

Effects of Low- and High-Mineral Content Water on the Relative Bioavailability of a Coformulated Abacavir/Dolutegravir/Lamivudine Dispersible Tablet in Healthy Adults

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Background: The fixed-dose combination (FDC) tablet formulation of abacavir/dolutegravir/lamivudine is indicated for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥ 40 kg. Alternative formulations with acceptable palatability and convenient dosing are needed for children who require smaller doses and have difficulty swallowing tablets.

Setting: A phase 1, open-label, randomized study was conducted in healthy adults to evaluate the relative bioavailability of a novel dispersible FDC tablet of abacavir 150 mg/dolutegravir 10 mg/lamivudine 75 mg administered under 4 different dosing conditions compared with dolutegravir plus abacavir/lamivudine nondispersible, film-coated tablets.

Methods: The test treatments were 4 dispersible FDC tablets reconstituted in water with high- or zero-mineral content and administered either immediately or after a 30-minute delay. The reference treatment was 4 nondispersible dolutegravir 10-mg tablets

plus 1 nondispersible abacavir 600-mg/lamivudine 300-mg tablet administered with zero-mineral content water. The primary endpoints were area under the concentration–time curve from time 0 extrapolated to infinity and the maximum observed plasma concentration.

Results: Following administration of dispersible abacavir/dolutegravir/lamivudine, the relative bioavailability of dolutegravir was approximately 50% higher. Abacavir and lamivudine demonstrated bioequivalence when administered as the dispersible FDC tablet compared with coadministration of dolutegravir plus abacavir/lamivudine nondispersible, film-coated tablets. Neither the mineral content of the water nor dosing times affected the pharmacokinetics of individual components. The dispersible tablet was safe and well tolerated, and the palatability was acceptable.

Conclusions: These pharmacokinetic results support further development of a dispersible FDC tablet of abacavir/dolutegravir/lamivudine for future use in pediatric patients.

Key Words: dispersible, bioequivalence, pharmacokinetics, palatability, Contrex water

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INTRODUCTION

The United Nations reported that 160,000 children younger than 15 years of age worldwide were diagnosed with HIV-1 infection in 2016, and 2.1 million children were living with HIV infection.¹ Therapeutic options for pediatric patients living with HIV-1 infection continue to improve; however, there is a need for alternative formulations and dosing strategies, especially for patients who may have difficulty swallowing tablets. Therefore, strategies for alternative formulations are being evaluated as options for pediatric patients, with dispersible tablets being the preferred solid oral option according to guidelines from the World Health Organization.²

In HIV-infected, treatment-naïve adult study populations, dolutegravir plus abacavir and lamivudine were demonstrated superior to both ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate/emtricitabine in the ARIA trial³ and efavirenz plus tenofovir disoproxil fumarate/emtricitabine in the SINGLE trial.⁴ Consequently, a fixed-dose combination (FDC)

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of dolutegravir/abacavir/lamivudine is approved for the treatment of HIV-1 infection in adults and adolescents older than 12 years who weigh ≥ 40 kg.⁴⁻⁶ Based on the superior efficacy of dolutegravir-based regimens, availability of dolutegravir-containing formulations suitable for pediatric patients could expand access to more patients in need. Currently, abacavir and lamivudine are available worldwide for the treatment of HIV-1 infection in adults and children 3 months and older.^{7,8} A solid tablet formulation of dolutegravir has also been approved in the United States to treat pediatric patients with HIV infection who weigh ≥ 30 kg.⁹ Various pediatric formulations of dolutegravir are under evaluation in the ongoing International Maternal Pediatric Adolescent AIDS Clinical Trials Group P1093 study of children 4 weeks of age and older (ClinicalTrials.gov identifier, NCT01302847). Hence, a dispersible tablet formulation of abacavir/dolutegravir/lamivudine is in development, with the aim of improving the ease of administration in some pediatric populations.

Because dolutegravir is a metal-binding molecule and its solubility is impacted by the divalent metal concentration in dissolution media, the solubility and time lag after dolutegravir dispersion may be affected by the presence of divalent metals in the solvent,¹⁰⁻¹² possibly impacting the bioavailability of dolutegravir. In addition to altered solubility in the presence of metal ions, solubility of dolutegravir also varies in low- and high-mineral content water (unpublished data). Single-agent, film-coated dolutegravir (with abacavir and lamivudine) has solubility of $\sim 45\%$ when dissolved in high-mineral content water (unpublished data). Solubility of film-coated dolutegravir increases to $\sim 70\%$ when dissolved in low-mineral content water; however, dolutegravir solubility is reduced to $\sim 16\%$ when the solution is withheld for 30 minutes before consumption (unpublished data). No change in solubility of single-agent, film-coated dolutegravir was observed when dissolved in high-mineral content water and withheld for 30 minutes (unpublished data). In addition, the bioavailability of single-agent, film-coated dolutegravir was reduced when dolutegravir was coadministered with calcium carbonate 1200 mg (~ 480 -mg elemental calcium) or ferrous fumarate 324 mg (~ 107 -mg elemental iron) under fasted conditions.¹³ Therefore, a suitable ion concentration is needed for optimum solubility of dolutegravir in the presence of abacavir and lamivudine.

