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Effect of a High-Fat Meal on the Pharmacokinetics of the HIV Integrase Inhibitor Cabotegravir

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Abstract

Cabotegravir is an integrase inhibitor in clinical development for the treatment and prevention of HIV infection using oral tablets for short-term, lead-in use before subsequent administration of a long-acting injectable formulation. This phase 1, single-center, randomized, 2 × 2 crossover study evaluated the effect of a high-fat meal on the pharmacokinetics (PK) of oral cabotegravir. Healthy adults received oral cabotegravir 30 mg as a single dose on 2 separate occasions, either after fasting or following a high-fat meal (~53% fat, ~870 kcal). Safety evaluations and serial PK samples were collected, and a mixed-effects model was used to determine within-participant treatment comparison of noncompartmental PK parameters. Twenty-four patients were enrolled and had a mean body mass index of 25.6 kg/m^2; 67% were male. Compared with the fasting state, coadministration of cabotegravir with a high-fat meal increased plasma cabotegravir area under the concentration-time curve and maximal drug concentration, each by 14%. The slight 14% to 17% increase in exposure associated with a high-fat, high-calorie meal was not considered clinically significant. No grade 3/4 adverse events (AEs), drug-related AEs, or AEs leading to discontinuation were reported.

Keywords

integrase inhibitor, food, absorption, high-fat, pharmacokinetics

Combination antiretroviral therapy has transformed infection with HIV-1 to a chronic, manageable condition.[1] However, the success of antiretroviral therapy depends on patient compliance with treatment regimens, with incomplete adherence potentially leading to drug resistance or treatment failure.[1] In addition, some regimens require coadministration with food, thus impacting dosing convenience and adherence.[2–4] Treatment regimens that provide an alternative to oral dosing could improve convenience, increase compliance, and potentially lead to better treatment outcomes for some patients.

Cabotegravir is an integrase strand inhibitor in clinical development for the treatment and prevention of HIV-1 infection.[5] Cabotegravir is formulated as a 30-mg oral tablet given daily for use during a safety lead-in phase followed by transition to a 200-mg/mL long-acting injectable for intramuscular administration given every 4 or 8 weeks.[6] Cabotegravir is in phase 3 development (Clinicaltrials.gov: NCT03164564, NCT02951052, NCT02938520, and NCT03299049) for use in combination with long-acting injectable rilpivirine for the treatment of HIV infection and as monotherapy for pre-exposure prophylaxis.[6,7]

Cabotegravir is highly bound to serum albumin and has an in vitro protein-adjusted 90% inhibitory concentration of 166 ng/mL.[1] It is a class 2 compound (Biopharmaceutics Drug Disposition Classification System) exhibiting high passive permeability and low solubility.[8] Cabotegravir is primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT)1A1 with a minor contribution by UGT1A9 to form glucuronic acid conjugates.[9] The primary metabolite, M1, and unchanged cabotegravir are

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both excreted in bile. Due high intrinsic membrane permeability, the impact of efflux transporters on intestinal absorption of cabotegravir is minimal.[8]

In vitro and clinical studies demonstrate that cabotegravir has low potential for clinically significant drug interactions.[8] At clinically relevant concentrations, cabotegravir does not inhibit or induce the major cytochrome P450, UGT enzymes, or intestinal drug transporters (except OAT1 and OAT3) in vitro. Cabotegravir had no significant effect on the pharmacokinetics (PK) of midazolam, a sensitive cytochrome P450 3A4 probe substrate, a levonorgestrel/ethinyl estradiol–containing oral contraceptive, or the nonnucleoside reverse-transcriptase inhibitor rilpivirine.[8,10,11] Rifampin significantly reduced cabotegravir exposures, therefore, potent enzyme inducers should not be coadministered with cabotegravir.[12]

Single-dose oral cabotegravir 30 mg is readily absorbed with a median time to peak plasma concentration (t_{max}) of 2 hours and has a plasma apparent terminal-phase half-life ($t_{1/2}$) of approximately 38.5 hours under fasted conditions and an area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) of 146 μg•h/mL.[12,13] Previous studies demonstrated that a moderate-fat meal (30% fat, ~670 calories) did not significantly affect the PK of cabotegravir administered at 10- and 30-mg doses, respectively, using early prototype formulations (Supplemental Data). Furthermore, the time to maximal drug concentration (t_{max}) and half-life of cabotegravir 30 mg given with a moderate-fat meal were a median of 3.0 hours (range, 1.0-6.0) and a geometric mean of 38.6 hours (95% confidence interval, 35.0-42.7), respectively (Supplemental Data). A study to evaluate the maximum impact on cabotegravir absorption following a high-fat meal has not been conducted. Thus, the present study sought to investigate whether a high-fat meal would significantly affect the PK of oral cabotegravir 30 mg using the intended commercial formulation.

