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A Phase I Study to Evaluate the Pharmacokinetics and Safety of Cabotegravir in Adults With Severe Renal Impairment and Healthy Matched Control Participants

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Abstract

This study investigates the impact of severe renal impairment on the pharmacokinetics of cabotegravir, an investigational HIV-1 integrase inhibitor. This was a phase I, open-label, parallel-group, multicenter study conducted in 8 participants with severe renal impairment (creatinine clearance <30 mL/min; no renal replacement therapy) and 8 healthy participants (creatinine clearance >90 mL/min; 2 women/group; 6 men/group) matched for sex, age (±10 years), and body mass index (±25%). Participants received a single 30-mg oral cabotegravir tablet to determine total and unbound plasma cabotegravir concentrations. Arithmetic and geometric least squares means were calculated, and cabotegravir noncompartmental pharmacokinetic parameters were compared using geometric least squares mean ratios with 90% confidence intervals. Safety was assessed throughout the study. Geometric least squares mean ratios (90% confidence intervals) were 0.97 (0.84–1.14) for area under the plasma concentration-time curve extrapolated to infinity, 1.01 (0.87–1.17) for maximum observed plasma concentration, 1.31 (0.84–2.03) for unbound cabotegravir 2 hours after dosing, and 1.51 (1.19–1.92) for unbound cabotegravir 24 hours after dosing. All adverse events were grade 1, except grade 3 lipase elevation in a participant with renal impairment. Severe renal impairment did not impact plasma cabotegravir exposure, and cabotegravir may be administered without dose adjustment in renal impairment among patients not receiving renal replacement.

Keywords

cabotegravir, HIV-1, integrase inhibitor, pharmacokinetics, renal impairment

Cabotegravir (formerly known as GSK1265744) is a potent integrase strand transfer inhibitor in clinical development as both oral and long-acting (LA) injectable formulations for the treatment and preexposure prophylaxis of HIV-1 infection.[1–3] Although oral antiretrovirals have long been a mainstay of treatment for people living with HIV and have shown efficacy in prevention of infection, LA injectable formulations dosed monthly or bimonthly may provide a convenient alternative treatment approach for managing and preventing HIV infection, particularly for those who face challenges adhering to daily antiretroviral regimens.[4] Poor adherence to daily oral preexposure prophylaxis therapy has led to suboptimal efficacy in some populations, supporting a need for longer-acting modalities.[5]

Renal disease is a commonly reported complication of HIV infection, and renal toxicity has been reported with the use of some oral antiretroviral agents, including tenofovir disoproxil fumarate, which is approved for the treatment and prevention of HIV

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infection in some countries.[6,7] Current guidelines recommend the assessment of kidney function in all patients at the time of HIV diagnosis and at intervals of 6 months to 1 year in patients at high risk as well as in those receiving tenofovir disoproxil fumarate for HIV preexposure prophylaxis.[8] Before the advent of highly active antiretroviral therapy, chronic kidney disease (CKD) was largely a result of HIV-associated nephropathy, although the rapid progression of HIV-associated nephropathy to end-stage renal disease has substantially declined following the adoption of antiretroviral therapy.[9,10] However, despite highly active antiretroviral therapy, loss of kidney function continues to occur among HIV-infected persons, a phenomenon likely related to increasing age as well as other traditional risk factors of CKD (eg, diabetes, hypertension) commonly observed in this population.[10,11]

