

Pharmacokinetics, Safety, and Tolerability of a Single Oral Dose of Abacavir/Dolutegravir/Lamivudine Combination Tablets in Healthy Japanese Study Participants

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Abstract

Pharmacokinetics, safety, and tolerability of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg were assessed in this phase I, single-arm, open-label, single-dose study in fasted healthy male ($n = 4$) and female ($n = 8$) participants of Japanese heritage. Participants received a single dose of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg after an 8-hour fast, with safety assessments and blood samples for pharmacokinetic parameters collected through 72 hours after dosing. Geometric mean maximum plasma concentrations were 5.22 $\mu\text{g/mL}$ (time to maximum concentration [t_{max}], 1.01 hours) for abacavir, 4.13 $\mu\text{g/mL}$ (t_{max} , 3.50 hours) for dolutegravir, and 3.35 $\mu\text{g/mL}$ (t_{max} , 2.98 hours) for lamivudine. Geometric mean area under the concentration-time curve values were 18.20, 71.60, and 16.60 $\mu\text{g} \cdot \text{h/mL}$ for abacavir, dolutegravir, and lamivudine, respectively. No adverse events were reported, and no clinically significant findings were observed in laboratory values, physical examinations, or 12-lead electrocardiographic parameters. Single-tablet administration of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg was well tolerated in Japanese participants. Exposure to abacavir and lamivudine was comparable with that seen in previous studies. A modest increase in exposure to dolutegravir vs previous clinical studies was observed but is not expected to impact the clinical management of HIV-1 or increase the risk for adverse events.

Keywords

HIV-1, Japan, antiretroviral therapy, safety, tolerability

HIV infection is a substantial global health burden. The goal of antiretroviral therapy is to reduce viral load to improve morbidity and mortality and prevent transmission. Abacavir/dolutegravir/lamivudine (Triumeq; ViiV Healthcare, Research Triangle Park, North Carolina) is a fixed-dose, single-tablet regimen approved in several countries, including the United States, those in the European Union, Canada, and Japan, for treatment of HIV-1 infection. Abacavir/dolutegravir/lamivudine is administered once daily and is composed of the therapeutic compounds dolutegravir, a next-generation integrase inhibitor with a long plasma half-life that does not require pharmacokinetic (PK) boosting, and nucleoside analogue reverse transcriptase inhibitors (abacavir and lamivudine).¹ Mechanistically, dolutegravir binds HIV integrase and blocks retroviral DNA integration.² Abacavir and lamivudine inhibit HIV-1 reverse transcriptase by direct substrate competition, thereby inducing chain termination and preventing viral DNA incorporation.^{3,4}

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The antiviral efficacy of dolutegravir, abacavir, and lamivudine has been demonstrated for the constituent compounds alone and in various combinations.^{5–10} Efficacy, including an ability to suppress viral replication, has been demonstrated for coadministration of dolutegravir 50 mg with abacavir 600 mg/lamivudine 300 mg.^{8–10} This combination also exhibited improved safety and efficacy through 144 weeks of repeat dosing compared with fixed-dose combination therapy of efavirenz/tenofovir disoproxil fumarate/emtricitabine and had fewer discontinuations due to adverse events (AEs).^{8,9} In addition, switching to the single-tablet regimen abacavir/dolutegravir/lamivudine was noninferior to continuing current antiretroviral therapy in a phase 3b study of adults infected with HIV-1 and stable viral suppression.¹⁰

Clinical PK studies are performed to characterize absorption, distribution, metabolism, and elimination in the target population. Data obtained from these studies are necessary for extrapolation of the efficacy and safety obtained in clinical trials at the tested dose. The PK of dolutegravir, abacavir, and lamivudine has been separately studied for each compound^{11–13} and in combination as abacavir 600 mg/lamivudine 300 mg¹² and as dolutegravir 50 mg coadministered with abacavir 600 mg/lamivudine 300 mg, with the latter combination administered as either dolutegravir plus abacavir/lamivudine as separate tablets or as the bioequivalent abacavir/dolutegravir/lamivudine single-tablet regimen.¹⁴