Administration of dispersible tablets and granule formulations of single-agent dolutegravir 20 mg resulted in equivalent dolutegravir exposures.¹⁴ Dolutegravir plasma exposure was also similar for both the dispersible tablet and granule formulations of single-agent dolutegravir 20 mg dispersed in high- and low-mineral content water. Furthermore, immediate or 30-minute delayed administration of dispersible tablet and granule formulations of single-agent dolutegravir 20 mg did not affect dolutegravir exposure.

To investigate whether altered solubility of dolutegravir with time and mineral content in water affects the pharmacokinetics (PK) of abacavir/dolutegravir/lamivudine in a dispersible form, we evaluated the relative bioavailability of dolutegravir, abacavir, and lamivudine after the reconstitution of dispersible FDC tablets of abacavir/dolutegravir/lamivudine in high- and zero-mineral content purified water with and without a 30-minute delay.

METHODS

Study Design

A phase 1, open-label, randomized, 5-period crossover, relative bioavailability study was conducted in healthy adults from September 12, 2016, to November 25, 2016, at a single center in the United States (ClinicalTrials.gov identifier, NCT02893488; ViiV-clinicalstudyregister.com identifier, 200402).

The test formulation was composed of a novel, dispersible, FDC preparation that contained 4 tablets of abacavir 150 mg/dolutegravir 10 mg/lamivudine 75 mg mixed with 3.0 mg/mL of acesulfame potassium, 1.2 mg/mL of sucralose, and 1.2 mg/mL of strawberry-cream flavor in 40 mL of either high-mineral content water (calcium, 468 mg/L; magnesium, 74.5 mg/L; Contrex, Nestlé Waters, Vevey, Switzerland) or purified, zero-mineral content water.¹⁵ Participants were randomized (1:1:1:1:1) to 1 of 5 treatment groups over 5 dosing periods as follows (Figure, Supplemental Digital Content 1, <http://links.lww.com/QAI/B218>, which illustrates the study design): reference treatment of abacavir 600 mg/lamivudine 300 mg plus 4 tablets of dolutegravir 10 mg administered with 200–250 mL of purified, zero-mineral content water without dispersion (tablets were nondispersible, film-coated); abacavir/dolutegravir/lamivudine dispersed in high-mineral content water and administered immediately; abacavir/dolutegravir/lamivudine dispersed in high-mineral content water with administration delayed for 30 minutes; abacavir/dolutegravir/lamivudine dispersed in purified, zero-mineral content water and administered immediately; and abacavir/dolutegravir/lamivudine dispersed in purified, zero-mineral content water with administration delayed for 30 minutes. All treatments were orally administered in the morning on an empty stomach, and food intake was prohibited for 4 hours following administration. There were 7 days of washout between each dosing period.

The study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice, and the principles of the Declaration of Helsinki 2013. The protocol was approved by the Midlands Independent Review Board (Overland Park, KS), and informed consent was obtained from each participant before the start of the study.

Study Population

Healthy men and women aged 18–65 years were eligible for the study if they had a body mass index of 18.5–31.0 kg/m² and weighed ≥ 50 kg for men and ≥ 45 kg for women. Individuals positive for *HLA-B*5701* allele, those who had > 1.5 times the upper limit of normal levels for alanine aminotransferase and bilirubin, a QT correction using the Fridericia formula of > 450 msec, or creatinine clearance of < 60 mL/min were excluded from study enrollment. Participants were permitted to use acetaminophen (≤ 2 g/d) during the study. All other concomitant medications were reviewed by the medical monitor and were permitted on a case-by-case basis only if they did not interfere with the safety of the participant or interfere with

TABLE 1. Summary of Patient Demographics

Variable	Total (N = 20)
Age, mean (SD), yrs	44.8 (15.93)
Sex, n (%)	
Female	6 (30)
Male	14 (70)
BMI, mean (SD), kg/m ²	26.7 (3.0)
Height, mean (SD), cm	172.3 (9.9)
Weight, mean (SD), kg	79.5 (12.2)
Ethnicity, n (%)	
Hispanic or Latino	2 (10)
Not Hispanic or Latino	18 (90)
Race, n (%)	
African American	5 (25)
White	15 (75)

BMI, body mass index.

study procedures. If there was potential for concomitant drug interference with the study treatment, then participants were asked to abstain from taking prescription or nonprescription drugs, including vitamins and dietary or herbal supplements (including St John's wort), within 7 days (for potential enzyme inhibitors) and 14 days (for potential enzyme inducers) or for 5 half-lives for any drug (whichever was longer) before administration of the first dose and continuing until completion of the follow-up visit.

