Effect of Sorbitol on the Pharmacokinetic Profile of Lamivudine Oral Solution in Adults: An Open-Label, Randomized Study

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In children aged ≤4 years, the relative bioavailability of lamivudine oral solution was 37% lower than that of a tablet formulation. An open-label, four-way crossover study was conducted in healthy adults to evaluate the effect of sorbitol, a common liquid excipient, on the pharmacokinetics of lamivudine oral solution (ClinicalTrials.gov identifier, NCT02634073). Sixteen subjects were randomized to one of four sequences consisting of four doses of lamivudine 300 mg (10 mg/mL) alone or with sorbitol 3.2, 10.2, or 13.4 g. Sorbitol 3.2, 10.2, and 13.4 g decreased lamivudine maximum concentration (C_{max}) by 28%, 52%, and 55% and area under the concentration–time curve from time 0 to 24 h ($AUC_{0\text{-}24}$) by 20%, 39%, and 44%, respectively. Three subjects (19%) reported five nonserious adverse events (one drug-related). The dose-dependent effects of sorbitol on lamivudine C_{max} and $AUC_{0\text{-}24}$ reveal an absorption-based interaction that may decrease lamivudine exposure in patients coadministered sorbitol-containing medicines.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Studies in HIV-1–infected children demonstrated that lamivudine oral solution coadministered with other liquid antiretroviral medications has lower plasma lamivudine exposure than tablets. Sorbitol is used as an excipient or sweetener in liquid drug formulations and may decrease intestinal transit time for lamivudine via osmotic laxative effects.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study addressed how various sorbitol doses affect pharmacokinetic parameters of lamivudine oral solution in healthy adults under fasting conditions.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ Single-dose coadministration of lamivudine and sorbitol solutions resulted in dose-dependent reductions in lamivudine plasma exposure. Sorbitol had the greatest impact on lamivudine C_{max} and $AUC_{0\text{-}24}$, suggesting that an absorption-based interaction is the likely mechanism for reduced lamivudine exposure in this study and in prior studies in HIV-1–infected children receiving combination antiretroviral therapy.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ Caution should be used when coprescribing lamivudine oral solution with oral formulations containing large amounts of sorbitol, which may lead to suboptimal antiviral activity due to reduced lamivudine plasma exposure.

Lamivudine is a nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children.[1] Intracellularly, lamivudine is sequentially phosphorylated to the pharmacologically active 5′-triphosphate form, which acts as a competitive inhibitor of viral reverse transcriptase, leading to DNA chain termination and prevention of HIV-1 replication.[2]

The results of the ARROW trial, which was conducted in children aged ≤17 years living with HIV-1 infection in Uganda and Zimbabwe,[3] supported once-daily dosing of lamivudine and abacavir in pediatric patients. Once-daily administration of lamivudine with abacavir and one or more other antiretroviral drugs was shown to be noninferior in terms of virologic suppression to twice-daily dosing, over a median follow-up period of 114 weeks, regardless of whether pediatric patients received oral solution or tablets. However, a subgroup comparison of drug formulations showed that, irrespective of dosing frequency, pediatric subjects receiving lamivudine as tablets were more than twice as likely to achieve virologic suppression compared with those receiving oral solution (adjusted odds ratio, 2.55; 95% confidence interval (CI), 0.89–6.39; $P = 0.08$).[3] A pharmacokinetic (PK) substudy of ARROW conducted in children aged 1.8–4.0 years receiving the combination of lamivudine, abacavir, and zidovudine showed that the relative bioavailability of lamivudine solution was 37%

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Table 1 Summary of demographics

Demographics	Total (*N* = 16)
Age, mean (SD), y	40.6 (12.30)
Sex, n (%)	
Female	2 (13)
Male	14 (88)
BMI, mean (SD), kg/m^2	25.95 (3.63)
Height, mean (SD), cm	173.31 (5.93)
Weight, mean (SD), kg	78.10 (12.59)
Ethnicity, *n* (%)	
Hispanic or Latino	1 (6)
Not Hispanic or Latino	15 (94)
Race, *n* (%)	
African American/African heritage	6 (38)
White (White/Caucasian/European heritage)	10 (63)