Renal impairment may affect drug pharmacokinetics (PK), potentially increasing the risk of adverse drug reactions.[12] Regulatory guidelines recommend evaluating drug PK in individuals with renal impairment to facilitate appropriate dosing recommendations.[13] The PK profile of cabotegravir following administration of oral or LA injectable formulations has been well characterized.[14] Cabotegravir is rapidly absorbed after oral administration and the previously reported geometric mean (95% confidence interval [CI]) of the area under the concentration-time curve (AUC) was 146 (128–167) μg · h/mL with single-dose administration of a 30-mg tablet; it is slowly cleared with a long apparent terminal elimination half-life ($t_{1/2}$) of 38.5 hours.[15] Results from a recent food-effect study revealed that both plasma cabotegravir AUC and maximum observed cabotegravir concentration (C_{max}) increase by 14% in the presence of a high-fat meal.[16] The PK parameters increased proportionally to dose from 5 to 30 mg but were less than proportional to dose from 30 to 60 mg.[2,16] Cabotegravir LA exhibits absorption-limited (flip-flop) kinetics and has been detected in plasma up to 48 weeks at a concentration of approximately 0.1 μg/mL after a single 400-mg intramuscular injection.[17] The geometric means of the area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) range from 920 to 5872 μg · h/mL with intramuscular injections at doses of 100 to 800 mg, and the apparent $t_{1/2}$ after administration of cabotegravir LA is absorption-rate limited, ranging from approximately 25 to 54 days.[18] Following the repeat daily administration of oral cabotegravir at doses of 5 and 30 mg, the accumulation ratio ranges from 2.36 to 2.51; for the LA formulation, repeat injections result in a modest accumulation less than 2-fold.[19]

Cabotegravir is greater than 99% bound to plasma proteins,[19] and it is predominantly metabolized by uridine 5'-diphosphoglucuronosyltransferase 1 polypeptide A1 (UGT1A1), with a minor contribution from UGT1A9.[14] Following administration of a single 30-mg radiolabeled oral dose of cabotegravir, approximately 59% of the dose was recovered in the feces, with approximately 27% excreted in the urine as glucuronide metabolites. Cabotegravir was the only component circulating in plasma and was not observed in urine as unchanged drug. Metabolic profiling was similar for pooled samples obtained following single-dose administration of oral and LA cabotegravir, suggesting that the pathways of biotransformation and excretion of cabotegravir are independent of the route of administration.[14]

Given that cabotegravir is primarily metabolized, renal impairment is unlikely to significantly impact cabotegravir disposition. The impact of severe renal impairment on cabotegravir PK was evaluated in this study using a reduced study design in accordance with regulatory guidance.[13]

Methods

Study Design

A phase I, open-label, multicenter, single-dose study was conducted in adults with severe renal impairment (with no renal replacement therapy) and matched healthy participants with normal renal function at 3 centers (DaVita Clinical Research, Lakewood, Colorado, principal investigator: Michal Kazimir; DaVita Clinical Research, Minneapolis, Minnesota, principal investigator: Jolene Berg; Quintiles, Overland Park, Kansas, principal investigator: Philip Leese [no participants were enrolled at this site]) in the United States from July 13, 2015, to November 1, 2016. Severe renal impairment was defined as creatinine clearance (CrCl) of <30 mL/min, as determined by 24-hour urine CrCl at screening. Healthy participants were required to have CrCl ≥90 mL/min and were matched to the participants with severe renal impairment for sex, age (±10 years), and body mass index (BMI; ±25%). A single oral dose of cabotegravir 30 mg was administered to all participants under fasting conditions, and PK parameters were assessed. A follow-up visit took place 10 to 14 days after administration of cabotegravir. End points included total plasma cabotegravir PK parameters, unbound plasma concentrations 2 and 24 hours after dosing, safety, and tolerability.

The study was compliant with the principles stated in the 2013 Declaration of Helsinki. Midlands Institutional Review Board (Overland Park, Kansas) approved the research protocol. Written informed consent was obtained from all individuals before initiation of the study at Quintiles (Overland Park, Kansas) and DaVita Clinical Research (Lakewood, Colorado, and

Minneapolis, Minnesota; ClinicalTrials.gov identifier, NCT02354937; ViiV clinical study register identifier, 201480).