Methods

Study Design

A phase 1, randomized, open-label, single-dose, 2-way balanced crossover study was conducted in healthy adults from June 28, 2016, to August 25, 2016 (Clinicaltrials.gov identifier, NCT02799264). Participants were randomized (1:1) to receive oral cabotegravir 30 mg either after ≥10 hours of fasting (treatment A) or within 30 minutes of completing a high-fat meal (~53% fat, ~870 calories; treatment B) in the first period and the opposite treatment in the second. A 14-day washout period followed each dosing period. The final study follow-up visit was 14 days after the last dose.

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

The primary end points included cabotegravir $AUC_{0-\infty}$, maximal drug concentration (C_{max}), and concentration at 24 hours postdose (C_{24}). Secondary PK parameters included $t_{1/2}$, t_{max}, and clearance following oral dosing (CL/F).

Selection of Study Participants

Individuals aged ≥18 and ≤65 years with a body weight of ≥50 kg, body mass index between 18.5 and 31.0 kg/m^2, and judged as healthy by physical examination, medical history, and evaluation by the investigator were permitted to enter the study. Key exclusion criteria included a positive HIV or hepatitis C virus antibody test result; positive hepatitis B virus surface antigen test result or a positive hepatitis B core antibody with a negative hepatitis B surface antibody at screening or within 3 months before the first dose of the study treatment; history of regular alcohol consumption within 6 months of the study; use of prescription or nonprescription drugs, including vitamins and herbal or dietary supplements within 7 to 14 days before the first dose and throughout the study; and hypersensitivity to the study medication.

Study Assessments

Serial plasma PK samples were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours postdose. Noncompartmental PK analysis was performed with Phoenix WinNonlin version 6.3 (Certara, Princeton, New Jersey). The point estimates of geometric least-squares mean ratios of the high-fat treatment compared with the fasting treatment and associated 90% confidence intervals for within-participant treatment comparisons for cabotegravir were generated by a mixed-effects model, with fixed-effects terms for treatment and period and a random-effect term for participant. Similar treatment comparisons were performed for observed C_{max}, C_{24}, $t_{1/2}$, t_{max}, and CL/F as secondary analyses. The PK population included all participants in the study who had evaluable cabotegravir data following plasma PK sampling.

Safety assessments were conducted during each treatment period, including assessments of vital signs, electrocardiography, clinical laboratory tests, and monitoring for adverse events (AEs). All individuals who were enrolled in the study and received ≥1 dose of the study drug were included in the safety population.

Table 1. Pharmacokinetic Parameters of Cabotegravir After a 30-mg Single Dose in a Fasted State and With a High-Fat Meal

	Fasted State (n = 21)		High-Fat Meal (n = 21)		Fasted State vs High-Fat Meal (n = 21)
PK Parameter	Mean (SD)[a]	Geometric Mean (95% CI) [CVb%][a]	Mean (SD)[a]	Geometric Mean (95% CI) [CVb%][a]	GLS Mean Ratio (90% CI)
$AUC_{0-\infty}$, h·μg/mL	148 (41.0)	143 (126-162) [28.3]	169 (45.3)	163 (144-185) [28.7]	1.14 (1.02-1.28)
C_{max}, μg/mL	3.45 (0.940)	3.33 (2.95-3.77) [27.4]	3.95 (0.905)	3.85 (3.46-4.28) [23.8]	1.14 (1.03-1.27)
C_{24}, μg/mL	1.66 (0.400)	1.62 (1.45-1.81) [24.5]	1.93 (0.429)	1.88 (1.69-2.10) [24.0]	1.17 (1.04-1.30)
$t_{1/2}$, h	41.1 (6.05)	40.6 (38.0-43.5) [15.0]	41.1 (6.57)	40.6 (37.8-43.7) [16.1]	0.997 (0.964-1.03)
t_{max}, h	3.00 (1.00-4.00)[b]	...	3.01 (1.00-8.02)[b]	...	...
CL/F, L/h	0.218 (0.0611)	0.210 (0.185-0.239) [28.3]	0.191 (0.0553)	0.184 (0.162-0.209) [28.7]	0.875 (0.785-0.977)

$AUC_{0-\infty}$ indicates area under the concentration curve from time 0 extrapolated to infinity; C_{24}, concentration at 24 hours postdose; CL/F, apparent oral clearance; C_{max}, maximal drug concentration; CVb, coefficient of variation between subject; GLS, geometric least squares; NA, not applicable; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time at maximal concentration.