BMI, body mass index; SD, standard deviation.

lower than that of a scored adult-tablet formulation.[4] In contrast with the pediatric findings, an earlier relative bioavailability study in adults demonstrated that lamivudine solution provided equivalent exposures to lamivudine tablets and capsules when both the test and reference formulations were administered alone.[5] Additionally, two relative bioavailability studies of pediatric-strength, three-drug, fixed-dose combination tablet formulations that were conducted in children (aged 0.5–12 years) showed that lamivudine solution given in combination with either stavudine/nevirapine or zidovudine/nevirapine liquid formulations had 29% or 44% lower lamivudine exposures than lamivudine administered as part of a three-drug tablet,[6,7] despite these three-drug tablet formulations having been shown to be equivalent to solutions in adult relative bioavailability studies.[8,9] Unlike studies in adults, the pediatric relative bioavailability studies were conducted in children being treated for HIV-1 with lamivudine in combination with one or more antiretroviral drugs. Two of the drugs, abacavir solution and nevirapine suspension, contain high amounts of sorbitol (340 and 162 mg/mL, respectively), an excipient used to sweeten and improve palatability of some liquid formulations. Therefore, we hypothesized that the decreased bioavailability of liquid lamivudine may be due to its interaction with sorbitol.

Interactions between sorbitol and active ingredients in medications have been reported in the literature.[10] Like other nonabsorbed sugar alcohols, sorbitol increases osmotic pressure in the intestine, pulling water into the lumen and accelerating small intestine transit time. This results in decreased absorption and bioavailability of low permeability drugs that are sensitive to changes in gastrointestinal (GI) motility and transit time.[10,11] Lamivudine is a highly soluble and well-absorbed drug with an absolute bioavailability of 86% in adults[5]; however, there are conflicting reports as to whether lamivudine is a low or high permeability drug,[12] with the results of an *in vitro* Caco-2 study characterizing its permeability as moderate.[13] Although the lamivudine oral solution itself does not contain sorbitol, if the permeability of lamivudine is in the low-to-moderate range, it may be susceptible to an absorption-based interaction with sorbitol present in coadministered antiretroviral drugs, such as abacavir oral solution and nevirapine suspension, as well as other chronically administered liquid formulations of prescription or over-the-counter medications used to treat comorbidities. Therefore, the objective of this study was to determine the extent to which sorbitol influences the absorption of lamivudine and potentially explain the reduced exposure observed in children when lamivudine oral solution was coadministered with sorbitol-containing oral formulations of antiretroviral medications.

RESULTS

Patient characteristics

A total of 37 individuals were screened, 16 of whom were deemed eligible and were randomized to receive treatment. The mean age of the subjects was 40.6 years, and the majority were men (88%), white (63%), and not Hispanic or Latino (94%; **Table 1**). The first subject was enrolled on January 4, 2016, and the last subject completed the study on March 11, 2016. All subjects completed the study and were included in analyses of PK and safety endpoints.

Three protocol deviations were reported and attributed to issues related to assessment or timepoint completion (i.e., 4-min out-of-window blood sample collection, missing urinalysis sample, and missing blood pressure/pulse rate assessment). None of the deviations led to the exclusion of any subject's data or were considered to affect the interpretation of the results.