Selection of Study Participants

Men or women aged 18 to 70 years with a body weight of ≥50 kg and BMI within the range ≥19 and ≤38.0 kg/m^2 were enrolled in the study. Participants were eligible to be considered healthy comparators if judged healthy by physical examination, medical history, laboratory tests, and cardiac monitoring, and if CrCl was ≥90 mL/min as determined by a 24-hour urine CrCl assessment at screening. Participants with severe renal impairment with CrCl <30 mL/min were included if they were clinically stable in the opinion of the study investigator. Women were ineligible if they were pregnant, lactating, or capable of becoming pregnant. Key exclusion criteria for all participants included evidence of active infection, cardiac abnormalities, current or chronic history of liver disease (including acute or chronic hepatitis B or C), a positive HIV antibody test result, history of inflammatory bowel disease or cholecystectomy, history of peptic ulceration or pancreatitis, history of regular alcohol consumption within 6 months of the study (defined as an average weekly intake of >14 drinks for men and >7 drinks for women), and a positive finding on drug/alcohol screening. Specific exclusion criteria for renally impaired participants included fluctuating or rapidly deteriorating renal function, clinically significant elevation in serum potassium level, serum sodium level ≤125 mEq/L, CrCl <15 mL/min, and history of renal transplant.

Patients were required to abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days if the drug was a potential enzyme inhibitor, 14 days if the drug was a potential enzyme inducer, or 5 half-lives (whichever is longer) before the first dose of study medication until completion of the follow-up visit, unless the medication had no potential to interfere with the study in the opinion of the investigator and sponsor. Antacids, vitamins, calcium and iron supplements, and other medications containing polyvalent cations or with the ability to interfere with gastric absorption were held on the day of study dosing.

Bioanalytical Methods

Serial plasma PK samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours after dosing. Concentrations of cabotegravir were determined using a validated analytical method over the range 25.0 to 25,000 ng/mL in human plasma and 1.00 to 2500 ng/mL in human plasma ultrafiltrate: human plasma (90:10) based on protein precipitation, followed by high-performance liquid chromatography tandem mass spectrometry analysis.[20] Cabotegravir was extracted from 25 µL (0.0250 mL) of human plasma or 50 µL of human plasma ultrafiltrate: human plasma (90:10) using an isotopically labeled internal standard ([$^{13}C^2H_2{}^{15}N$]-GSK1265744) in 50/50, acetonitrile/water, by protein precipitation in acetonitrile. Extracts were injected (5–15 µL, not to exceed 35 µL when analyzing for human plasma ultrafiltrate: human plasma [90:10]; 2–7 µL, not to exceed 7 µL when analyzing for human plasma) onto an analytical column, Luna C18(2)-HST, 50 × 3.0 mm, 2.5 µm (Phenomenex, Torrance, California) maintained at 45°C and eluted with a binary mobile phase gradient using water: formic acid, 1000:4, v:v (A) and 25 mM of ammonium formate in acetonitrile: water, 800:200, v:v (B), with a constant flow rate of 0.800 mL/min.

Using a Shimadzu Prominence 20 Series liquid chromatography system (Shimadzu Corporation, Kyoto, Japan), the initial mobile phase condition of 60:40, A:B was held until 0.3 minutes. From 0.3 to 2.00 minutes, the mobile phase changed to 10:90, A:B and was held at this composition until 2.50 minutes and reverted to the initial conditions, 60:40, A:B, at 2.51 minutes. Detection was performed by positive ion electrospray set to 500°C on an Applied Biosystems/MDS Sciex API-4000 (Sciex Corporation, Framingham, Massachusetts) with multiple reaction monitoring (m/z 406→ 263 for cabotegravir and m/z 410.1→ 263 for the internal standard).

For human plasma, the maximum within-run and between-run precision observed was ≤6.8% and ≤9.1%, respectively. Accuracy ranged from 8.8% to 8.0% bias. For human plasma ultrafiltrate: human plasma (90:10), the maximum within-run and between-run precision observed was ≤7.2% and ≤12.6%, respectively. Accuracy ranged from 14.8% to 8.0% bias. The complete analysis of cabotegravir with all the necessary parameters has been previously described.[16,20]