When studied as individual components, abacavir 600 mg and lamivudine 300 mg are both rapidly absorbed and extensively distributed, with a maximum concentration of $4.26 \pm 1.19 \mu\text{g/mL}$ and $2.04 \pm 0.54 \mu\text{g/mL}$, respectively.^{12,13} The dolutegravir in abacavir/dolutegravir/lamivudine is absorbed more slowly than abacavir or lamivudine, with a maximum plasma concentration of ≈ 3.67 to $4.56 \mu\text{g/mL}$ ^{1,14} reached ≈ 2 to 3 hours after administration. The majority of PK, safety, and tolerability data for the single-tablet regimen abacavir/dolutegravir/lamivudine has been collected in White participants, with less information gathered from Japanese participants. Before the current study, the primary PK information in Japanese participants came from EPZ104807 (ClinicalTrials.gov identifier: NCT00337922),¹⁵ which evaluated the PK of abacavir and lamivudine administered as abacavir/lamivudine in 9 Japanese participants infected with HIV; from ING115381 (ClinicalTrials.gov identifier: NCT01332565),¹⁶ which evaluated the PK of dolutegravir following a single oral dose in 10 healthy participants of Japanese heritage; and from ongoing postmarketing surveillance of abacavir/lamivudine in Japan.

This study was conducted to augment the existing knowledge of HIV pharmacotherapy in Japan by characterizing the PK, safety, and tolerability parameters of single-dose abacavir/dolutegravir/lamivudine exclusively in healthy adult participants of Japanese heritage.

Methods

Study Design and Treatment

This was a phase 1, single-arm, single-dose, open-label study in healthy Japanese adults to evaluate the PK and safety of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg when administered orally as a tablet under fasted conditions. The study was conducted between October 6, 2015, and November 6, 2015 (ClinicalTrials.gov identifier: NCT02539576), at the Parexel Early Phase Clinical Unit (Glendale, California) in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines as set forth by the International Council on Harmonization and the US Code of Federal Regulations, as well as all applicable local regulations. Before study initiation, the study protocol, amendments, and written consent forms were reviewed and approved by Aspire Independent Review Board (Santee, California). Written informed consent was obtained from all participants before study initiation.

All participants received a single oral dose of abacavir/dolutegravir/lamivudine (batch 142385863) administered with ≈ 240 mL of water following an 8-hour fast. Safety and PK parameters were followed through 72 hours, with a follow-up visit scheduled 7 to 14 days after the last blood sample collection.

Study Population

Eligible participants were healthy men and women aged 18 to 55 years (inclusive) who were born in Japan, had 4 ethnic Japanese grandparents, had not lived outside of Japan for >10 years, and held a current or expired Japanese passport. Study participants had a body mass index within the range of 18.5 to 31.0 kg/m² (inclusive); men and women weighed ≥ 50 and ≥ 45 kg, respectively. Overall health was determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and laboratory tests. Women were enrolled only if they were of nonchildbearing potential or of childbearing potential with a negative pregnancy test and agreed to follow approved guidelines for contraception. To mitigate the risk for abacavir hypersensitivity, only individuals who were negative for HLA-B*5701 were enrolled.¹⁷

Individuals were excluded from the study if they had alanine aminotransferase and bilirubin >1.5 times the upper limit of normal; had a chronic history of liver disease or known hepatic/biliary abnormalities (except for Gilbert syndrome or asymptomatic gallstones); had a

QT interval corrected for heart rate according to Fridricia's formula (QTcF) >450 milliseconds; were HIV positive; were current users of illicit drugs or had a positive result on a prestudy drug/alcohol screening; regularly used tobacco- or nicotine-containing products ≤6 months of screening; had a history of regular alcohol consumption (>14 drinks/week for men and >7 drinks/week for women); had a history of sensitivity to the study medications; were positive for either hepatitis B or hepatitis C virus; or had creatinine clearance <60 mL/min, indicating renal impairment.

Study participants were to refrain from using prescription and nonprescription drugs, including vitamins and herbal and dietary supplements, ≤7 days (≤14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) before the first dose of study medication.