PK analyses

Lamivudine was readily absorbed with no observed lag time after any of the treatment regimens. The median t_{max} occurred 0.75–1.26 h after dosing, depending on the treatment, with longer t_{max} associated with sorbitol coadministration (**Table 2**). Coadministration of lamivudine with sorbitol resulted in dose-dependent reductions in plasma lamivudine C_{max} (**Figure 1**), with decreases of 28%, 52%, and 55% observed after treatment with sorbitol 3.2, 10.2, and 13.4 g, respectively (**Table 3**). Plasma lamivudine exposure was also decreased in a dose-dependent manner, with sorbitol 3.2, 10.2, and 13.4 g, resulting in decreases of 20%, 39%, and 44% in $AUC_{0\text{-}24}$, and 14%, 32%, and 36% in $AUC_{0\text{-}\infty}$, respectively. Lamivudine CL/F increased by 17%, 48%, and 57% corresponding to increasing sorbitol doses. There was a small increase in the apparent $t_{1/2}$ of lamivudine when coadministered with sorbitol.

Safety analysis

Adverse events were reported in three subjects (19%), including gastroenteritis, vaginal infection, vessel puncture-site pain, myalgia, and dizziness (n = 1 (6%) for each). Two adverse events (AEs) (gastroenteritis and vessel puncture-site pain) were reported during treatment with lamivudine 300 mg + sorbitol 3.2 g. One AE of dizziness was reported during lamivudine

Table 2 Summary of plasma lamivudine PK parameters

PK parameter	Lamivudine 300 mg ($n = 16$)	Lamivudine 300 mg + sorbitol 3.2 g ($n = 16$)	Lamivudine 300 mg + sorbitol 10.2 g ($n = 16$)	Lamivudine 300 mg + sorbitol 13.4 g ($n = 16$)
C_{max}, geometric mean (%CV), μg/mL	3.3 (34.9)	2.4 (32.7)	1.6 (27.2)	1.5 (30.9)
t_{max}, median (range), h	0.75 (0.50–1.50)	1.00 (0.50–1.50)	1.00 (0.50–2.50)	1.26 (0.50–3.00)
$AUC_{0\text{-}24}$, geometric mean (%CV), μg·h/mL	12.4 (23.6)	10.0 (22.6)	7.5 (23.7)	6.9 (28.9)
$AUC_{0\text{-}t}$, geometric mean (%CV), μg·h/mL[a]	12.9 (23.0)	10.6 (21.6)	8.2 (22.9)	7.6 (26.8)
$AUC_{0\text{-}\infty}$, geometric mean (%CV), μg·h/mL	13.2 (22.3)	11.3 (21.2)[b]	8.9 (22.1)	8.6 (24.1)[c]
$t_{1/2}$, geometric mean (%CV), h	13.9 (20.9)	19.0 (40.6)[b]	21.2 (47.3)	17.3 (48.6)[c]
CL/F, geometric mean (%CV), L/h	22.7 (22.3)	26.6 (21.2)[b]	33.6 (22.1)	34.9 (24.1)[c]

$AUC_{0\text{-}24}$, area under the concentration–time curve from time zero to 24 h; $AUC_{0\text{-}t}$, AUC from time zero to the last quantifiable timepoint; $AUC_{0\text{-}\infty}$, AUC from time 0 extrapolated to infinity; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; $t_{1/2}$, terminal elimination phase half-life; t_{max}, time of occurrence of C_{max}.
[a]Time of the last measurable concentration (t) was 48 h for all subjects and all treatments. [b]$n = 14$. [c]$n = 13$.

300 mg + sorbitol 10.2 g treatment, one AE of vaginal infection was reported during lamivudine 300 mg + sorbitol 13.4 g treatment, and one AE of myalgia was reported during treatment with lamivudine 300 mg alone. The vaginal infection was the only AE considered by the investigator to be related to the study treatment. There were no serious AEs, Grade 3 or 4 AEs, or deaths reported during the study. Treatment-emergent laboratory abnormalities were reported in two subjects during follow-up visits, including a Grade 1 increase in sodium and a Grade 1 increase in aspartate aminotransferase. These events were not reported as AEs. No vital sign abnormalities or pregnancies were reported during the study.