At 2 and 24 hours after dosing with cabotegravir, plasma samples were collected to determine bound and unbound plasma cabotegravir concentrations. Plasma protein binding of cabotegravir was determined in quadruplicate by equilibrium dialysis using a molecular weight cutoff of 8000 Daltons for 5 hours against plasma dialysate. Plasma dialysate was analyzed using a validated analytical method using high-performance liquid chromatography–tandem mass spectrometry. Plasma was prepared at a 90:10 dilution with K_3EDTA. Reference standards included cabotegravir, [$^{13}C^2H_2{}^{15}N$]-cabotegravir, ultrafiltrated human plasma diluted 1:9 in K_3EDTA, and lipemic human plasma with a triglyceride concentration of ≥300 mg/dL in K_3EDTA.The linear range of detection of cabotegravir from a 50-µL sample of plasma dialysate was 1 to 2500 ng/mL. Quality-control samples

containing 3 different concentrations of cabotegravir in plasma dialysate were analyzed with each batch of participant samples against calibration standards, which were prepared by spiking individual samples of blank matrix with the analyte at concentrations of 1, 2, 10, 100, 500, 1000, 2250, 2500 ng/mL.

Bioanalytical assay acceptance criteria for the plasma cabotegravir concentration and protein binding of plasma cabotegravir were that no more than one-third of the quality-control results could deviate >15% from the nominal concentration and that ≥50% of the results from each quality-control concentration should be within 15% of the nominal concentration.

Pharmacokinetic Assessments

Plasma cabotegravir concentration-time data were analyzed by noncompartmental PK analysis with Phoenix WinNonlin version 6.3 (Certara, Princeton, New Jersey). Total plasma PK parameters included $AUC_{0-\infty}$, AUC from time 0 to time of the last quantifiable concentration (AUC_{0-t}), the percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{ex}$), C_{max}, cabotegravir concentration 24 hours after dosing, time to maximum concentration (t_{max}), and $t_{1/2}$. In addition, unbound concentrations of cabotegravir and unbound fraction expressed as a percentage of the total cabotegravir concentration in plasma at 2 and 24 hours after dosing were determined.

With sex and group as fixed effects and age and BMI as continuous variables, log-transformed PK parameters (except $\%AUC_{ex}$ and t_{max}) observed in renally impaired participants were compared with those of healthy participants by analysis of covariance. Point estimates and 90%CIs were generated using a mixed linear model within the SAS/STAT module of SAS version 9.4 (SAS Institute, Cary, North Carolina) for the renal impairment group compared with healthy participants. Geometric least squares mean ratios were estimated for selected PK parameters. PK parameters for t_{max} and $\%AUC_{ex}$ were summarized descriptively. The PK concentration population included all participants in the study who had evaluable cabotegravir assay results after plasma PK sampling.

The unbound fraction was calculated using the total and unbound plasma concentrations of cabotegravir generated at 2 and 24 hours after dosing in the following formula:

$$fu_{xhr} = C(unbound)/C(total),$$

where *fu* is the unbound fraction and *C*(*unbound*) and *C*(*total*) are the unbound and total concentrations of cabotegravir in plasma, respectively. Values are expressed as a percentage of the total cabotegravir concentration by multiplying fu_{xhr} by 100.

Table 1. Participant Demographics and Baseline Characteristics

Parameter	Severe Renal Impairment (n = 8)	Healthy Participants[a] (n = 8)
Age, mean (SD), y	55.6 (11.1)	52.3 (11.3)
Sex, n (%)		
Female	2 (25.0)	2 (25.0)
Male	6 (75.0)	6 (75.0)
BMI, mean (SD), kg/m^2	28.5 (3.4)	28.1 (3.8)
Height, mean (SD), cm	171.9 (7.0)	174.2 (10.9)
Weight, mean (SD), kg	84.2 (10.7)	85.8 (16.6)
Race, n (%)		
American Indian/Alaska Native	0	1 (12.5)
Black/African American	3 (37.5)	1 (12.5)
White	5 (62.5)	6 (75.0)
Creatinine clearance, mean (SD), mL/min	22.1 (3.8)	121.3 (21.7)

BMI, body mass index; SD, standard deviation.
[a]Healthy and severely renally impaired participants were matched for sex, age (± 10 y), and BMI (± 25%).

