FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1b Randomized, Open Label, Active-Controlled Study to Assess the Safety, Viral Kinetics, and Anti-HBV Activity of GS-7340 in Treatment-Naive Adults with Chronic Hepatitis B (CHB) Infection
Name of Test Drug:	Tenofovir alafenamide (TAF; previously referred to as GS-7340)
Dose and Formulation:	TAF 8-, 25-, and 40-mg tablet TDF 300-mg tablet
Indication:	Hepatitis B virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-320-0101
Phase of Development:	Phase 1b
IND No.: **EudraCT No.:**	115,561 2011-004586-33
Study Start Date: **Study End Date**	20 December 2011 (First Subject Screened) 30 April 2013 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Kosh Agarwal, MD FRCP Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: John Flaherty, PharmD Telephone: PPD Fax: PPD
Report Date:	15 November 2013

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-320-0101:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: Study GS-US-320-0101: A Phase 1b Randomized, Open Label, Active-Controlled Study to Assess the Safety, Viral Kinetics, and Anti-HBV Activity of GS-7340 in Treatment-Naive Adults with Chronic Hepatitis B (CHB) Infection
Investigators: This was a multicenter study.
Study Centers: There were a total of 12 sites: 3 sites each in Australia, Canada, and United Kingdom, 2 sites in the United States, and 1 site in New Zealand,
Publications: Kosh Agarwal, Scott K. Fung, Tuan T. Nguyen, Wendy Cheng, Eric Sicard, Stephen D. Ryder, John F. Flaherty, Eileen Lawson, Sally Zhao, Mani Subramanian, John G. McHutchison, Edward J. Gane, Graham R. Foster. Twenty Eight Day Safety and Efficacy of Tenofovir Alafenamide (TAF) Fumarate in Chronic Hepatitis B (CHB) Patients. Sixty fourth Annual Meeting of the American Association for the Study of Liver Diseases, November 1-5, 2013, Washington, DC. Abstract #973.
Study Period: 20 December 2011 (First subject screened) 30 April 2013 (Last subject observation)
Phase of Development: Phase 1b

Objectives:

The primary objective of this study was as follows:

- To evaluate the differences in short-term antiviral activity between doses of tenofovir alafenamide (TAF; previously referred to as GS-7340) (8, 25, 40, and 120 mg) with respect to the time weighted average change from baseline through Week 4 ($DAVG_4$) in serum hepatitis B virus (HBV) deoxyribonucleic acid (DNA) (log_{10} IU/mL)

The secondary objectives of this study were as follows:

- To compare the short-term antiviral activity of TAF compared with tenofovir disoproxil fumarate (TDF) 300 mg
- To characterize the viral dynamics of HBV DNA associated with the use of TAF through 28 days of therapy
- To investigate the plasma pharmacokinetics (PK) of tenofovir (TFV) and TAF following single and multiple doses of TAF and the PK of TFV following single and multiple doses of TDF
- To characterize the safety of TAF through 28 days of therapy

The exploratory objectives of this study were as follows:

- To characterize the changes in quantitative hepatitis B surface antigen (HBsAg) through 28 days of therapy
- To characterize the changes in alanine aminotransferase (ALT) level through 28 days of therapy
- To characterize the kinetics of viral rebound in subjects during follow-up who chose not to continue on an oral anti-HBV therapy
- To investigate the effects of TAF and TDF on bone and renal biomarkers during and following 28 days of therapy

Methodology: This Phase 1b, randomized, open label, active-controlled study assessed the safety, viral kinetics, and anti-HBV activity of TAF in adult subjects with CHB infection over 28 days of therapy.

Subjects were screened within 45 days prior to study drug dosing. Following screening and baseline/Day 1 assessments, 51 eligible subjects were enrolled and randomized 1:1:1:1:1 to receive treatment with TAF at 8, 25, 40, or 120 mg or TDF 300 mg orally once daily. Subjects came in for a visit at the investigational site on baseline/Day 1, and Days 2, 5, 8, 10, 15, 19, 22, 29/Early Termination (ET), Follow-up Visit 1 (15 days after last dose), and Follow-up Visit 2 (30 days after last dose).