Assessments

The primary objective of the study was to evaluate the relative bioavailability of the FDC of abacavir/dolutegravir/lamivudine dispersed and administered using 4 different dosing conditions compared with dolutegravir plus abacavir/lamivudine coadministered orally in nondispersible, film-coated tablets. The primary endpoint was plasma dolutegravir, abacavir, and lamivudine area under the concentration–time curve (AUC) from time 0 (predose) extrapolated to infinity (AUC_{0–∞}) and the maximum observed plasma concentration (C_{max}).

Secondary endpoints for dolutegravir, abacavir, and lamivudine included other PK parameters, such as AUC from time 0 (predose) to 24 hours (AUC_{0–24}), AUC from time 0 (predose) to the last time of quantifiable concentration within participants across all treatments (AUC_{0–t}), apparent clearance after oral dosing (CL/F), time of occurrence of C_{max} (t_{max}), observed concentration at 24 hours after dose (C₂₄), terminal elimination phase half-life (t_{1/2}), and plasma dolutegravir lag time for absorption (t_{lag}).

Serial plasma PK samples were collected before dose and at the following time points after each dose: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours. Frozen samples were shipped at agreed time points and analyzed using validated analytical methods based on protein precipitation followed by high-performance liquid chromatography tandem-mass spectrometry by Pharmaceutical Product

Development (Middleton, WI). The linear range of detection for dolutegravir was 20–20,000 ng/mL from a 25-μL plasma sample and 2.5–2500 ng/mL from a 50-μL plasma sample for abacavir and lamivudine. For each analytical method, quality-control samples containing dolutegravir or abacavir and lamivudine at 5 different concentrations were analyzed with each batch of participant samples and used as experimental acceptance criteria. For the analysis to be acceptable, no more than one-third of the quality-control results could deviate >15% from the nominal concentration, with ≥50% of the results from each quality-control concentration within 15% of nominal concentration. For the relative bioavailability/bioequivalence calculations, the slope cutoff (r² < 0.85) was selected as the standard to avoid any potential bias in AUC_{0–∞} calculations.

Secondary objectives included safety and tolerability of the abacavir/dolutegravir/lamivudine dispersible tablet. Safety assessments were monitored throughout the study, including assessments of adverse events (AEs), pregnancies, clinical laboratory screens, electrocardiography, vital signs, and physical examinations. Participants had a follow-up visit within 7–10 days after the last dose.

Exploratory objectives were to evaluate the palatability of the dispersible formulations. A palatability questionnaire was administered to each participant within 10 minutes of dosing of a dispersion. Response to sensory attributes such as color, taste, sweetness, bitterness, and mouth feel was measured. A 3-point scale, with 1 being “unpleasant/unacceptable” and 3 being “very good/pleasant/desirable,” was used to measure overall acceptability of the sensory attributes. The questionnaire also collected perception data using predefined descriptors of these attributes and used a 3-point scale to collect recommendations for modifying each attribute (flavor, aroma, sweetness, sour/tartness, and consistency).

Pharmacokinetic and Statistical Analyses

All individuals who were enrolled in the study and received ≥1 dose of the study drug were included in the safety population. The PK population included all individuals in the study who had evaluable assays after plasma PK sampling.

Based on a sample size of 15 evaluable participants, the half-width of the 90% confidence interval (CI) for the treatment difference on log-scale was estimated to be within 14% of the point estimate for AUC_{0–∞} and C_{max}. If the point estimate of the ratio of geometric means is 1, then the 90% CI would be approximately 0.88–1.14. The sample size calculations assumed that the within-participant coefficient of variation would be 22%.

Noncompartmental PK analysis was performed on dolutegravir, abacavir, and lamivudine concentration–time data using Phoenix WinNonlin version 6.3 (Certara, Princeton, NJ). The PK parameters for dolutegravir, abacavir, and lamivudine were log-transformed, and point estimates of geometric least-squares (LS) mean ratios (test/reference) and associated 90% CIs for within-participant treatment comparisons were generated by a mixed-effects model, with

TABLE 2. Select PK Parameters for Dolutegravir, Lamivudine, and Abacavir Administered in Different Dosing Formulations at Different Times