Safety Assessments

Safety assessments included a full physical examination at screening (assessment of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems as well as height and weight) and brief physical examinations on day 1 and at follow-up (assessment of the skin, lungs, cardiovascular system, and abdomen [ie, liver and spleen]); assessment of vital signs at screening, day 1, day 4, day 6, day 8, and follow-up; electrocardiography at screening, day 1, and day 2; clinical laboratory tests at screening, day –1, day 4, day 8, and follow-up; and monitoring for adverse events (AEs) throughout the study. Individuals who were enrolled in the study and received study drug were included in the safety population.

Statistical Analysis

Point estimates for the PK parameters and the associated 90%CIs for the cohort difference (renal impairment vs healthy controls) were calculated. Log-transformed PK parameters (except $\%AUC_{ex}$ and t_{max}) were analyzed by analysis of covariance, which considered cohort and sex as fixed effects and age and BMI as continuous covariates.

Results

Baseline Characteristics

Sixteen patients (8 with severe renal impairment and 8 healthy participants) were enrolled and completed all study assessments. Participant demographics and baseline characteristics were well matched between groups and are summarized in Table 1. In both groups, 75.0%

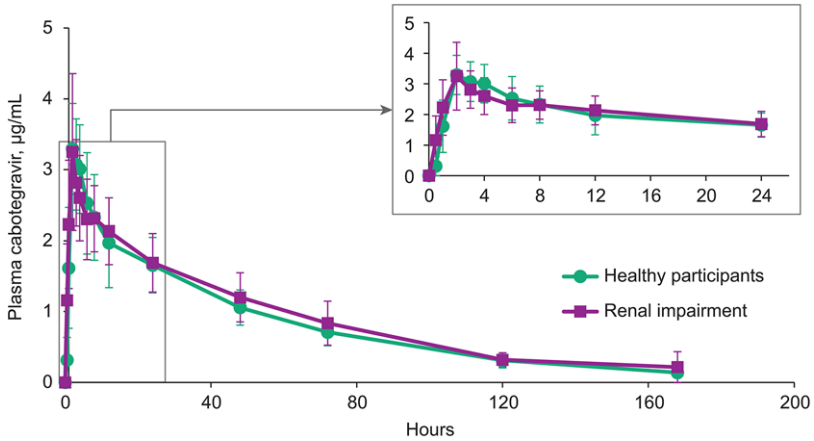

Figure 1. Mean (± standard deviation) cabotegravir plasma concentration-time profiles in severe renally impaired and healthy participants after a single 30-mg tablet administration.

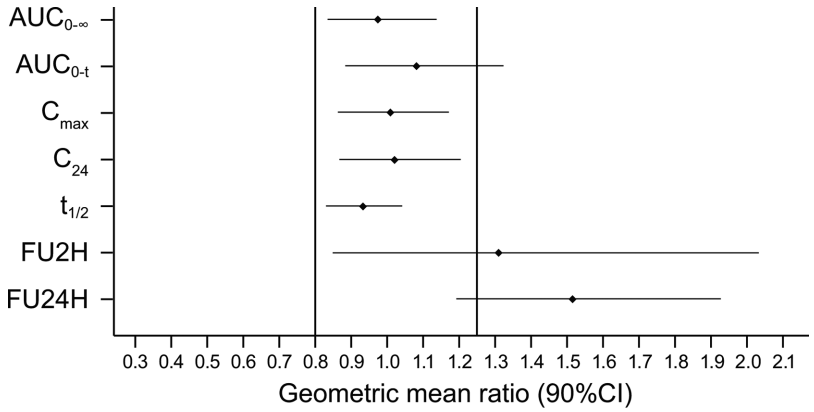

Figure 2. Geometric mean ratios and 90%CIs for comparisons of cabotegravir pharmacokinetic parameters by group (severe renal impairment vs healthy participants). $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; C_{24}, concentration observed 24 hours after dosing; CI, confidence interval; C_{max}, maximum observed concentration; FU2H, unbound fraction at 2 hours; FU24H, unbound fraction at 24 hours; $t_{1/2}$, terminal elimination phase half-life.

of participants were male, and the majority of the renally impaired group (62.5%) and matched control group (75.0%) were white. Mean CrCl values were 22.1 mL/min and 121.3 mL/min in the renally impaired and control groups, respectively.