Hepatitis B viral DNA levels were measured at all visits starting at screening and at 4 and 8 hours following dosing on Day 1. Assessment of adverse events (AEs) and concomitant medications continued throughout the duration of the study. Laboratory analyses, physical examinations including vital signs, and electrocardiograms (ECGs) were performed at defined intervals throughout the study.

All subjects were followed for safety for 30 days after the 28-day treatment.

An optional blood sample was obtained for exploratory pharmacogenomic discovery research at any time during the study or at a separate poststudy visit, if necessary. Subjects who agreed to have blood drawn for pharmacogenomic research signed a separate informed consent form.

Number of Subjects (Planned and Analyzed):
Planned: 50 subjects
Analyzed: 51 subjects

TAF 8 mg: 10 subjects
TAF 25 mg: 10 subjects
TAF 40 mg: 11 subjects
TAF 120 mg: 10 subjects
TAF 300 mg: 10 subjects

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were males or nonpregnant, nonlactating females with documented CHB infection at least 6 months in duration, treatment naive, 18 to 65 years old, with an estimated creatinine clearance (CL_{cr}) $\geq$ 70 mL/min (using the Cockcroft-Gault method), and noncirrhotic based on recent biopsy or noninvasive assessment.

Duration of Treatment: 28 days of treatment

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

- **TAF (8 mg)**: TAF 8 mg (1 × 8-mg tablet) administered orally once daily for 28 days
- **TAF (25 mg)**: TAF 25 mg (1 × 25-mg tablet) administered orally once daily for 28 days
- **TAF (40 mg)**: TAF 40 mg (1 × 40-mg tablet) administered orally once daily for 28 days
- **TAF (120 mg)**: TAF 120 mg (3 × 40-mg tablet) administered orally once daily for 28 days

The lot numbers of TAF administered was the following:

TAF 8 mg: CM1101B1, CM1101B1-A, CM1201B1, CM1201B1-A
TAF 25 mg: CM1102B1, CM1102B1-A, CM1202B1, CM1202B1-A
TAF 40 mg: CM1103B1, CM1103B1-A, CM1203B1-A and CM1203B1-A

Reference Therapy, Dose, Mode of Administration, and Batch No.:

- **TDF (300 mg)**: TDF 300 mg (1 × 300-mg tablet) administered orally once daily for 28 days

TDF 300 mg: FDB084, 02008946, 02008946 A

Criteria for Evaluation:

Efficacy: Subjects who were enrolled in the study prior to Protocol Amendment 1, dated 06 June 2012, had blood samples for HBV DNA testing collected at screening, predose, 4, 8, and 12 hours postdose on Days 1, 2, and 3, predose on Days 5, 8, 10, 15, 19, 22, 29 and follow up visits 1 and 2.

Protocol Amendment 1 changed the timepoints for blood sample collection for HBV DNA testing to the following: screening, predose, 4 and 8 hours postdose on Day 1, predose on Days 2, 5, 8, 10, 15, 19, 22, Day 29, and follow up visits 1 and 2.

Pharmacokinetics: Subjects who were enrolled in the study prior to Protocol Amendment 1, dated 06 June 2012, had blood samples collected for PK assessment at screening, predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours postdose on Day 1, predose, 4, 8, 12 hours postdose on Days 2 and 3, and on Days 5, 8, 10, 15, 19, 22, and 29.

Protocol Amendment 1 changed the timepoints for blood sample collection for PK assessment to the following: predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours postdose on Day 1, predose on Days 2, 5, 8, 10, 15, 19, and 22, and on Day 29.

Safety: Safety assessments included monitoring of AEs and concomitant medication, clinical laboratory analyses, physical examinations, 12-lead ECGs, and vital sign measurements at prespecified intervals throughout the study.

Statistical Methods:

Efficacy: For each of the 4 TAF treatment groups and TDF treatment group, only summary statistics were reported for both the primary and secondary endpoints

Pharmacokinetics: Plasma TAF and TFV PK parameters were summarized by treatment group using descriptive statistics (including mean, geometric mean, median, minimum, maximum, and sample size). Dose proportionality of TAF was explored using a power model and a linear fixed effect model.

Safety: Incidence of treatment-emergent AEs and graded laboratory abnormalities were summarized by treatment group. Changes in renal and bone biomarkers were summarized by treatment group.