DISCUSSION

This study was designed to address the question of whether sorbitol affects the PK of lamivudine and therefore explain the findings of reduced exposures in children administered lamivudine in combination with other sorbitol-containing medications.[4,6,7]

The key finding of this study was that coadministration of lamivudine with sorbitol resulted in a dose-dependent reduction in lamivudine plasma exposures, with higher doses of sorbitol resulting in lower lamivudine AUC and C_{max} values. Sorbitol had the greatest impact on lamivudine C_{max} and $AUC_{0\text{-}24}$, and delayed t_{max}, which suggests that sorbitol's effect was primarily on the absorption and bioavailability of lamivudine. These findings are consistent with the observed dose-dependent effects of sugar alcohols on GI transit time and the PK parameters of low permeable drugs such as ranitidine and cimetidine.[10,14] For example, ranitidine t_{max} was delayed, and a linear relationship was noted between the dose of sorbitol and ranitidine bioavailability, with 7.2%, 25%, and 45.5% reduction in ranitidine AUC, respectively, as the amount of sorbitol was increased from 1.25 to 2.5 to 5 g.[10] Sorbitol (5 g) had less effect on the higher permeability drugs metoprolol (17% reduction in bioavailability) and theophylline (no effect). Based on the known osmotic properties of sorbitol, its effect on lamivudine likely results from accelerated intestinal

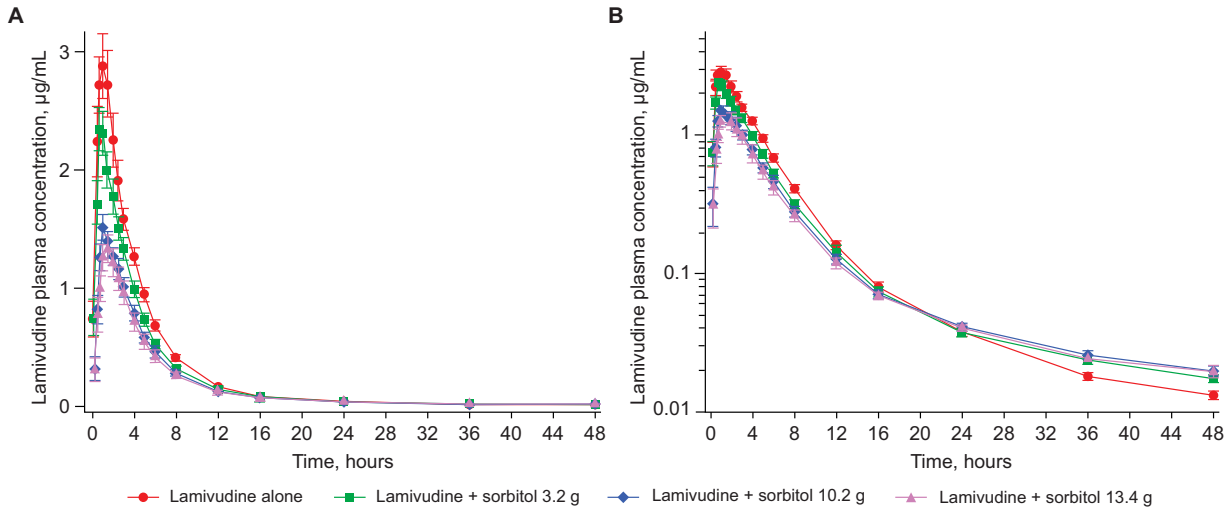

Figure 1 (**a**) Linear and (**b**) semilogarithmic plots of mean ± SEM plasma lamivudine concentration as a function of time after dosing. SEM, standard error of the mean.