Pharmacokinetics

Mean concentration-time profiles of participants with severe renal impairment and those of healthy participants are shown in Figure 1, and geometric mean ratios and 90%CIs for comparisons of cabotegravir PK parameters by group are shown in Figure 2; selected PK parameters are summarized in Table 2. The primary end points of $AUC_{0-\infty}$ and C_{max} were similar between renally impaired and healthy participants, as indicated by the geometric least squares mean ratios (90%CI) of 0.97 (0.84–1.14) and 1.01 (0.87–1.17), respectively (Table 2). Cabotegravir was readily absorbed after a single oral dose, with C_{max} occurring 2 hours after dosing in both groups (renally impaired, mean [standard deviation (SD)]: 3.44 µg/mL [0.937]; healthy participants, mean [SD]: 3.40 µg/mL [0.514]), followed by a multiphasic decline in plasma concentrations with a mean $t_{1/2}$ of 39.6 hours in the renally impaired group and 40.8 hours in healthy participants. Median (range) t_{max} was similar between renally impaired and healthy participants (2 hours [1.0–4.2] vs 2 hours [1.0–4.0], respectively). At 168 hours, the plasma concentrations were measurable but below the limit of quantification (renally impaired: mean [SD], 0.215 µg/mL [0.218]; healthy participants: 0.138 µg/mL [0.053]). The $\%AUC_{ex}$ was <10% for all individuals in both groups except for 1 participant, who was excluded due to R^2 <0.85 and $\%AUC_{ex}$ >20%. The arithmetic means (SD) for $\%AUC_{ex}$ for participants with severe renal impairment and the healthy controls were 5.51% (2.09) and 5.66% (1.66), respectively. In addition to AUC and C_{max}, plasma $t_{1/2}$ and concentration 24 hours after dosing were similar after

Table 2. Summary of Pharmacokinetic Parameters of Cabotegravir

Pharmacokinetic Parameter	Severe Renal Impairment (n = 8)		Healthy Participants[b] (n = 8)		GLS Mean Ratio (90%CI)
	Arithmetic Mean (SD)	Geometric Mean (95%CI) [CVb%][a]	Arithmetic Mean (SD)	Geometric Mean (95%CI) [CVb%][a]	
$AUC_{0-\infty}$, μg · h/mL	146 (33.3)[c]	143 (115–177) [23][c]	144 (35.7)	140 (116–170) [23]	0.97 (0.84–1.14)
AUC_{0-t}, μg · h/mL	147 (39.3)	143 (115–178) [27]	136 (32.4)	133 (110–160) [23]	1.08 (0.89–1.32)
C_{max}, μg/mL	3.44 (0.94)	3.34 (2.67–4.17) [27]	3.40 (0.51)	3.37 (2.96–3.83) [15]	1.01 (0.87–1.17)
C_{24}, μg/mL	1.69 (0.41)	1.65 (1.34–2.02) [25]	1.66 (0.39)	1.62 (1.34–1.96) [23]	1.02 (0.87–1.20)
$t_{1/2}$, h	39.6 (5.92)[c]	39.2 (33.9–45.4) [16][c]	40.8 (4.58)	40.5 (36.9–44.5) [11]	0.93 (0.83–1.04)
t_{max}, h[a]	...	2.00 (1.0–4.2)	...	2.00 (1.0–4.0)	NA
CU2H, μg/mL	0.0068 (0.0034)	0.0056 (0.0034–0.0129)[a]	0.0056 (0.0044)	0.0047 (0.0022–0.0162)[a]	1.32 (0.81–2.15)
CU24H, μg/mL	0.0031 (0.0008)	0.0030 (0.0022–0.0050)[a]	0.0019 (0.0005)	0.0020 (0.0013–0.0025)[a]	1.67 (1.33–2.09)
FU2H, %	0.19 (0.056)	0.18 (0.14–0.23) [29]	0.16 (0.143)	0.14 (0.08–0.22) [63]	1.31 (0.84–2.03)
FU24H, %	0.17 (0.028)	0.17 (0.15–0.19) [17]	0.12 (0.034)	0.11 (0.09–0.14) [30]	1.51 (1.19–1.92)
CL/F, L/h	0.22 (0.050)[c]	0.21 (0.17–0.26) [23][c]	0.22 (0.047)	0.21 (0.18–0.26) [23]	1.03 (0.88–1.20)