PK Parameter, Geometric Mean (CV _b %) [*]	Treatment				
	Ref (n = 20)	Abacavir/Dolutegravir/Lamivudine–High Mineral—Immediate (n = 20)	Abacavir/Dolutegravir/Lamivudine–High Mineral—Delayed (n = 20)	Abacavir/Dolutegravir/Lamivudine–Zero Mineral—Immediate (n = 20)	Abacavir/Dolutegravir/Lamivudine–Zero Mineral—Delayed (n = 19)
Dolutegravir					
AUC _(0–∞) , μg·h/mL	48.4 (26.1)	75.7 (17.5)	74.1 (16.0)	76.3 (21.0)	75.4 (17.6)
C _{max} , μg/mL	2.5 (28.0)	4.0 (12.8)	3.9 (14.3)	3.9 (17.4)	4.0 (17.6)
C ₂₄ , μg/mL	0.7 (27.0)	1.1 (17.2)	1.1 (14.2)	1.2 (23.4)	1.1 (19.9)
t _{1/2} , h	15.0 (20.0)	15.6 (18.9)	15.4 (20.7)	14.9 (19.1)	15.1 (20.3)
t _{max} , h†	2.5 (0.5–5.0)	2.0 (1.0–4.0)	2.3 (0.5–4.0)	2.0 (1.5–5.0)	2.5 (1.0–4.1)
Lamivudine					
AUC _(0–∞) , μg·h/mL‡	15.1 (27.2)	14.8 (28.5)	15.4 (28.0)	15.3 (27.0)	14.6 (28.5)
C _{max} , μg/mL	2.6 (27.4)	2.4 (29.7)	2.5 (25.9)	2.3 (28.7)	2.4 (32.2)
C ₂₄ , μg/mL	0.05 (34.5)	0.05 (34.7)	0.05 (33.2)	0.05 (39.8)	0.05 (35.9)
t _{1/2} , h‡	20.0 (33.8)	20.9 (30.7)	19.4 (37.9)	23.6 (52.9)	20.4 (36.6)
t _{max} , h†	2.0 (1.0–4.1)	2.0 (1.0–4.0)	2.3 (1.5–4.0)	2.0 (0.5–4.0)	2.0 (1.0–3.0)
Abacavir					
AUC _(0–∞) , μg·h/mL	16.6 (23.3)	16.0 (27.2)	16.2 (25.3)	16.5 (28.0)	16.7 (22.6)
C _{max} , μg/mL	5.68 (26.7)	5.75 (32.4)	5.37 (29.0)	5.53 (25.2)	5.78 (24.3)
C ₂₄ , μg/mL§	0.01 (49.4)	0.01 (30.8)	0.01 (52.8)	0.01 (52.6)	0.01 (47.8)
t _{1/2} , h	2.63 (24.1)	2.87 (25.0)	2.82 (21.4)	2.78 (28.0)	2.81 (31.5)
t _{max} , h†	1.0 (0.5–3.0)	1.0 (0.5–2.5)	1.0 (0.5–4.0)	1.0 (0.5–3.0)	1.0 (0.5–2.5)

Lag time for absorption was a value of 0 for all treatments.

*Unless otherwise noted.

†Median (range).

‡Ref, n = 19; abacavir/dolutegravir/lamivudine–high mineral—immediate, n = 20; abacavir/dolutegravir/lamivudine–high mineral—delayed, n = 18; abacavir/dolutegravir/lamivudine–zero mineral—immediate, n = 20; abacavir/dolutegravir/lamivudine–zero mineral—delayed, n = 19.

§Ref, n = 16; abacavir/dolutegravir/lamivudine–high mineral—immediate, n = 16; abacavir/dolutegravir/lamivudine–high mineral—delayed, n = 18; abacavir/dolutegravir/lamivudine–zero mineral—immediate, n = 17; abacavir/dolutegravir/lamivudine–zero mineral—delayed, n = 15.

AUC_(0–∞), AUC from time 0 extrapolated to infinity; C₂₄, concentration at 24 hours after dose; C_{max}, maximum observed plasma drug concentration; CV_b, between-participant coefficient of variation; Ref, reference; t_{1/2}, terminal elimination phase half-life; t_{max}, time of occurrence of C_{max}.

fixed-effect terms for treatment and period and a random-effect term for participants.

Safety data, PK data (t_{max} and t_{lag}), and data from the palatability questionnaire were summarized descriptively. Data were analyzed, and the tables and figures generated using Statistical Analysis Software version 9.4 or higher (SAS, Cary, NC).