Pharmacokinetic Sampling

Blood samples (4 mL) for determining abacavir, dolutegravir, and lamivudine plasma concentrations were collected before study drug administration (≤15 minutes of dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours after dosing.

Safety Assessments

Safety was assessed throughout the study and at follow-up by monitoring AEs, pregnancy, clinical laboratory values (chemistry, hematology, urinalysis, pregnancy test, HIV/hepatitis, HLA-B*5701, and creatinine clearance), physical examinations, vital signs (blood pressure, pulse, temperature), and 12-lead ECG. AEs and laboratory events were graded according to the Modified Division of AIDS Table for Grading Severity of Adult Adverse Experiences, November 2014.¹⁸

Sample Size

The estimated participant enrollment (n = 12) was based on feasibility as well as prior experience, including from study ING115381,¹⁶ which assessed the PK of dolutegravir in healthy Japanese participants, and study EPZ104807, which assessed the PK of abacavir and lamivudine administered as combination therapy. Based on those studies, it was expected that an enrollment size of 12 participants would allow PK evaluation in ≥10 participants; thus, the size would be sufficient to assess variability of the 3 components. With regard to sample size sensitivity, the probability values of reporting ≥1 event (eg, AE, laboratory toxicity) with a sample size of 12 were estimated at 69.8%, 45.1%, 11.3%, 5.8%, and 1.2% for 10.0%, 5.0%, 1.0%, 0.5%, and 0.1% ranges of true rates, respectively.

Bioanalytical Methods

Plasma samples were analyzed for dolutegravir, abacavir, and lamivudine concentrations by Pharmaceutical Product Development (Middleton, Wisconsin) using a validated analytical method based on solid phase extraction, followed by high-performance liquid chromatography with tandem mass spectrometry analysis. The lower and upper limits of quantification in ethylenediaminetetraacetic acid-treated plasma were 20.0 and 20 000 ng/mL, respectively, for dolutegravir and 2.5 and 2500 ng/mL, respectively, for abacavir and lamivudine. Linear regression analysis calculations were performed using Pharmaceutical Product Development Assist LIMS, version 5 (Pharmaceutical Product Development, Wilmington, North Carolina). The details of the bioanalytical methods are listed below.

Dolutegravir: Column: XBridge BEH C18 column (130 Å, 3.5 μm, 2.1 × 50 mm; Waters Corporation, Milford, Massachusetts); mobile phase: isocratic elution with 60% of 0.1% formic acid in water and 40% of 0.1% formic acid in acetonitrile with flow rate of 0.475 mL/min; run time: 1.5 minutes; internal standard (IS): GSK1349572-d7-15N; dolutegravir m/z: 420.30/277.20 Da; IS m/z: 428.30/283.20 Da; within-run precision (coefficient of variation [%CV]): ≤13.6%; between-run precision (%CV): ≤8.01%.

Lamivudine: Column: BetaSil Silica 100 column (100 Å, 5 μm, 3.0 × 50 mm; Thermo Scientific, Waltham, Massachusetts); mobile phase: gradient elution with mobile phase A, 10 mmol/L ammonium formate with 0.1% formic acid in water and mobile phase B, 0.1% formic acid in acetonitrile; stepwise flow rate of 0.65 to 1 mL/min; run time: 4 minutes; IS: [13C,15N2]-lamivudine; lamivudine m/z: 230.00/112.20 Da; IS m/z: 233.00/115.20 Da; within-run precision (%CV): ≤18.9%; between-run precision (%CV): ≤11.4%.

Abacavir: Column: BetaSil Silica 100 column (100 Å, 5 μm, 3.0 × 50 mm; Thermo Scientific); mobile phase: gradient elution with mobile phase A, 10 mmol/L ammonium formate with 0.1% formic acid in water; and mobile phase B, 0.1% formic acid in acetonitrile; stepwise flow rate of 0.65 to 1 mL/min; run time: 4 minutes; IS: abacavir-d4; abacavir m/z: 287.00/191.00 Da; IS m/z: 291.00/195.00 Da; within-run precision (%CV): ≤17.4%; between-run precision (%CV): ≤12.3%.