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; AUC_{ex}, $\%AUC_{0-\infty}$ obtained by extrapolation; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; C_{24}, concentration observed 24 hours after dosing; CI, confidence interval; C_{max}, maximum observed concentration; CU2H, unbound concentration at 2 hours; CU24H, unbound concentration at 24 hours; CVb, between-participant coefficient of variation; FU2H, unbound fraction at 2 hours; FU24H, unbound fraction at 24 hours; GLS, geometric least squares; NA, not applicable; SD, standard deviation; $t_{1/2}$, terminal elimination phase half-life; t_{max}, time of occurrence of maximum concentration.
[a]Presented as median (range).
[b]Healthy participants and participants with severe renal impairment were matched for sex, age (± 10 y), and body mass index (± 25%).
[c]N = 7; parameters associated with the terminal phase for 1 participant were excluded from the pharmacokinetic summary population because the coefficient of determination was <0.85 and percentage of AUC_{ex} was >20%.

administration of a single dose of cabotegravir 30 mg in renally impaired and healthy participants (Table 2).

At 2 hours after dosing, the mean (SD) percentage of unbound of cabotegravir was 0.19% (0.056%) in renally impaired participants, corresponding to a mean (SD) unbound concentration of 0.0068 μg/mL (0.0034), and 0.16% (0.143%) in healthy participants, corresponding to a mean (SD) unbound concentration of 0.0056 μg/mL (0.0044; Table 2 and Figure 2). No apparent relationship was observed between renal function and cabotegravir PK parameters or percentage of unbound cabotegravir at 2 hours after dosing.

At 24 hours after dosing, the mean (SD) percentage of unbound cabotegravir was significantly higher in renally impaired participants compared with healthy participants (0.17% [0.028%] vs 0.12% [0.034%]; $P = .012$). Similarly, the concentrations of unbound plasma cabotegravir in participants with severe renal impairment were higher than those observed in healthy participants at 24 hours after dosing (0.0031 μg/mL [0.0008] vs 0.0019 μg/mL [0.0005]).

Safety

Overall, a total of 9 AEs were recorded for 5 of 16 (31%) participants (3 of 8 [38%] renally impaired and 2 of 8 [25%] healthy participants). No AEs were common to both the renally impaired and healthy participant groups.

In the renally impaired group, 2 of 8 (25%) participants experienced a total of 5 AEs considered to be drug related, including 1 who experienced gastrointestinal pain, nausea, and vomiting (all grade 1 intensity), and 1 who experienced pain at the site of a phlebotomy catheter (grade 1 intensity) and increased lipase (grade 3 intensity). For this participant, grade 3 elevated lipase (1882 U/L; normal range: 73–393 U/L) was recorded on day 10 and was considered by the investigator as possibly related to the study drug because the lipase elevation was higher than historical values, including a grade 2 elevation of 976 U/L on day –1, before receipt of study drug. At an unscheduled visit (day 14), the lipase value was recorded as 350 U/L and the AE was reported as resolved. Finally, somnolence was recorded for 1 participant but was not considered to be drug related.

Among healthy participants, 1 participant experienced change in bowel habit and 1 participant had diarrhea and conjunctival hemorrhage; none of these AEs were considered drug related. No deaths or serious AEs were reported in either group. No abnormalities in vital signs or on electrocardiography were observed during the study.