RESULTS

Participant Disposition

Of the 50 individuals screened, 20 were enrolled and randomized, and 19 completed the study. Most participants were male (70%) and white (75%) with a mean (SD) age of 44.8 (15.9) years. Mean (SD) body mass index, height, and weight were 26.7 (3.0) kg/m², 172.3 (9.9) cm, and 79.5 (12.2) kg, respectively (Table 1). Nine participants received concomitant medications during the study, but none of these medications were considered to affect the PK of the study treatment. One individual withdrew from the study before receiving the final treatment (abacavir/dolutegravir/

lamivudine–zero mineral—delayed) because of a drug-related adverse event (urticaria); however, PK data from the previous treatments were included in the PK analysis. Plasma concentrations at 24 hours (C₂₄) for abacavir were below the limit of detection for 5 participants; therefore, C₂₄ and AUC_{0–24} for abacavir were excluded from the statistical analyses: reference treatment, abacavir/dolutegravir/lamivudine–high mineral—immediate, abacavir/dolutegravir/lamivudine–zero mineral—immediate, and abacavir/dolutegravir/lamivudine–zero mineral—delayed for 1 participant; reference treatment, abacavir/dolutegravir/lamivudine–high mineral—immediate and abacavir/dolutegravir/lamivudine–zero mineral—delayed for 1 participant; abacavir/dolutegravir/lamivudine–zero mineral—delayed for 1 participant; and all 5 treatments for 2 participants. Parameters from lamivudine for 2 participants did not meet standard operating procedure–defined criteria for acceptance because the regression coefficient was <0.85. Therefore, AUC_(0–∞) for the reference treatment and abacavir/dolutegravir/lamivudine–high mineral—delayed for 1 participant and abacavir/dolutegravir/lamivudine–high mineral—delayed from 1 participant were excluded from statistical analyses.

