FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1, Single-Dose, Cross-Over Study Evaluating the Relative Bioavailability of a Pediatric Oral Granule Formulation of Tenofovir Alafenamide in Healthy Adults
Name of Test Drug:	Tenofovir alafenamide
Dose and Formulation:	Tenofovir alafenamide 25-mg oral granules
Indication:	Chronic hepatitis B
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-320-1196
Phase of Development:	Phase 1
IND No.: **EudraCT No.:**	115561 2019-003269-16
ClinicalTrials.gov Identifier:	Not Applicable
Study Start Date:	12 August 2019 (First Subject Screened)
Study End Date:	19 October 2019 (Last Subject Last Observation for the Primary Endpoint and for this Report)
Principal or Coordinating Investigator:	Name: PPD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	27 March 2020

STUDY SYNOPSIS

Study GS-US-320-1196
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 1, Single-Dose, Cross-Over Study Evaluating the Relative Bioavailability of a Pediatric Oral Granule Formulation of Tenofovir Alafenamide in Healthy Adults
Investigators: PPD
Study Centers: One site in the United States
Publications: There were no publications at the time of this clinical study report.
Study Period: 12 August 2019 (First Subject Screened) 19 October 2019 (Last Subject Last Observation for the Primary Endpoint and for this Report)
Phase of Development: Phase 1
Objectives: The primary objective of this study was as follows: • To evaluate the relative bioavailability of a pediatric oral granule formulation of tenofovir alafenamide (TAF) relative to the adult tablet formulation The secondary objective of this study was as follows: • To evaluate the safety and tolerability of a single dose of a pediatric oral granule formulation of TAF in healthy subjects

Methodology: This Phase 1, randomized, open-label, single-center, single-dose, 2-period, crossover study evaluated the relative bioavailability of a pediatric oral granule formulation of TAF relative to the adult tablet formulation in healthy adult subjects. The safety and tolerability of the pediatric oral granule formulation of TAF was evaluated.

Following completion of screening and admission assessments, subjects were randomized to 1 of 2 treatment sequences and received each of the 2 treatments (A and B) with an 11-day washout period between each treatment. The treatments and treatment sequences were as follows:

- **Treatment A:** Single dose of the TAF 25-mg adult tablet (1 × 25-mg tablet) administered orally under fed conditions
- **Treatment B:** Single dose of the TAF 25-mg pediatric oral granule formulation (2 × 12.5-mg unit) administered orally under fed conditions

Period	**1**		**2**	
Treatment Sequence	**Day 1**	**Days 2–12**	**Day 13**	**Day 19**
AB (planned N = 17)	A	Washout	B	Discharge
BA (planned N = 17)	B	Washout	A	Discharge

Number of Subjects (Planned and Analyzed):

Planned: 34 subjects

Analyzed: 37 subjects (18 subjects for treatment sequence AB and 19 subjects for treatment sequence BA)
PK Analysis Sets: 37 total subjects for each analyte of interest (TAF and tenofovir [TFV])

Diagnosis and Main Criteria for Inclusion: Eligible subjects were healthy males and nonpregnant, nonlactating females, 18 to 45 years of age (inclusive) with body mass index (BMI) ≥ 19.0 and ≤ 30.0 kg/m^2, normal 12-lead electrocardiogram (ECG), normal renal function (estimated glomerular filtration rate calculated using the Cockcroft-Gault equation [$eGFR_{CG}$] ≥ 90 mL/min), no significant medical history, and in good general health as determined by the investigator at the screening evaluation performed no more than 28 days prior to the scheduled first dose.

Duration of Treatment: All subjects received a single dose of study drug on Days 1 and 13. Study duration was up to 29 days (not including screening window).

Test Product, Dose, Mode of Administration, and Batch No.: Single dose of TAF 25-mg pediatric oral granule formulation (2 × 12.5-mg unit) administered orally under fed conditions.