For each analytical method, quality control samples containing dolutegravir, abacavir, and lamivudine at 5 different concentrations were stored with study samples and subsequently analyzed with each batch of samples against separately prepared calibration standards.

Table 1. Pharmacokinetic Parameters for Abacavir, Dolutegravir, and Lamivudine Following Single Oral Administration to Japanese Study Participants Under Fasted Conditions

Sex	Parameter	Abacavir	Dolutegravir	Lamivudine
Overall (N = 12)	C_{max} , $\mu\text{g/mL}$	5.38 (1.44)	4.21 (0.838)	3.43 (0.813)
	AUC_{0-t} , $\mu\text{g} \cdot \text{h/mL}$	18.6 (4.00)	73.0 (14.6)	16.7 (1.67)
	$AUC_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	18.7 (4.00)	75.2 (15.1)	16.8 (1.71)
	C_{24} , $\mu\text{g/mL}$	0.00675 (0.00777)	1.15 (0.256)	0.0387 (0.0127)
	CL/F, L/h	33.7 (8.54)	0.691 (0.145)	18.0 (1.82)
	$t_{1/2}$, h	2.84 (1.06)	14.0 (2.77)	19.6 (5.59)
	t_{max} , h	1.01 (0.98, 3.00)	3.50 (1.02, 5.00)	2.98 (2.00, 4.00)
Male (N = 4)	C_{max} , $\mu\text{g/mL}$	4.60 (1.05)	3.75 (0.83)	2.98 (0.61)
	AUC_{0-t} , $\mu\text{g} \cdot \text{h/mL}$	17.80 (2.54)	72.25 (17.74)	15.85 (1.75)
	$AUC_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	17.83 (2.52)	74.88 (18.86)	16.00 (1.76)
	C_{24} , $\mu\text{g/mL}$	0.0071 (0.0070)	1.18 (0.30)	0.0509 (0.0124)
	CL/F, L/h/kg	0.54 (0.14)	0.01 (0.002)	0.30 (0.07)
	$t_{1/2}$, h	2.77 (0.80)	14.60 (1.16)	19.75 (4.54)
	t_{max} , h	0.99 (0.98, 2.0)	4 (3.0, 4.02)	2.5 (2.0, 3.0)
Female (N = 8)	C_{max} , $\mu\text{g/mL}$	5.77 (1.50)	4.45 (0.79)	3.65 (0.84)
	AUC_{0-t} , $\mu\text{g} \cdot \text{h/mL}$	19.06 (4.69)	73.43 (14.17)	17.10 (1.58)
	$AUC_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	19.10 (4.67)	75.38 (14.37)	17.24 (1.63)
	C_{24} , $\mu\text{g/mL}$	0.0066 (0.0086)	1.13 (0.26)	0.0326 (0.0077)
	CL/F, L/h/kg	0.63 (0.22)	0.01 (0.003)	0.33 (0.07)
	$t_{1/2}$, h	2.87 (1.22)	13.73 (3.35)	19.48 (6.36)
	t_{max} , h	1.51 (0.98, 3.0)	2.98 (1.02, 5.0)	2.98 (2.0, 4.0)

$AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve over the dosing interval; C_{max} , maximum concentration; C_{24} , concentration at 24 hours after dosing; CL/F, apparent clearance; $t_{1/2}$, elimination half-life; t_{max} , time to maximum concentration.

All values given as arithmetic mean (standard deviation), except t_{max} , which is given as median (range). Values were calculated from all 12 study participants in the pharmacokinetic population with no exclusions.

Pharmacokinetic Analysis

The PK population included all participants who underwent plasma PK sampling and had evaluable PK assay results for ≥ 1 of the analytes. Plasma concentration-time data for abacavir, dolutegravir, and lamivudine were analyzed by noncompartmental methods with Phoenix WinNonlin, version 6.3 (Certara USA, Princeton, New Jersey). Actual sampling times relative to time of dose administration were used for the analysis. From the plasma concentration-time data, the following PK parameters were determined for each of the 3 analytes: maximum concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve (AUC) for the dosing interval, elimination half-life, AUC from time 0 to infinity ($AUC_{0-\infty}$), apparent clearance after oral dosing (CL/F), concentration after 24 hours, and the terminal elimination rate constant.