Table 3 Treatment comparisons

PK parameter	Ratio of GLS means (90% CI)		
	Lamivudine 300 mg vs. lamivudine 300 mg + sorbitol 3.2 g ($n = 16$)	Lamivudine 300 mg vs. lamivudine 300 mg + sorbitol 10.2 g ($n = 16$)	Lamivudine 300 mg vs. lamivudine 300 mg + sorbitol 13.4 g ($n = 16$)
C_{max}	0.724 (0.657, 0.798)	0.479 (0.434, 0.527)	0.454 (0.412, 0.500)
$AUC_{0\text{-}24}$[a]	0.803 (0.747, 0.864)	0.608 (0.566, 0.655)	0.557 (0.518, 0.599)
$AUC_{0\text{-}t}$	0.819 (0.766, 0.876)	0.636 (0.595, 0.680)	0.585 (0.548, 0.626)
$AUC_{0\text{-}\infty}$	0.855 (0.799, 0.914)[b]	0.677 (0.635, 0.721)	0.637 (0.594, 0.682)[c]
$t_{1/2}$	1.37 (1.11, 1.69)[b]	1.53 (1.25, 1.88)	1.29 (1.04, 1.61)[c]
CL/F	1.17 (1.09, 1.25)[b]	1.48 (1.39, 1.58)	1.57 (1.47, 1.68)[c]

$AUC_{0\text{-}24}$, area under the concentration–time curve from time zero to 24 hours; $AUC_{0\text{-}t}$, AUC from time zero to the last quantifiable time point; $AUC_{0\text{-}\infty}$, AUC from time 0 extrapolated to infinity; CI, confidence interval; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; GLS, geometric least squares; PK, pharmacokinetic; $t_{1/2}$, terminal elimination phase half-life.
[a]Time of the last measurable concentration (t) was 48 h for all subjects and all treatments. [b]$n = 14$. [c]$n = 13$.

transit, leading to decreased absorption in the small intestine.[15,16] Another possible explanation is sorbitol inhibition of an unidentified transporter involved in GI absorption of lamivudine.[16] A small increase in the apparent $t_{1/2}$ of lamivudine was noted across treatments when lamivudine was coadministered with sorbitol. The slightly longer $t_{1/2}$ may reflect the delayed absorption of small amounts of lamivudine in the latter parts of the intestinal tract; however, regional absorption of lamivudine in humans has not been studied, and it is unknown whether absorption can occur in the latter parts of the GI tract.

The results of this drug interaction study in adults implicate sorbitol as the perpetrator and underlying mechanism for the lower plasma lamivudine exposures in the aforementioned relative bioavailability studies in children with HIV-1 infection who received repeated doses of lamivudine oral solution in combination with other antiretroviral drug formulations that contained sorbitol as an excipient.[4,6,7] In each of those pediatric studies, lamivudine oral solution was coadministered with abacavir solution, which is formulated with high concentrations of sorbitol (340 mg/mL). In some studies, children also received nevirapine suspension (162 mg of sorbitol/mL) or the prophylactic antibiotic trimethoprim-sulfamethoxazole as a suspension (sorbitol amounts vary depending on the manufacturer). This interaction between lamivudine and sorbitol may also explain previous reports of lower exposures in younger/lower-weight children compared with older/higher-weight children[17–20] because younger children are more likely to be prescribed liquid medications for ease of swallowing.

Although the results suggest a plausible mechanism for the observation of lower lamivudine plasma exposures, some limitations of the study should be noted. One limitation is the application of single-dose PK results to real-world scenarios in which sorbitol is chronically administered through medications and leads to more sustained GI transit effects. Additionally, because all subjects underwent the same 8-h overnight fast, the study provides no insight on the effect of the fasted vs. fed state on the interaction between sorbitol and lamivudine. Another limitation is the enrollment of healthy adults rather than children infected with HIV, who are expected to be the target population for oral solution formulations. Adults were enrolled because of ethical and feasibility challenges associated with conducting drug interaction studies in children. However, precise extrapolation of the magnitude of interaction on lamivudine AUC, which is considered to be the best plasma PK predictor of antiretroviral effect for nucleoside reverse transcriptase inhibitor drugs, from adults to children may be affected by the dose-dependent GI effects of sorbitol and age-dependent differences between adults and children in GI physiology, intestinal volume, and cumulative doses/frequency of sorbitol administration. Physiologically based pharmacokinetic modeling may be a useful tool for future investigation or prediction of sorbitol effect in young children, provided that GI physiological parameters that affect absorption have been measured and are available for children across a broad age range, especially birth to age 2 years, who are more likely to be administered solution formulations. Finally, this study measured plasma lamivudine concentrations rather than intracellular concentrations of the pharmacologically active triphosphate metabolite. Studies have shown relationships between intracellular concentrations of lamivudine triphosphate and the rate of decline in HIV viral load and rise in CD4+ cell count with treatment; however, sample collection and measurement of intracellular triphosphate is technically more challenging and less amenable to routine patient care than measurement of plasma concentrations.[21] Therefore, the plasma lamivudine AUC is commonly used as a surrogate measure of intracellular concentration and antiviral activity, even though the relationship between plasma lamivudine concentrations and intracellular active triphosphate concentrations is complex,[21] and makes it difficult to define the clinical significance of a plasma PK drug interaction.