Discussion

As the population of patients infected with HIV ages, the proportion of patients developing long-term

conditions such as kidney disease increases, with some estimates indicating that the prevalence of CKD is as high as 17% in patients infected with HIV.[21] In addition to the traditional risk factors for CKD (eg, diabetes, hypertension) commonly observed in individuals infected with HIV, HIV-specific factors such as high HIV-associated viremia and low CD4+ counts have also been associated with kidney impairment and end-stage renal disease.[10,11,22] Furthermore, some antiretroviral agents themselves have been associated with potential nephrotoxicity.[21,23] Renal impairment has been associated with changes in absorption, distribution, metabolism, and active transport in the kidney, liver, and gastrointestinal tract[12,24]; therefore, PK assessment of drugs, including antiretroviral agents, in patients with compromised renal function is important to inform proper selection of therapy and dose adjustments.[13]

Cabotegravir is predominantly metabolized by UGT1A1, with renal elimination of cabotegravir metabolites.[14] Given the metabolism and excretion profile of cabotegravir,[14] renal impairment would not be expected to have a significant effect on cabotegravir PK. Findings from the present study support this hypothesis, with geometric mean cabotegravir plasma C_{max} and $AUC_{0-\infty}$ of 3.34 μg/mL and 143 μg · h/mL, respectively, in participants with severe renal impairment (CrCl <30 mL/min) vs 3.37 μg/mL and 140 μg · h/mL, respectively, in healthy participants after a single oral dose of cabotegravir 30 mg. Additionally, $t_{1/2}$ was similar between the renally impaired and healthy participants.

At 2 and 24 hours after dosing, the percentage of free cabotegravir in participants with severe renal impairment was higher, respectively, than that observed in healthy participants, and the concencentrations of unbound cabotegravir were similarly higher in participants with severe renal impairment at the same time points. The percentage of protein binding remained >99% in those with renal impairment. The observed elevation in the percentage of free cabotegravir may be due to reduced albumin-binding capacity, which was previously demonstrated in CKD.[25] Although the impact of renal impairment on the unbound fraction is significant, the unbound concentrations remain very low in the single-digit ng/mL range. Furthermore, cabotegravir 60 mg once daily, which would be expected to have higher unbound concentrations, was studied in HIV-infected participants for nearly 2 years and was shown to be well tolerated.[2] These data are consistent with the results of a study investigating dolutegravir, a close analog of cabotegravir, that demonstrated similar modest changes in dolutegravir plasma exposures and no requirement for dose adjustment in patients with renal impairment.[26] Because of the similar disposition pathway of cabotegravir following oral and LA administration and because the therapeutic cabotegravir LA exposures are below those following oral cabotegravir, the results from the study support no requirement for dose modification in patients with mild, moderate, and severe renal impairment following cabotegravir LA administration. Few AEs were observed, with most considered mild (grade 1). No serious AEs were observed, and no new safety concerns were identified after a review of the safety data.

This study demonstrates that no dose adjustment is required in patients with severe renal impairment (CrCl <30 mL/min and not on renal replacement therapy), with extension to patients with mild to moderate renal impairment. Although it was not studied, cabotegravir disposition is unlikely to be affected in patients receiving dialysis because of the high degree of protein binding.

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Declaration of Conflicting Interests

RP, SLF, and KKB are employees of and own stock in GlaxoSmithKline. YL and CF are employees of PAREXEL International. ART, CT, WRS, and PP are employees of ViiV Healthcare and own stock in GlaxoSmithKline.

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Author Contributions

All listed authors meet the criteria for authorship set forth by the International Committee of Medical Journal Editors. Y.L., C.T., and W.R.S. contributed to the conception of the study. S.L.F., Y.L., A.R.T., C.T., and W.R.S. contributed to the design of the study. S.L.F., Y.L., K.K.B., A.R.T., and P.P. contributed to the acquisition of data. R.P., S.L.F., and C.F. contributed to the analysis of data. All authors contributed to the interpretation of data. R.P. and P.P. contributed to the drafting of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the manuscript for publication.

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