The batch number of the TAF 25-mg pediatric oral granule formulation administered in this study was GD1901D1.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Single dose of TAF 25-mg adult tablet (1 × 25-mg tablet) administered orally under fed conditions.

The batch number of the TAF 25-mg adult tablet administered in this study was CM1605B1.

Criteria for Evaluation:

Efficacy: No efficacy analyses were performed for this report.

Pharmacokinetics: Intensive pharmacokinetic (PK) blood sampling occurred relative to dosing of TAF at the following time points on Days 1 and 13:

- Predose (≤ 5 minutes), 5 minutes postdose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose

A blood sample for PK analysis was also collected at the early termination visit, if applicable.

Plasma concentrations of TAF and its metabolite, TFV were determined, and the following plasma PK parameters were calculated for each analyte, as applicable: AUC_{inf}, AUC_{last}, CL/F, $t_{1/2}$, and V_z/F.

Safety: Safety was evaluated by assessment of clinical laboratory tests, complete or symptom-directed physical examinations, vital signs measurements, ECGs, and by the documentation of adverse events (AEs) and concomitant medications.

Statistical Methods:

Efficacy: No efficacy analyses were performed for this report.

Pharmacokinetics: The primary analyses assessed the relative bioavailability of the TAF oral granule formulation compared with the tablet formulation. Analyses were conducted using a mixed-effects statistical model with treatment, period, and sequence as fixed effects, and subject within sequence as a random effect.

Plasma concentrations and PK parameters were listed and summarized by analyte and treatment using descriptive statistics (number of subjects, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum). An analysis of variance (ANOVA) was performed for the natural logarithms of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for TAF and TFV.

The-test-to-reference ratio and associated 90% confidence interval (CI) were calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach. Pharmacokinetic equivalence was concluded if the geometric least-squares mean (GLSM) ratios and corresponding 90% CIs for TAF and TFV AUC_{inf}, AUC_{last}, and C_{max} were within the prespecified equivalence boundaries of 70% to 143%.

Safety: The Safety Analysis Set included all randomized subjects who received at least 1 dose of study drug. Safety data included all data collected on or after the date of the first dose of study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 37 subjects were enrolled, were randomized into the study, received study drug, and were included in both PK analysis sets; 18 subjects in the AB treatment sequence and 19 subjects in the BA treatment sequence. One subject in the BA treatment group prematurely discontinued study drug due to subject decision, and discontinued study due to loss to follow-up. The majority of subjects were male (62.2%, 23 subjects), white (73.0%, 27 subjects), and were not Hispanic or Latino (67.6%, 25 subjects). Subjects had a mean (SD) age of 33 (6.3) years (range: 22 to 44 years). Mean (SD) BMI was 24.5 (range: 19.1 to 29.5) kg/m^2, and mean (SD) creatinine clearance (CL_{cr}) was 112 (range: 91 to 157) mL/min at baseline.

Efficacy Results: Efficacy was not evaluated in this study.

Pharmacokinetics Results:

Plasma PK parameters for TAF and TFV and statistical comparisons for relative bioavailability between the 25-mg adult tablet formulation (Treatment A) and the 25-mg pediatric oral granule formulation (Treatment B) are presented in the following table.

	Mean (%CV)		
	Test TAF Pediatric Granules (N = 37)	**Reference TAF Adult Tablet (N = 36)**	**%GLSM Ratio (90% CI)[a]**
TAF PK Parameter			
AUC_{last} (h*ng/mL)	208.9 (26.7)	196.9 (36.2)	110.25 (101.32, 119.96)
AUC_{inf} (h*ng/mL)	211.7 (26.0)	198.8 (35.6)	110.30 (101.53, 119.84)
C_{max} (ng/mL)	125.4 (37.4)	151.2 (63.8)	96.38 (81.80, 113.57)
TFV PK Parameter			
AUC_{last} (h*ng/mL)	235.4 (16.4)	226.3 (14.8)	104.17 (100.39, 108.10)
AUC_{inf} (h*ng/mL)	270.7 (15.9)	260.8 (14.6)	103.99 (100.31, 107.81)
C_{max} (ng/mL)	6.1 (16.1)	6.3 (18.0)	97.59 (92.59, 102.86)

CV coefficient of variation; GLSM geometric least squares mean; CI confidence interval.
N represents the number of subjects in the PK analysis set.
Means presented are unadjusted arithmetic means.
a GLSM ratios were calculated based on the 36 subjects who received both doses of study drug.

