FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1, Open-Label, Parallel-Group, Single Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide (TAF) in Subjects with Normal Hepatic Function and Subjects with Severe Hepatic Impairment
Name of Test Drug:	Tenofovir Alafenamide
Dose and Formulation:	25-mg tablet
Indication:	Chronic hepatitis B
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-320-1615
Phase of Development:	Phase 1
IND No.: **EudraCT No.:**	115561 2014-004426-18
ClinicalTrials.gov Identifier:	NCT02296853
Study Start Date:	22 December 2014 (First Subject Screened)
Study End Date:	17 April 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Thomas C. Marbury, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: John F. Flaherty, PharmD Telephone: PPD Fax: PPD
Report Date:	30 September 2015

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-320-1615

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 1, Open-Label, Parallel-Group, Single Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide (TAF) in Subjects with Normal Hepatic Function and Subjects with Severe Hepatic Impairment

Investigators: Edward Gane, Gernot Klein, Kenneth Lasseter, Eric Lawitz, and Thomas Marbury

Study Centers: This study was conducted at a total of 5 sites: 3 in the United States (US), 1 in New Zealand, and 1 in Germany.

Publications: At the time of this report, the results of this study had not been presented or published.

Study Period:

22 December 2014 (First Subject Screened)
17 April 2015 (Last Subject Observation)

Phase of Development: Phase 1

Objectives:

The primary objective of this study was as follows:

- To evaluate the single-dose pharmacokinetics (PK) of TAF and its metabolite tenofovir (TFV) in subjects with normal hepatic function and subjects with severe hepatic impairment

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of TAF in subjects with normal hepatic function and subjects with severe hepatic impairment

Methodology: This Phase 1, open-label, multicenter, single-dose, parallel-group study evaluated the safety, tolerability, and PK of TAF in subjects with normal hepatic function or severe hepatic impairment (Child-Pugh-Turcotte [CPT] classification C: score 10-15). Each subject in the healthy control group (hereafter referred to as the normal matched control group) was matched with a subject in the severe hepatic impairment group by age, sex, and body mass index (BMI). All subjects received a single oral dose of TAF 25 mg on Day 1. Subjects were confined at the study center from Day −1 until completion of PK and safety assessments on Day 7.

Number of Subjects (Planned and Analyzed):

Planned: 20 subjects (10 subjects in the severe hepatic impairment group and 10 in the normal matched control group) for a total of 16 evaluable (8 subjects per group)

Analyzed: All 20 subjects were analyzed and included in the Safety Analysis Set, PK TAF Analysis Set, and PK TFV Analysis Set.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were male and nonpregnant/nonlactating females 18 to 70 years old (inclusive), with a BMI of 18.0 to 38.0 kg/m^2 and creatinine clearance (CL_{cr}) ≥ 60 mL/min (using the Cockroft-Gault method). Eligible subjects were hepatitis B surface antigen (HBsAg) negative.

Subjects with hepatic impairment had CPT Class C (score 10-15) severe hepatic impairment that was caused by nonhepatitis B-induced liver cirrhosis. Subjects did not have evidence of worsening of clinical and/or laboratory signs of hepatic impairment within 2 months prior to the screening period. Each subject in the normal matched control group was matched for age (± 10 years), sex, and BMI (± 15%, and ≥ 18.0 and ≤ 38.0 kg/m^2) with a subject in the severe hepatic impairment group.

Duration of Treatment: 1 day

Test Product, Dose, Mode of Administration, and Lot No.:

The test product administered to all subjects was TAF 25 mg (1 × 25 mg tablet), administered in the morning with 240 mL of water after completion of a standardized, moderate-fat meal (~600 calories, 25% to 30% fat).

The lot number for the TAF 25-mg tablet was CM1401B1.

Reference Therapy, Dose, Mode of Administration, and Lot No.: None.

Criteria for Evaluation:

Efficacy:

No efficacy analyses were performed for this report.

Pharmacokinetics:

On Day 1, intensive PK sampling occurred predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120, and 144 hours postdose. Plasma concentrations of TAF and its metabolite (TFV) were determined and the following pharmacokinetic parameters were evaluated: AUC_{inf}, AUC_{last}, C_{max}, C_{last}, T_{max}, T_{last}, λ_z, $t_{1/2}$, $\%AUC_{exp}$, CL/F, and V_z/F.

Percent protein binding in plasma was determined at 0.5, 1, 2, and 3 hours postdose for TAF and TFV.

Urine samples for PK analysis were also collected predose and at postdose intervals between 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours, 48 to 60 hours, 60 to 72 hours, 72 to 96 hours, 96 to 120, and 120 to 144 hours, but were not analyzed.

Safety:

Safety was assessed during the study by clinical laboratory tests, electrocardiogram (ECG), physical examinations including vital signs at various time points during the study, and by documentation of adverse events (AEs) and concomitant medications throughout the study.

Statistical Methods:

Efficacy:

No efficacy analyses were performed for this report.

Pharmacokinetics:

PK parameters were summarized for individual subjects in the PK analysis set and summary statistics were provided for each analyte (where possible) evaluated in the study.
Individual subject concentration data and individual subject PK parameters (including percentage of protein binding of TAF and TFV were listed for all subjects and summarized for subjects in the corresponding PK analysis set by hepatic function group.

For PK parameter data, the geometric mean, geometric mean 95% CI, and the mean and standard deviation of the natural-log transformed values were also presented.

Safety:

Safety data were listed by subject and summarized by hepatic function group.

Treatment-emergent AEs were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18. All AEs, serious adverse events (SAEs), and AEs leading to discontinuation of study drug were listed by subject.
The frequency of subjects who experienced AEs was summarized by hepatic function group.
Adverse events were also summarized by relationship to study drug and severity.