The above considerations, plus global differences in HIV product availability, labeling, and prescribing practices, make it difficult to devise a comprehensive dose-adjustment guideline to ensure optimal plasma lamivudine AUC in children, especially very young children (aged $\leq$2 years) who are more likely to receive medications as oral solutions in real-world settings compared with older children. Therefore, to manage this drug

interaction, it is recommended that long-term, chronic coadministration of sorbitol-containing medications and lamivudine be avoided. Although unconfirmed, the occasional use of sorbitol-containing medicines is not expected to affect antiretroviral activity because of the importance of intracellular pooling of the pharmacologically active, long-lived triphosphate metabolite in the mechanism of action of lamivudine. Healthcare providers can find information about excipients in a specific medicinal product in the product information (United States: https://dailymed.nlm.nih.gov/dailymed/index.cfm) or summary of product characteristics (Europe: https://www.medicines.org.uk/emc/browse-documents).

Preferably, an all-tablet antiretroviral drug regimen should be used when possible to avoid a potential interaction with sorbitol-containing liquid drug formulations, such as abacavir or nevirapine. Generic, pediatric-friendly tablet formulations (e.g., low-dose dispersible lamivudine tablets, antiretroviral drug combination tablets) are available in some geographic regions for children who weigh <14 kg who need smaller doses than those that can be achieved with the innovator's scored adult tablet. In countries where generic pediatric-strength tablet formulations are not available, the scored adult tablet of lamivudine may be used with other antiretroviral drug tablets in children who weigh ≥14 kg. Although untested, the product labeling in some countries permits crushing of adult lamivudine tablets to ease tablet swallowing in children. For children <14 kg without access to generic pediatric-strength tablets or older children who are unable to swallow tablets, an upward dose adjustment from 8 mg/kg per day to 10 mg/kg per day of lamivudine solution may be appropriate if product labeling permits a dose increase. This 25% dose increase was based on the PK results of prior relative bioavailability studies in children receiving sorbitol[4,6,7] and assumed that an increase in dose would overcome the sorbitol interaction in a proportional manner in order to achieve plasma lamivudine exposures that are similar to those reported in adults at the efficacious dose of 300 mg once daily. The 25% increase in dose was also supported by population PK modeling and simulation of pediatric data performed by Janssen *et al.*,[19] who concluded that a dose of 10 mg/kg per day was appropriate for children ages 5 months to 18 years who weigh <14 kg. Regarding children specifically, lamivudine given alongside sorbitol-containing medicines should be used for the treatment of HIV infection only when the product label recommends a dose-adjustment of the oral solution or when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks, including lower virological suppression. More frequent monitoring of HIV-1 viral load should be considered when lamivudine is used with chronically administered sorbitol-containing medicines. Product labels should be consulted for detailed, country-specific prescribing instructions.