Statistical Analysis

This study was designed to estimate the effect of ethnic heritage on the PK of abacavir, dolutegravir, and lamivudine administered as a single tablet to participants of Japanese heritage. No formal hypothesis was

tested. Descriptive statistics were calculated for each PK parameter.

Results

Demographics and Disposition

Twelve participants were enrolled according to the inclusion criteria, resulting in a 100% Asian (Japanese) population. Most participants were women (67%). Study participants had a median age of 41.5 years (range, 22-47) and mean (standard deviation) weight of 57.3 (8.9) kg. All participants received a single oral dose of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg and completed all study assessments.

Pharmacokinetics

The PK population included all 12 participants. Mean plasma concentrations of the individual drug components peaked between 1 and 4 hours after single-dose administration of abacavir/dolutegravir/lamivudine and then decreased steadily for the remainder of the sampling time (Figure 1).

The PK parameters in healthy Japanese participants after administration of abacavir/dolutegravir/lamivudine are given in Table 1.

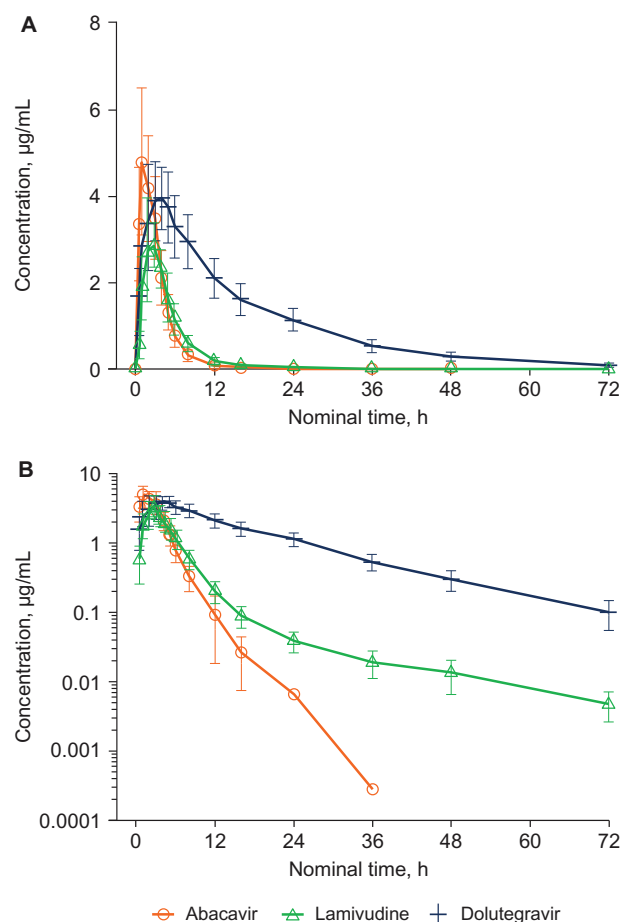


Figure 1. Arithmetic mean plasma concentrations (\pm standard deviation) of abacavir, dolutegravir, and lamivudine on a linear (A) or semilogarithmic (B) plot, with negative error bars removed. Mean plasma concentration-time profiles are for 12 study participants following a single dose of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg.

Abacavir was rapidly absorbed (median t_{max} , 1.01 hours), with dolutegravir and lamivudine reaching t_{max} 3 times more slowly. The geometric mean CL/F was 2 orders of magnitude higher for abacavir and lamivudine (32.9 and 17.9 L/h, respectively) vs dolutegravir (0.678 L/h). Exposure, as evaluated by the geometric mean of $AUC_{0-\infty}$, was ≈ 4 times higher for dolutegravir vs abacavir and lamivudine. Variability in exposure, expressed as the geometric CV%, was low for the 3 analytes, ranging from 22% to 26% for C_{max} and 10% to 24% for both AUC parameters.