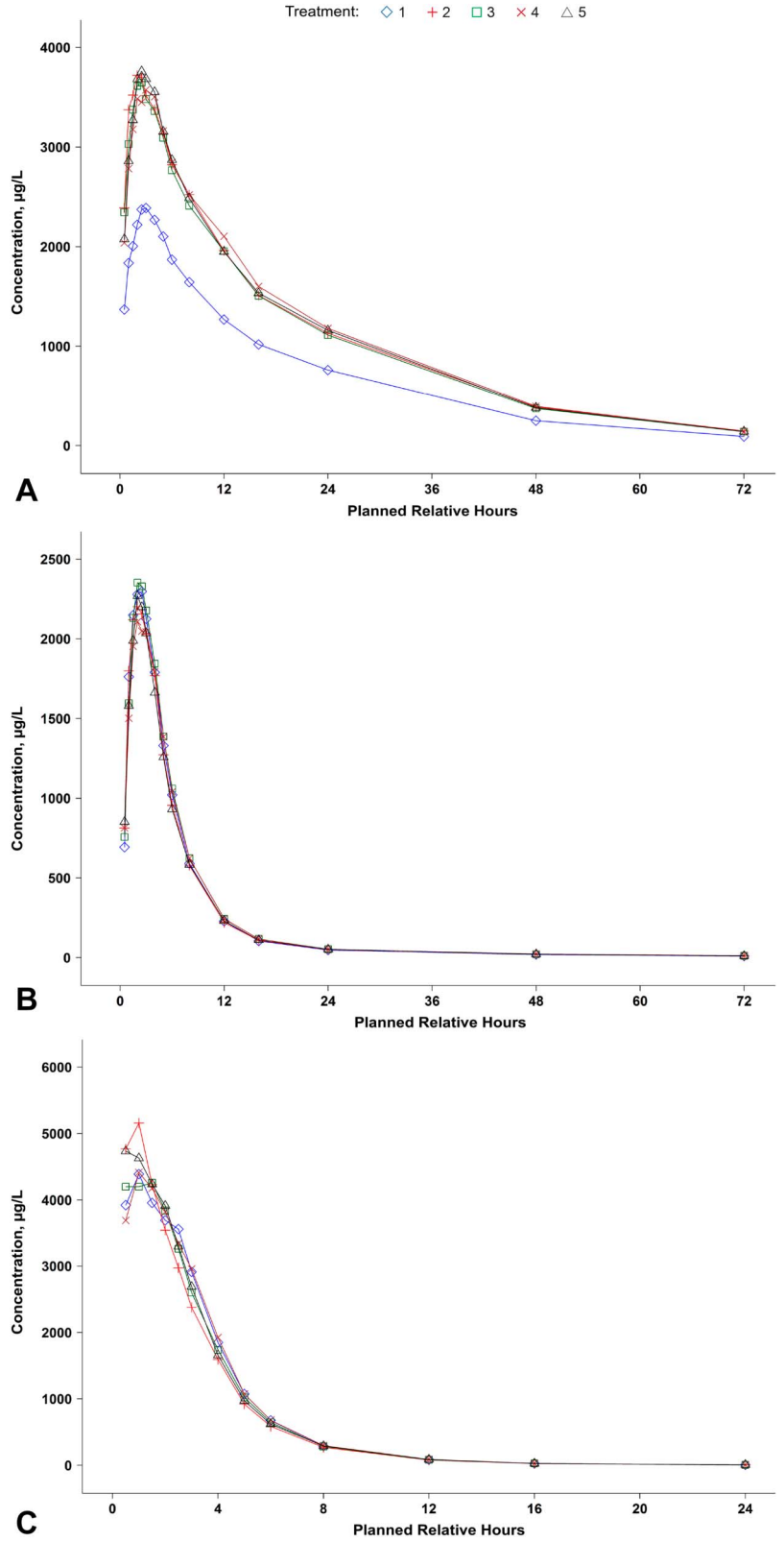


FIGURE 1. Mean plasma concentration–time profiles for (A) dolutegravir, (B) lamivudine, and (C) abacavir (linear scale). Treatment arms were as follows: 1 = reference; 2 = abacavir/dolutegravir/lamivudine–high mineral–immediate; 3 = abacavir/dolutegravir/lamivudine–high mineral–delayed; 4 = abacavir/dolutegravir/lamivudine–zero mineral–immediate; and 5 = abacavir/dolutegravir/lamivudine–zero mineral–delayed.

TABLE 3. Ratio of Geometric Least Squares Mean Values and 90% CIs of Select PK Parameters of Dolutegravir, Lamivudine, and Abacavir

PK Parameter	Abacavir/Dolutegravir/ Lamivudine–High Mineral— Immediate (n = 20) vs Ref (n = 20)	Abacavir/Dolutegravir/ Lamivudine–High Mineral— Delayed (n = 20) vs Ref (n = 20)	Abacavir/Dolutegravir/ Lamivudine–Zero Mineral— Immediate (n = 20) vs Ref (n = 20)	Abacavir/Dolutegravir/ Lamivudine–Zero Mineral— Delayed (n = 20) vs Ref (n = 20)
Dolutegravir				
AUC _(0–∞) , μg·h/mL	1.56 (1.49–1.64)	1.53 (1.46–1.6)	1.58 (1.5–1.65)	1.54 (1.47–1.62)
C _{max} , μg/mL	1.59 (1.50–1.70)	1.56 (1.46–1.66)	1.56 (1.46–1.66)	1.58 (1.48–1.68)
C ₂₄ , μg/mL	1.51 (1.43–1.60)	1.50 (1.42–1.58)	1.56 (1.48–1.65)	1.53 (1.45–1.62)
Lamivudine				
AUC _(0–∞) , μg·h/mL*	0.99 (0.94–1.04)	1.04 (0.98–1.10)	1.02 (0.97–1.08)	0.98 (0.93–1.03)
C _{max} , μg/mL	0.93 (0.85–1.01)	0.95 (0.88–1.04)	0.90 (0.83–0.98)	0.92 (0.84–1.01)
C ₂₄ , μg/mL	1.06 (1.01–1.12)	1.10 (1.05–1.16)	1.05 (1.0–1.11)	1.09 (1.04–1.15)
Abacavir				
AUC _(0–∞) , μg·h/mL	0.97 (0.93–1.01)	0.98 (0.94–1.02)	0.10 (0.96–1.04)	0.99 (0.95–1.03)
C _{max} , μg/mL	1.01 (0.93–1.10)	0.95 (0.87–1.03)	0.97 (0.89–1.06)	1.01 (0.93–1.10)
C ₂₄ , μg/mL†	1.08 (0.94–1.24)	0.92 (0.80–1.06)	1.01 (0.88–1.16)	0.99 (0.86–1.15)

*For lamivudine, AUC_(0–∞): ref, n = 19; abacavir/dolutegravir/lamivudine–high mineral—immediate, n = 20; abacavir/dolutegravir/lamivudine–high mineral—delayed, n = 18; abacavir/dolutegravir/lamivudine–zero mineral—immediate, n = 20; abacavir/dolutegravir/lamivudine–zero mineral—delayed, n = 19.

†For abacavir, C₂₄: ref, n = 16; abacavir/dolutegravir/lamivudine–high mineral—immediate, n = 16; abacavir/dolutegravir/lamivudine–high mineral—delayed, n = 18; abacavir/dolutegravir/lamivudine–zero mineral—immediate, n = 17; abacavir/dolutegravir/lamivudine–zero mineral—delayed, n = 15.

AUC_(0–∞), AUC from time 0 extrapolated to infinity; C₂₄, concentration at 24 hours after dose; C_{max}, maximum observed plasma concentration; ref, reference.

