevant changes were observed when COBI pharmacokinetics was compared in subjects with severe RI and their matched controls with normal RF³¹; hence, dose adjustment of COBI in RI is not warranted.

In conclusion, the results of this study showed that COBI lowers estimated GFR but does not affect actual GFR. The onset, magnitude and resolution of these changes were consistent with a “drug-interaction” effect of COBI altering creatinine secretion. Similar to the mechanism described for cimetidine, pyrimethamine, and trimethoprim,^{45,49–52} the proposed mechanism of COBI effect on eGFR is inhibition of MATE1 cationic renal transporters that mediate creatinine secretion.

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