[a]Unless otherwise noted.

[b]Median (range).

Bioanalytical Methods

The complete analysis of cabotegravir with all the necessary parameters has been previously described.[11] Plasma samples were analyzed for cabotegravir by Covance Laboratories (Madison, Wisconsin) using a validated analytical method based on protein precipitation, followed by high-performance liquid chromatography/mass spectroscopy/mass spectroscopy analysis.[11] The lower limit of quantification was 25 ng/mL using a 25-μL aliquot of EDTA plasma. The upper limit of quantification was 25,000 ng/mL. Quality-control (QC) samples containing cabotegravir prepared at 3 different analyte concentrations were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one third of the QC results could deviate from the nominal concentration >15%, and ≥50% of the results from each QC concentration should be within 15% of nominal.

Results

Participant Demographics

Twenty-four individuals were enrolled, and 22 completed the study. Two participants from treatment A group (cabotegravir 30 mg after fasting) withdrew from the study after receiving 1 dose: 1 because of lack of transportation to the site and 1 who moved out of state.

Most participants were male (n = 16/24; 67%) and white (n = 16/24; 67%). The mean (SD) age of the enrolled participants was 39.7 (14.7) years, and the mean (SD) body mass index was 25.6 (2.6) kg/m^2.

Pharmacokinetic Results

Coadministration of oral cabotegravir 30 mg with a high-fat meal increased cabotegravir plasma $AUC_{0-\infty}$, C_{max}, and C_{24} by 14% to 17% compared with that of cabotegravir administration after fasting (Table 1; Figure 1). Quantifiable predose concentrations were all <5% of their respective C_{max} values and did not affect any PK parameter estimates. CL/F for cabotegravir decreased 13% as a result of increased bioavailability when oral cabotegravir was coadministered with a high-fat meal compared with after fasting. Neither t_{max} nor $t_{1/2}$ was affected by the administration of a high-fat meal.

One participant was excluded from the PK analysis because PK parameters could not be calculated. This participant had very low cabotegravir concentrations that reached a peak concentration of 0.0987 μg/mL at 2 hours after dosing under fasting conditions and had 1 measurable concentration of 0.0258 μg/mL at 4 hours after dosing with a high-fat meal. Study investigators were unsuccessful in reaching this participant for further evaluation.

Safety

There were no AEs or serious AEs that led to discontinuation of the study drug. Three participants (13%) reported grade 1 AEs that were not considered to be drug-related: 1 individual in the fasting group reported headache, and 2 individuals in the fed group reported dizziness and vessel-puncture site hemorrhage (n = 1, respectively). Treatment-emergent laboratory abnormalities were reported in 2 participants: 1 individual had grade 2 hypoglycemia (2.78 mmol/L [lower limit of normal range, 3.89 mmol/L]) that the investigator determined to be related to the person's fasted state, and 1 individual had grade 3 increased direct bilirubin (10.26 μmol/L [upper limit of normal range, 6.84 μmol/L]) that the investigator determined to be not clinically relevant because the person was asymptomatic and the elevation was transient and not associated with elevations in liver enzymes. No clinically significant electrocardiographic or vital sign abnormalities were reported as AEs.

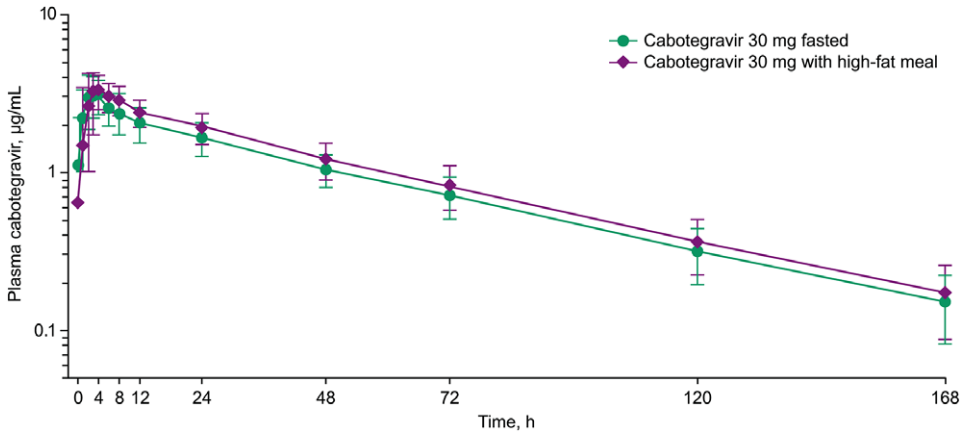

Figure 1. Mean (SD) concentration-time profiles of cabotegravir after administration in a fasted state or with a high-fat meal.