To our knowledge, the present study is the first to provide direct evidence and a potential mechanism for a link between sorbitol and decreased lamivudine plasma exposure. Although the results were obtained from adult subjects, their greatest effect may be in young children who are most likely to use oral solution formulations of lamivudine. It is recommended to avoid coadministration of lamivudine and sorbitol-containing medicines and switch to an all-tablet regimen as soon as feasible. In some countries, product labeling may permit a dose increase if the use of lamivudine oral solution with sorbitol-containing medications cannot be avoided.

METHODS

Study design and subjects

Study 204857 was conducted as an open-label, randomized, four-period Williams crossover design at a single center (Quintiles, Overland Park, KS). Healthy subjects aged 18–65 years with body weight ≥50 kg for men and >45 kg for women and body mass index (BMI) from 18.5–31.0 kg/m^2 were included in the study. Key exclusion criteria were alanine aminotransferase and bilirubin >1.5 × upper limit of normal; QT interval corrected by the Fridericia correction (QTcF) formula >450 ms; creatinine clearance (CrCL) <60 mL/min; a history of regular alcohol consumption or smoking within 6 months of the study; or a history of cholecystectomy, peptic ulceration, inflammatory bowel disease, pancreatitis, or other existing condition interfering with normal GI anatomy or motility, hepatic, and/or renal function that could interfere with the absorption, metabolism, and/or excretion of the study drug. Despite initial observations of low lamivudine exposure in children treated with the pediatric lamivudine oral solution, the study enrolled adults because drug interaction studies are not feasible with children.

Sixteen subjects were planned to be randomized to one of four treatment sequences (four subjects per sequence) in accordance with a randomization schedule generated before the start of the study. The four treatment regimens were lamivudine oral solution 300 mg alone, lamivudine 300 mg plus sorbitol 3.2 g (low dose), lamivudine 300 mg plus sorbitol 10.2 g (medium dose), and lamivudine 300 mg plus sorbitol 13.4 g (high dose). The 300-mg lamivudine dose represents the adult once-daily dose for the treatment of HIV. The low, medium, and high sorbitol doses were chosen to mirror the amounts of sorbitol found in an adult dose of nevirapine (Viramune; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) oral suspension, abacavir (Ziagen; ViiV Healthcare, Research Triangle Park, NC) oral solution, or the combined amount consumed when the nevirapine and abacavir preparations are taken together. Treatments were administered as separate oral solutions containing 10 mg/mL of lamivudine (Epivir Oral Solution; ViiV Healthcare) or 900 mg/mL of sorbitol (Geritrex Sorbitol Solution USP 70% w/w; Mount Vernon, NY). All treatments were administered with ~240 mL of water after an 8-h overnight fast and with a ≥7-day washout between doses. Subjects continued to fast for 4 h postdose and were required to refrain from consuming products that contain sugar alcohols (e.g., sorbitol, mannitol, xylitol, maltitol, isomalt), including sugar-free chewing gum, candy, or other processed food or drink, during the inpatient period of each dosing session (Day −1 through 48 h postdose). Subjects returned for a follow-up visit 7 to 14 days after receiving the last dose of study medication.

Written informed consent was obtained from each subject before any study-specific procedures were performed. The study protocol and informed consent were reviewed and approved by a regional Institutional Review Board in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and United States 21 Code of Federal Regulations 312.3(b). The study was registered with ClinicalTrials.gov under the identifier NCT02634073.

PK assessments

Blood samples (2 mL) for PK analysis were collected via an indwelling cannula or direct venipuncture into a dipotassium ethylenediaminetetraacetic acid tube before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 h postdose. Blood samples were centrifuged for 10 min at 1,500*g* to 2,000*g* at 4°C, and plasma was harvested, frozen, and stored at −20°C until analysis. Plasma lamivudine concentrations were measured using a validated method by Pharmaceutical Product Development (PPD; Middleton, WI). Lamivudine and the internal

standard, [$^{13}C^{15}N_2$]-lamivudine, were isolated through protein precipitation. The final extract was analyzed by high-performance liquid chromatography with tandem mass spectrometry using positive ion electrospray. The lower and upper limits of quantitation were 2.5 and 2,500 ng/mL, respectively, for a 50-μL plasma aliquot.