Pharmacokinetics

Between-participant coefficient of variation percentages for the primary endpoint, AUC_(0–∞) of dolutegravir, were lower in all 4 treatments of abacavir/dolutegravir/lamivudine dispersible tablets compared with the nondispersible reference treatment (Table 2 and Fig. 1). Compared with the reference treatment, the AUCs_(0–∞) for dolutegravir after abacavir/dolutegravir/lamivudine–high mineral—immediate, abacavir/dolutegravir/lamivudine–high mineral—delayed, abacavir/dolutegravir/lamivudine–zero mineral—immediate, and abacavir/dolutegravir/lamivudine–zero mineral—delayed were 56%, 53%, 58%, and 54% higher, respectively (Table 3). Furthermore, the 90% CI of the geometric LS mean ratios for all treatment comparisons were outside the standard bioequivalence interval (0.8–1.25). Between-participant coefficient of variation percentages for C_{max} of dolutegravir were also higher in all 4 treatments of the abacavir/dolutegravir/lamivudine dispersible tablet compared with the reference treatment.

Between-participant coefficient of variation percentages for AUCs_(0–∞) of lamivudine and abacavir were similar (Table 2). Between-participant coefficient of variation percentages for C_{max} for all the dispersible-tablet variations versus the reference treatment were comparable for both lamivudine and abacavir. The geometric LS of the mean ratios of lamivudine and abacavir for these parameters were within the standard bioequivalence interval (80%–125%; Table 3).

Similar PK results for dolutegravir, abacavir, and lamivudine were obtained for dispersible abacavir/dolutegravir/lamivudine regardless of mineral content in the water or

treatment time—immediate or delayed. There was no t_{lag} for dolutegravir. The median t_{max} for dolutegravir, lamivudine, and abacavir ranged from 2 to 2.5, 2–2.3, and 1 hour, respectively. The geometric mean t_{1/2} for dolutegravir, abacavir, and lamivudine was similar across all 5 treatments.

Safety

Of the 20 individuals in the safety population, 65% (n = 13) reported AEs (Table 4). Apart from headache (55%, n = 11) and nausea (45%, n = 9), no other AE was reported in more than 1 participant. No serious AEs or deaths were reported in the study. One participant withdrew with grade 1 urticaria (intermittent hives) considered to be related to the study drug. The participant was treated with aloe vera, and the AE resolved.

No potentially clinically important abnormalities in vital signs, electrocardiography, hematologic values, or urinalysis were reported. However, a grade 2 creatinine abnormality was reported for 1 participant, although this was not considered clinically relevant. One participant experienced a higher-than-normal level of potassium (6 mEq/L), which was believed to be due to a hemolyzed blood sample.

Palatability Questionnaire

Most participants (76%) rated the palatability of the dispersion tablet as “neutral/acceptable,” and for all attributes recommended to “leave as is” (Table, Supplemental Digital Content 2, <http://links.lww.com/QAI/B218>, which

TABLE 4. Drug-Related AEs

AE	Ref (n = 20)	Abacavir/Dolutegravir/ Lamivudine–High Mineral —Immediate (n = 20)	Abacavir/Dolutegravir/ Lamivudine–High Mineral —Delayed (n = 20)	Abacavir/Dolutegravir/ Lamivudine–Zero Mineral —Immediate (n = 20)	Abacavir/Dolutegravir/ Lamivudine–Zero Mineral —Delayed (n = 19)	Total (N = 20)
Any event, n (%)	4 (20)	9 (45)	9 (45)	9 (45)	7 (37)	13 (65)
Headache	3 (15)	5 (25)	6 (30)	6 (30)	5 (26)	11 (55)
Nausea	2 (10)	5 (25)	5 (25)	4 (20)	3 (16)	9 (45)
Dizziness	0	1 (5)	1 (5)	0	0	1 (5)
Diarrhea	0	1 (5)	1 (5)	1 (5)	1 (5)	1 (5)
Salivary hypersecretion	0	0	1 (5)	0	0	1 (5)
Fatigue	0	0	1 (5)	0	0	1 (5)
Flushing	0	0	0	0	1 (5)	1 (5)

Ref, reference.

summarizes participant responses from the palatability questionnaire). Similar results were reported for mouth feel and aroma. However, 51% of participants rated the aftertaste of the dispersion tablet as “unpleasant/unacceptable.”