Key fasting PK parameter values from this study are compared with values from historic studies in Tables 2 (abacavir and lamivudine) and 3 (dolutegravir).

Safety

The safety population included all 12 participants. No AEs were recorded from the beginning of the study

through the follow-up period, which occurred 7 to 14 days following the 72-hour PK sample. No abnormal findings were reported from physical examinations. Moderate fluctuations were noted in laboratory values, including some out of the reference laboratory normal range; however, these were judged not to be clinically significant, and none were reported as AEs. No clinically significant changes from baseline were recorded in laboratory values.

One participant had evidence of QT prolongation from screening through follow-up based on QT interval corrected by Bazett's formula (QTcB) values of 457 and 456 milliseconds at screening and follow-up, respectively, and a QTcF value of 454 milliseconds at follow-up. The remaining participants (91.7%) had QTcF values < 450 milliseconds at all time points, and no QTcB or QTcF values > 500 milliseconds were recorded. One participant recorded a 37-millisecond decrease in QTcB value from baseline to follow-up. No QTcF changes from baseline > 30 milliseconds were recorded, and all ECG parameter changes were deemed not to be clinically significant.

Discussion

Historic PK studies of combination abacavir, dolutegravir, and lamivudine have been predominantly conducted in White participants, including as abacavir/dolutegravir/lamivudine or as dolutegravir coadministered with abacavir 600 mg/lamivudine 300 mg,¹⁴ or in a limited number of Japanese participants as dolutegravir¹⁶ or abacavir/lamivudine alone (unpublished; results provided in GlaxoSmithKline clinical study registry).¹⁵ ING114580 showed that abacavir/dolutegravir/lamivudine was bioequivalent to dolutegravir 50 mg coadministered with abacavir/lamivudine in a majority White (52%)/Black (38%) population.¹⁴ Another of these studies, EPZ104807, evaluated the PK parameters of abacavir and lamivudine coadministered as single-tablet abacavir/lamivudine in Japanese participants infected with HIV-1.¹⁵

Abacavir and lamivudine administered as part of the single-tablet regimen abacavir/dolutegravir/lamivudine exhibited PK profiles in healthy Japanese participants that were similar to those observed previously in a Japanese population infected with HIV administered abacavir/lamivudine tablets (Table 2), with the exception of abacavir exposure (as measured by AUC for the dosing interval, which was ≈ 1.5 -fold higher in healthy Japanese individuals). Median t_{max} of lamivudine was 1.5-fold higher than previously reported in Japanese participants (abacavir/lamivudine formulation [EPZ104807]) but similar to the bioequivalence study in healthy participants (ING114580).

Table 2. Key Pharmacokinetic Parameters for Abacavir and Lamivudine Under Fasted Conditions From the Current Study vs Historic Studies

Analyte	Parameter	Current Study	Previous Studies	
		204662 (N = 12)	EPZ104807 ¹⁵ (N = 9)	ING114580 ¹⁴ (N = 62)
Abacavir	C_{max} , $\mu\text{g/mL}$	5.38 (1.44)	5.68 (2.03)	4.13 (0.95)
	AUC_{0-t} , $\mu\text{g} \cdot \text{h/mL}$	18.6 (4.0)	12.89 (4.2)	14.32 (3.53)
	$AUC_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	18.7 (4.0)	12.89 (4.2)	14.35 (3.54)
	t_{max} , h	1.01 (0.98, 3.00)	1.00 (0.50, 1.03)	2.00 (0.5, 3.0)
Lamivudine	C_{max} , $\mu\text{g/mL}$	3.43 (0.81)	3.58 (0.6)	2.20 (0.64)
	AUC_{0-t} , $\mu\text{g} \cdot \text{h/mL}$	16.7 (1.67)	16.3 (5.1)	12.70 (3.24)
	$AUC_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	16.8 (1.71)	16.36 (5.1)	13.13 (3.22)
	t_{max} , h	2.98 (2.0, 4.0)	2.00 (1.0, 3.0)	3.00 (1.0, 5.0)

$AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve over the dosing interval; C_{max} , maximum concentration; t_{max} , time to maximum concentration.