To ensure quality control, standard samples containing lamivudine at five prespecified concentrations were stored with study samples at the time of freezing and were analyzed with each batch against separately prepared calibration standards. Precision, measured as the percent coefficient of variation (%CV) of the set of values for each pool, ranged from 4.5–7.2%. Accuracy, expressed as the percent difference of the mean value for each pool from the theoretical concentration, was −3.9% to 5.0%.

The primary objective of this study was to compare PK parameters after administration of a single dose of lamivudine oral solution 300 mg with or without varying doses of sorbitol oral solution under fasting conditions. The main endpoints associated with the PK effects of interest were area under the concentration–time curve (AUC) from time zero to the last quantifiable timepoint ($AUC_{0\text{-}t}$), AUC from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$), and AUC from time zero to 24 h ($AUC_{0\text{-}24}$). Other PK parameters monitored were maximum observed plasma concentration (C_{max}), time of occurrence of C_{max} (t_{max}), concentration at 24-h postdose (C_{24}), last measurable concentration (C_t), time of last measurable concentration (t), absorption lag time (t_{lag}), terminal elimination phase half-life ($t_{1/2}$), and apparent oral clearance (CL/F). Plasma concentration–time data for lamivudine were analyzed by noncompartmental methods with WinNonlin 6.3 (Certara, Princeton, NJ). Calculations were based on the actual sampling times recorded during the study. The concentration–time profiles of two subjects in the sorbitol 3.2-g group and three subjects in the sorbitol 13.4-g group had relatively flat terminal phases, resulting in a percentage of extrapolated AUC >40%. Therefore, the $t_{1/2}$, $AUC_{0\text{-}\infty}$, and CL/F from these subjects were excluded from the statistical analysis of PK parameters, but other data from these subjects were retained for the safety analyses.

Safety assessments

The secondary endpoints comprised safety and tolerability parameters assessed as change from baseline in vital signs, number of subjects with adverse events (AEs), and toxicity grading of clinical laboratory tests. Information collected on AEs included duration (start and stop dates), severity (mild, moderate, severe), causality (reasonable possibility, yes/no), and actions taken/outcome. The safety assessments also included electrocardiograms, physical examinations, and pregnancy tests.

Statistical methods

Based on unpublished data from substudies in the ARROW trial, a sample size of 16 participants, with ≥14 evaluable participants, was chosen to obtain $AUC_{0\text{-}\infty}$ and C_{max} treatment difference values with 90% CI boundaries that fall within 17% of the point estimate on a logarithmic scale. Accordingly, if the point estimate of the ratio of geometric means was 1, then the upper and lower boundaries of the 90% CI were to be ~0.85 and 1.17.

An analysis of variance, considering treatment and period as fixed effects and subject as random effect, was performed using SAS Mixed Linear Models procedure (SAS, Cary, NC) to compare log-transformed plasma PK parameters. Comparisons between each of the three sorbitol-containing treatments and lamivudine alone were made by calculating the ratios of geometric least squares means and associated 90% CIs on the original scale for the selected PK parameters.

Safety data were tabulated and summarized descriptively with no formal statistical analyses conducted.

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CONFLICT OF INTEREST/DISCLOSURE

K.A., K.H., M.S., T.P., and C.M. are employees of ViiV Healthcare and own stock in GlaxoSmithKline. A.W., A.E., H.V., and Y.L. are or were employees of GlaxoSmithKline and own stock in the company. Z.Z. and Y.L. have received grants from ViiV Healthcare.

AUTHOR CONTRIBUTIONS

K.A., A.W., Y.L., Z.Z., A.E., T.P., H.V., K.H., M.S., and C.M. wrote the article; K.A., A.W., Y.L., K.H., and C.M. designed the research; K.A., A.W., Y.L., Z.Z., A.E., T.P., H.V., and C.M. analyzed the data.

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