Listings of individual subject laboratory results were provided. The incidence of treatment-emergent graded laboratory abnormalities was summarized by hepatic function group.

Individual data for vital signs measurements and 12-lead safety ECG results were summarized by hepatic function group.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 20 subjects were enrolled in the study with 10 subjects in each of the treatment groups (ie, severe hepatic impairment and normal matched control). All 20 subjects received study drug and completed the study. Demographic and baseline characteristics were generally balanced between the 2 treatment groups. Most of the subjects were white (95.0%, 19 subjects), non-Hispanic or Latino (65.0%, 13 subjects) with an even number of male and female subjects (50.0% in each group). Subjects had a mean (SD) age of 56 (8.2) years (range: 41 to 69 years), a mean (SD) BMI of 27.9 (4.05) kg/m^2, a mean (SD) CL_{cr} (Cockcroft-Gault) of 122.522 (30.755) mL/min, and a mean (SD) CL_{cr} (Cockcroft-Gault – ideal body weight) of 96.962 (26.549) mL/min.

Efficacy Results: No efficacy analyses were performed for this report.

Pharmacokinetics Results:

The plasma exposure parameters of TAF (AUC_{inf}, AUC_{last}, and C_{max}) were lower in subjects with severe hepatic impairment compared with normal matched control subjects, with geometric least-squares means (GLSMs) ratios (%) of 54.04%, 51.20%, and 45.10%, respectively. Similar to TAF, lower plasma exposures of TFV were observed in the severe hepatic impairment group compared with the normal matched control group. The GLSM ratios (%) of TFV were 63.06% (AUC_{inf}), 62.04% (AUC_{last}), and 89.88% (C_{max}).

PK Parameter	Severe Hepatic Impairment Group (N = 10)	Normal Matched Control Group (N = 10)	GLSM Ratio (%) (90% CI)
TAF 25 mg: Mean (%CV) (TAF PK Analysis Set)			
AUC_{inf} (ng•h/mL)	120.6 (28.2)	228.2 (37.4)	54.04 (41.98, 69.56)
AUC_{last} (ng•h/mL)	113.1 (27.3)	225.7 (37.7)	51.20 (40.11, 65.36)
C_{max} (ng/mL)	79.6 (49.4)	176.0 (45.3)	45.10 (31.66, 64.25)
TAF 25 mg: Mean (%CV) (TFV PK Analysis Set)			
AUC_{inf} (ng•h/mL)	219.9 (54.0)	304.0 (23.8)	63.06 (42.90, 92.70)
AUC_{last} (ng•h/mL)	184.2 (54.2)	256.7 (23.3)	62.04 (41.92, 91.82)
C_{max} (ng/mL)	7.5 (52.4)	7.6 (24.0)	89.88 (64.77, 124.72)

The lower mean total TAF exposures observed were accompanied by an increase of free fraction (as percent unbound TAF) in subjects with severe hepatic impairment (37.8%) compared with normal matched control subjects (20.4%). When the free fraction was considered, the free TAF exposures were comparable between the 2 study groups (AUC_{last} of 41.7 ng•h/mL and AUC_{inf} of 42.8 ng•h/mL in the severe hepatic impairment group versus AUC_{last} of 46.0 ng•h/mL and AUC_{inf} of 46.5 ng•h/mL in the normal matched control group). The percent unbound TFV was high in all subjects (> 95%) regardless of hepatic status.

Exploratory analyses indicated no clinically relevant correlations between TAF or TFV exposures (total concentrations) versus baseline CPT score. When TAF exposures (total concentrations) in all subjects were plotted against the individual laboratory components (ie, albumin, total bilirubin, and prothrombin time or international normalized ratio [INR]), correlations were consistent with the lower PK exposures of TAF and the characteristics of the severe hepatic impairment group. In severe hepatic impairment subjects, lower albumin values, higher total bilirubin, prolonged prothrombin time, and higher INR were correlated with lower TAF exposures. Similar but less prominent trends were observed with TFV. When the free fraction of TAF was considered, no significant correlation was observed between the free TAF exposures and the individual laboratory components of the CPT score.

Safety Results:

No life-threatening (Grade 4) AEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE. One subject in the severe hepatic impairment group had an SAE of Grade 3 hepatic failure during the posttreatment follow-up phase of the study that was assessed by the investigator as unrelated to study drug.

At least 1 AE occurred in 4 subjects in the severe hepatic impairment group and 3 subjects in the normal matched control group. Most AEs were mild in severity and considered unrelated to treatment. Adverse events in at least 2 subjects in either group included mild headache and mild nausea; all other AEs occurred in at most 1 subject per group.

No clinically relevant changes from baseline in median values in any hematology or chemistry parameter for any group were noted. Most of the laboratory abnormalities were either Grade 1 or 2 in severity; no Grade 4 abnormalities occurred. No clinically significant changes in vital signs or safety ECGs were observed during this study.

CONCLUSIONS:

The conclusions of Study GS-US-320-1615 are as follows:

- Total (bound and unbound) TAF exposure (AUC_{last}) was 49% lower in subjects with severe hepatic impairment relative to normal matched control subjects; however, due to an increase of free fraction (ie, as percent unbound TAF) in subjects with severe hepatic impairment, the free TAF exposure was comparable between the 2 study groups. Accordingly, as the free TAF moiety is associated with therapeutic effect, no change in TAF efficacy is expected in patients with severe hepatic impairment.
- Dose adjustment of TAF is not necessary for patients with severe hepatic impairment
- A single dose of TAF 25 mg was safe and well tolerated by subjects with severe hepatic impairment and normal matched control subjects.