Values for C_{max} and AUC are presented as arithmetic mean (standard deviation), except t_{max} , which is given as a median (range) value. Study participant numbers (N) represent the pharmacokinetic populations in the associated clinical study. EPZ104807 evaluated the pharmacokinetics of a single dose of abacavir 600 mg/lamivudine 300 mg in Japanese study participants with active HIV infection. ING114580 evaluated the pharmacokinetics of a single dose of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg in predominantly White/Black healthy study participants. All studies were conducted in fasted study participants by GlaxoSmithKline.

Table 3. Key Pharmacokinetic Parameters for Dolutegravir Under Fasted Conditions From the Current Study vs Historic Studies

Parameter	Current Study	Previous Studies	
	204662 (N = 12)	ING115381 ¹⁶ (N = 10)	ING114580 ¹⁴ (N = 62)
C_{max} , $\mu\text{g/mL}$	4.21 (0.84)	2.37 (1.23)	2.53 (0.70)
AUC_{0-t} , $\mu\text{g} \cdot \text{h/mL}$	73.00 (14.6)	46.07 (23.77)	42.75 (13.15)
$AUC_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	75.20 (15.1)	47.71 (24.56)	47.12 (15.41)
t_{max} , h	3.5 (1.02, 5.0)	3.0 (2.0, 4.0)	3.0 (1.0, 8.0)

$AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve over the dosing interval; C_{max} , maximum concentration; t_{max} , time to maximum concentration.

Values for C_{max} and AUC are presented as arithmetic mean (standard deviation); t_{max} is presented as a median (range) value. Study participant numbers (N) represent the pharmacokinetic populations in the associated clinical study. ING115381 evaluated the pharmacokinetics of a single dose of dolutegravir 50 mg in healthy Japanese study participants. ING114580 evaluated the pharmacokinetics of a single dose of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg in predominantly White/Black healthy study participants. All studies were conducted in fasted study participants by GlaxoSmithKline.

The PK profile in healthy Japanese individuals following abacavir/dolutegravir/lamivudine administration demonstrated that C_{max} and AUC were higher for both abacavir and lamivudine than a predominantly White/Black population (ING114580; Table 2). C_{max} and AUC were also higher in Japanese participants following administration of abacavir/lamivudine vs a predominantly White/Black population (ING114580). $AUC_{0-\infty}$ values for both abacavir and lamivudine were ≈ 1.3 -fold greater in healthy Japanese participants than in participants from the ING114580 study. Maximum concentrations were 1.3- and 1.6-fold greater for abacavir and lamivudine, respectively. Overall, the 95% confidence interval range for abacavir C_{max} and AUC values tended to be wider for Japanese participants ($n = 12$) than participants in the ING114580 study ($n = 62$);

this difference may be partially due to lower sample size in this study. For lamivudine, the geometric mean and upper and lower bounds of the 95% confidence interval tended to be higher for C_{max} and AUC in Japanese participants than for the predominantly White/Black participants. However, geometric mean exposures were slightly higher in the Japanese population compared with the White population. These differences were not considered clinically significant.

The observed dolutegravir exposure (both C_{max} and AUC values) was higher in this study compared with those observed in previous studies. Specifically, exposure was ≈ 1.7 -fold higher than in predominantly White/Black participants who received a single oral dose of single-tablet regimen abacavir/dolutegravir/lamivudine (ING114580) and 1.9-fold

higher than in healthy Japanese participants administered a single oral dose of dolutegravir 50 mg alone (ING115381), although the range of values for each study overlapped (Table 3).