Discussion

Many oral antiretroviral therapy regimens—typically 1 or 2 tablets or capsules administered daily—may work more effectively when administered with food.[14] However, the requirement to be administered with food can negatively impact patient adherence, and thus, the flexibility to administer treatment without regard to meals is advantageous.[4]

This study evaluated the effect of a high-fat, high-calorie meal on the PK of oral cabotegravir using the intended commercial tablet formulation at a therapeutic 30-mg dose. Slight, nonclinically relevant increases in cabotegravir exposure were observed when cabotegravir was coadministered with a high-fat, high-calorie meal compared with when it was administered during a fasted state. These findings support administration of oral cabotegravir without food restrictions, which may promote adherence and dosing convenience for patients. The results of this study are consistent with those of 2 earlier studies that showed that coadministration of cabotegravir 10 or 30 mg with moderate-fat meals had a minimal 8% to 15% increase in cabotegravir exposure when compared with the exposure observed with fasted administration (Supplemental Data).

Previous studies have investigated the effect of the fat content of a meal on the level of drug exposure of integrase inhibitors.[15,16] Raltegravir has been shown to exhibit considerable PK variability when it is administered with meals containing differing amounts of fat.[15,16] Raltegravir AUC from time 0 to 12 hours and C_{max} were increased 2-fold following coadministration of raltegravir 400 mg twice daily with a high-fat meal.[15] Raltegravir AUC from time 0 to last observation following raltegravir 1200 mg (2 × 600 mg) once daily was increased 1.9% when the drug was administered following a high-fat meal but was decreased 42% when administered following a low-fat meal.

Dolutegravir, an analogue of cabotegravir, demonstrated increases in plasma $AUC_{0-\infty}$ of 33%, 41%, and 66% following single-dose administration of dolutegravir 50 mg with low-, moderate-, and high-fat meals, respectively.[4] In contrast with data on raltegravir and dolutegravir, plasma cabotegravir exposure increased minimally after administration with a high-fat meal, which typically increases absorption and systemic exposure of class 2 compounds through inhibition of efflux transporters.[17] The lack of effect of a high-fat meal on a class 2 compound suggests that the inhibition of uptake transporters attenuates the impact on efflux transporters; however, cabotegravir is not a substrate for intestinal uptake transporters such as OATP.[8] Because cabotegravir is rapidly absorbed and exhibits dose-proportional kinetics and low variability in humans as well as high bioavailability in preclinical animal models, the minimal impact of a high-fat meal on cabotegravir PK in this study suggests that absorption of the intended therapeutic dose of 30 mg is near complete in the fasted state and has minimal potential for food to impact its oral bioavailability.[4,15] The impact of a moderate-fat meal was minimal on dolutegravir 20 mg (2 × 10 mg of a developmental tablet formulation), suggesting that the oral bioavailability of dolutegravir may be higher at lower doses (Supplemental Data). Although cabotegravir trough concentration has been shown to increase in proportional to dose,[18] less-than-dose-proportional increases in cabotegravir AUC and C_{max} have been observed when the dose was increased from 30 to 60 mg (Supplemental Data)—a dose comparable with the approved dolutegravir 50-mg tablet formulation and for which the impact of food may be greater.

In summary, the presence of a high-fat, high-calorie meal resulted in a slight 14% to 17% increase in cabotegravir exposure, which is not considered to be clinically relevant. Cabotegravir may be administered

with or without food regardless of the fat or caloric content of meals. Lack of food restriction may provide important flexibility in the context of preexposure prophylaxis when oral cabotegravir monotherapy is administered during an oral lead-in phase to evaluate individual safety and tolerability before switching to long-acting injectable cabotegravir.[7]

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Declaration of Conflicting Interests

P.P., A.R.T., and W.S. are currently employees of ViiV Healthcare. S.L.F., K.B., and R.P. are currently employed by GlaxoSmithKline (S.L.F. was previously employed by PAREXEL International). Y.L. was previously employed by GlaxoSmithKline, and Y.L. and Z.Z. are employees of PAREXEL International. P.P., A.R.T., Y.L., and W.S. own stock in GlaxoSmithKline.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.