DISCUSSION

For pediatric patients infected with HIV who may find swallowing tablets challenging, it is important to evaluate alternative formulations for antiretroviral medications. The primary objective of this study was to evaluate the relative oral bioavailability of dolutegravir, abacavir, and lamivudine when the FDC abacavir/dolutegravir/lamivudine tablet was dispersed in water with high- or zero-mineral content, as well as when the dispersible tablet was taken immediately or after a 30-minute delay. By varying these parameters (mineral content of water and dispersion time), the relative oral bioavailability of dolutegravir, abacavir, and lamivudine was compared with the reference: dolutegravir plus abacavir/lamivudine coadministered as nondispersible, film-coated tablets with zero-mineral content water. As measured by plasma $AUC_{(0-\infty)}$ and C_{max} , the relative bioavailability for dolutegravir following administration as a dispersible tablet ranged from 53% to 59% higher across all 4 treatments compared with the nondispersible reference treatment. In addition, time of dispersion of dolutegravir did not impact solubility. By contrast, the relative bioavailability as measured by plasma $AUC_{(0-\infty)}$ and C_{max} for lamivudine and abacavir following administration as 4 dispersible formulations was within the bioequivalence range of 80%–125% and comparable with the nondispersible reference treatment, indicating that the method of preparation is interchangeable. The increased relative bioavailability of dolutegravir in the dispersible abacavir/dolutegravir/lamivudine formulation (dolutegravir 40 mg) compared with nondispersible, film-coated dolutegravir plus abacavir/lamivudine (dolutegravir 40 mg) was consistent with previous results observed in adults in whom the dolutegravir 50-mg pediatric granule formulation had greater bioavailability than the dolutegravir tablet formulation.¹⁶ After immediate dispersion or with a 30-minute delay, plasma exposures for dolutegravir, lamivudine, and

abacavir, as measured by $AUC_{(0-\infty)}$ and C_{max} , were comparable between high- and zero-mineral content water, indicating that the mineral content of water or dosing time had no impact on relative bioavailability. Furthermore, the PK parameters were similar, regardless of whether dolutegravir plus abacavir/lamivudine was dispersed in high- or zero-mineral content water or if it was administered immediately or after a 30-minute delay.

Within the active site of the HIV integrase enzyme, 2 metal cofactors (eg, magnesium and manganese) are essential for viral DNA integration into the host genome.¹¹ Dolutegravir inhibits HIV integrase by binding these metal cofactors.¹⁷ One study found that dolutegravir administered with a magnesium (80 mg/mL)- and aluminum (80 mg/mL)-containing antacid reduced dolutegravir exposure by >70%.¹² In addition, supplementation with calcium carbonate 1200 mg (~480-mg elemental calcium) or iron 324 mg (~107-mg elemental iron) under fasting conditions resulted in reduced dolutegravir (in tablet form) exposure up to 39% and 57%, respectively, but administration with a moderate-fat meal reversed the effect and resulted in comparable dolutegravir plasma exposures.¹³ Results from these studies suggest that high concentrations of divalent and trivalent metal cations can affect the binding of dolutegravir to integrase and reduce absorption and plasma exposures.^{12,13} In this study, high-mineral content water containing magnesium 468 mg/L (0.468 mg/mL) and calcium 74.5 mg/L (0.0745 mg/mL) did not impact the exposure of dolutegravir. Both high- and zero-mineral content water represent the range of mineral content that might be found in select bottled waters, including natural mineral or purified water¹⁸; thus, this study indicates that, in practice, no particular care is likely needed when selecting a particular water source. However, the concentration of divalent cations administered in high-mineral content water in this study was much lower than the amounts given in the mineral supplement and antacid studies (magnesium concentration ~170-fold lower),^{12,13} which may explain the lack of any effect of high-mineral content water compared with zero-mineral content water on dolutegravir bioavailability observed in this study. These

results are consistent with a previous study that compared a lower dose, 20-mg dolutegravir dispersible tablet with a dolutegravir granule formulation, showing that relative bioavailability was comparable regardless of whether the dispersible tablet was administered in high- or zero-mineral content water immediately or after a delay of 30 minutes.¹⁴

Dolutegravir, lamivudine, and abacavir demonstrated rapid absorption with median t_{max} values ranging from 2 to 2.5, 2–2.3, and 1 hour, respectively, following the administration of dispersible FDC abacavir/dolutegravir/lamivudine tablets or the reference treatment of dolutegravir plus abacavir/lamivudine.

The safety profile of the dispersible tablet was comparable with that of the nondispersible, film-coated tablet, and most participants were satisfied with the palatability of the dispersible tablet and recommended no changes for all attributes surveyed. According to the palatability questionnaire, more than 75% of participants rated the overall palatability, mouth feel, and aroma of the abacavir/dolutegravir/lamivudine dispersion as “neutral/acceptable,” whereas 51% of participants did not like the aftertaste, rating it “unpleasant/unacceptable.”

Limitations of this study include its small sample size and that it was performed only in adults. As such, a generalization of PK, safety, and palatability preferences to pediatric patients infected with HIV may be limited.

These results indicate that the bioavailability of dolutegravir was higher from the dispersible FDC tablet when compared with the nondispersible, film-coated tablet formulation; however, bioequivalence for abacavir and lamivudine was achieved. Regardless of mineral content, delay in administration, and taste additives, no difference was observed in bioavailability of dolutegravir as a dispersible tablet, suggesting the likelihood that any clean water source from any region could be used for dispersion. In addition to safety, these PK data and palatability results support further development of the dispersible tablet for future use in pediatric patients for whom swallowing tablets may be difficult.

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