Several factors could affect exposure to dolutegravir, including participant covariates such as body weight and sex, and there are potential effects from genetic variants of metabolic enzymes or transporters. Mean body weight of Japanese participants enrolled in the current study was 57.3 kg, which was ≈ 10 kg lower than healthy Japanese participants in ING115381 (mean weight, 66.4 kg) and 17 kg lower than participants in ING114580 (mean weight of fasted population, 74.7 kg).^{14,16} Population PK models for dolutegravir indicate that body weight is a significant covariate on dolutegravir clearance, with increasing weights correlating with decreased exposure, which may have partially contributed to the higher exposure in the current study; however, the total magnitude of change from weight is likely to be $<30\%$.¹⁹ The current study also had a higher proportion of female participants (67% vs 40% [ING115381] and 33% [ING114580]). Although previous studies have shown that the oral bioavailability of dolutegravir is $\approx 21\%$ higher in women than men,¹⁹ there were no substantial differences in exposure or weight-normalized CL/F between male and female participants in this study (Table 1). While body weight and sex may explain some of the differences in dolutegravir exposures in this study vs prior studies, these are likely not the only contributing factors.

Another possible contributor relates to the potential for genetic variations that could reduce the efficiency of dolutegravir metabolism. Genotype information was not collected in this study. Dolutegravir is a substrate for uridine diphosphate glucuronosyltransferase family 1 member A1 (UGT1A1).¹⁹ The UGT1A1*6 polymorphism of this gene exhibits reduced enzymatic activity, and the homozygous genotype is highly represented in Japanese individuals, with a frequency of $\approx 16\%$.²⁰ Yagura et al²¹ showed that median dolutegravir trough concentrations in UGT1A1*6 homozygous patients were ≈ 1.7 -fold greater than homozygous normal individuals. An evaluation of 9 phase 1/2 clinical studies demonstrated that dolutegravir exposure increased by ≈ 1.4 -fold in UGT1A1*6 heterozygous individuals.²²

Transporter effects are another potential contributor to the elevated dolutegravir concentrations observed in the present study. Dolutegravir is a substrate of the adenosine triphosphate-binding cassette subfamily G transport protein (ABCG2), and the level of dolutegravir exposure is demonstrably higher in individuals with the ABCG2 genetic variant 421AA.²³ This variant is characterized by lower expression of the efflux pump, with a genetic frequency ≈ 7 times higher in Asians than

non-Asians (frequencies of $\approx 40\%$ and 9% for heterozygous and homozygous genotypes, respectively).²⁴ However, because the participants in the various PK studies were not genotyped, the potential impact of this genetic variant on the observed dolutegravir concentrations is unknown.

Although the precise mechanism leading to higher dolutegravir exposure may be a multifactorial mix of some or all of the possible contributors discussed above, or of others yet to be identified, it is also possible that at least some of the differences have arisen simply due to interstudy variability. This is supported by the observation that individual C_{\max} and AUC values from this study overlap with those of previous studies.

Regardless of the cause, elevated dolutegravir exposure in the clinically relevant range has not been shown to be associated with increased risk for AEs²⁵; therefore, the increased dolutegravir concentration observed in the current study is unlikely to be clinically significant. Indeed, the dolutegravir component of abacavir/dolutegravir/lamivudine is already approved for dosing regimens exceeding the one used in this study, including for twice-daily dosing^{26–28} (geometric mean AUC from time 0 to 24 hours of $75.10 \mu\text{g} \cdot \text{h/mL}$ and C_{\max} of $4.15 \mu\text{g/mL}^4$) as well as for once-daily dosing with atazanavir, a UGT1A1 inhibitor that increases dolutegravir exposure by ≈ 2 -fold.¹¹ In addition, the single-dose administration of abacavir/dolutegravir/lamivudine in this study was well tolerated and demonstrated a favorable safety profile with no AEs reported, and no clinically significant changes were observed in clinical laboratory evaluations, physical examinations, vital signs, or ECG findings.

Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg administered as a single oral tablet was well tolerated in Japanese participants, with abacavir and lamivudine exposures comparable with those observed in previous studies and a modest increase in dolutegravir exposure. The observed increase in dolutegravir exposure is not expected to impact the clinical management of HIV infection or increase the risk for AEs.

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Conflicts of Interest

RPS was an employee of GlaxoSmithKline at the time the study was conducted and may own stock in the company. AW and JH are employees of and own stock in GlaxoSmithKline. KA and BW are employees of ViiV Healthcare and own stock in GlaxoSmithKline.

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