TAF and TFV exposure parameters (AUC_{last}, AUC_{inf}, and C_{max}) were compared between the TAF pediatric oral granule formulation (2 × 12.5-mg units) and the TAF adult formulation (1 × 25-mg tablet). The 90% CI for the GLSM ratios for all exposure parameters, for both TAF and TFV, were contained within the more stringent bioequivalent criteria of 80% to 125% for the pediatric oral granule formulation relative to the adult tablet. Thus, these data demonstrate that the oral granule formulation and tablet formulation of TAF are bioequivalent.

Safety Results: No deaths, serious AEs, Grade 3 or 4 AEs, or AEs that led to study drug discontinuation were reported. All AEs were Grade 1 or 2 in severity. The percentage of subjects experiencing AEs while receiving the 25-mg pediatric oral granule formulation (Treatment B) was higher than the percentage of subjects experiencing AEs while receiving the 25-mg adult tablet formulation (Treatment A) (Treatment A: 4 subjects, 11.1%; Treatment B: 9 subjects, 24.3%). Only 2 subjects experienced more than 1 AE. The most commonly reported AEs were headache reported by 2 subjects (5.6%) while receiving the 25-mg adult tablet formulation (Treatment A), and headache and somnolence reported by 2 subjects each (5.4% each) while receiving the 25-mg pediatric oral granule formulation (Treatment B). The 4 instances of headache were reported in 4 unique subjects; no individual subject experienced an AE of headache during both Treatment A and Treatment B. No more than 2 subjects experienced AEs within a given system organ class (SOC) while receiving the 25-mg adult tablet formulation (Treatment A); however, 4 subjects (10.8%) experienced AEs within the gastrointestinal disorders SOC and 5 subjects (13.5%) experienced AEs within the nervous system disorders SOC while receiving the 25-mg pediatric oral granule formulation (Treatment B).

The percentage of subjects experiencing AEs related to study drug while receiving the 25-mg pediatric oral granule formulation (Treatment B) was higher than the percentage of subjects experiencing AEs related to study drug while receiving the 25-mg adult tablet formulation (Treatment A). One subject (2.8%) had a Grade 1 AE of headache assessed by the investigator to be related to study drug while receiving the 25-mg adult tablet formulation (Treatment A), and 5 subjects (13.5%) experienced Grade 1 AEs assessed by the investigator to be related to study drug while receiving the 25-mg pediatric oral granule formulation (Treatment B).

Twelve subjects (33.3%) experienced a graded laboratory abnormality while receiving the 25-mg adult tablet formulation (Treatment A), and 9 subjects (24.3%) experienced a graded laboratory abnormality while receiving the 25-mg pediatric oral granule formulation (Treatment B). One subject (2.8%) experienced a Grade 3 abnormality of occult blood in the urine while receiving the 25-mg adult tablet formulation (Treatment A). All other reported laboratory abnormalities were Grade 1 or 2 in severity. No clinically relevant changes in vital signs or weight were reported during the study, and all subject ECG results were reported as either normal or abnormal but not clinically significant during the study.

CONCLUSIONS: The conclusions from Study GS-US-320-1196 are as follows:

- TAF pediatric oral granules (2 × 12.5-mg) and adult strength tablet (1× 25-mg) were bioequivalent.
- Single doses of the TAF pediatric oral granule formulation and the TAF adult tablet formulation were well tolerated. No difference in safety has been observed between oral granules and adult tablet formulation administration.