SUMMARY – RESULTS:

Subject Disposition and Demographics:

A total of 112 subjects were screened, 61 were screen failures, and 51 eligible subjects were randomized into the study. Ten subjects received TAF 8 mg, 10 subjects received TAF 25 mg, 11 subjects received TAF 40 mg, 10 subjects received TAF 120 mg, and 10 subjects received TDF 300 mg. A total of 50 subjects completed the study, 1 subject completed study drug treatment and was subsequently lost to follow-up.

Overall, the majority of subjects were male (66.7%), and of Asian descent (56.9%). Of the 51 randomized subjects, 27 (52.9%) and 24 (47.1%) were hepatitis B early antigen (HBeAg)-negative and HBeAg-positive, respectively. Median age among groups ranged from 34.0 years in the 8- and 25-mg TAF groups, to 40.0 and 41.5 years in the 40- and 120- mg TAF groups, respectively; median age in the TDF group was 33.5 years. The most common HBV genotype at enrollment was genotype C (16/51; 31.4%), with similar proportions within groups of other genotypes: A (7/51; 13.7%), B (10/51; 19.6%), D (9/51; 17.6%), and E (9/51; 17.6%). The distribution of HBV genotypes was similar within groups, with the exception of a higher proportion (5 of 11 [45.5%]) of subjects in the 40-mg TAF group having genotype B.

Efficacy Results: Similar declines in HBV DNA levels were observed across TAF groups as well as in the TDF group over 28 days of treatment. The lack of difference was apparent during a preliminary ad hoc analysis (22 subjects) of HBV DNA levels performed as a component of the EOP2 submission to the FDA for the TAF HIV development program, and confirmed when a second ad hoc analysis (51 subjects completing 28 days of treatment) was conducted for a Pre-Phase 3 submission to the FDA for the TAF HBV development program. Given this, the inferential comparison between TAF treatment groups to select the optimal dose and noninferiority assessment between the TAF optimal dose and TDF based on $DAVG_4$, which were planned in the study protocol, were not done for final analysis. Only summary statistics were provided for the primary and secondary efficacy endpoints.

The median $DAVG_4$ for serum HBV DNA after 28 days of treatment were −2.18, −2.05, −1.69, −2.15, and −2.31 $\log_{10}$ IU/mL in TAF 8, 25, 40, 120 mg and TDF 300 mg, respectively. Median $DAVG_1$, $DAVG_2$, and $DAVG_3$ were comparable across all TAF treatment groups, except TAF 40 mg and were comparable to the TDF group. As early as

Week 2, smaller DAVG values were seen in the TAF 40-mg group which is reflective of the lower baseline HBV DNA values seen in this treatment group as some subjects had reached the lower limit of assay detection (29 IU/mL) prior to Week 2.

All treatment groups demonstrated similar viral suppression over the treatment duration of 28 days (4 weeks), with no perceivable differences in the potency of TAF across the dose range of 8 to 120 mg. Viral suppression with TAF 8, 25, 40, and 120 mg was comparable with that seen with TDF 300 mg over 4 weeks. Consistently smaller declines in HBV DNA, and slightly lower median change from baseline in HBV DNA at Day 29 were observed in the TAF 40-mg group which is likely due to lower baseline HBV DNA values in comparison to the other groups. In the TAF 40-mg group, the first quartile (Q1) at baseline (3.42 $\log_{10}$ IU/mL) was the smallest among all groups indicating more subjects with lower baseline values were randomized into this group. Consistent with this finding, in the TAF 40-mg group, 8 of 11 subjects (72.7%) were HBeAg- and mean changes in HBV DNA were similar for this group compared to the other TAF groups and TDF.

Median first phase decay slopes were −0.101, −0.090, −0.071, −0.097, and −0.087 $\log_{10}$ IU/mL for the TAF 8-, 25-, 40-, 120-mg, and TDF 300-mg treatment groups, respectively. No inferential comparisons were made between the TAF and TDF treatment groups.

Over 28 days of treatment, ALT levels changed minimally across treatment groups. Consistent slight declines in median ALT levels were observed in the TAF 8- and 25-mg groups, whereas consistent slight increases or no change in ALT levels were observed in the TAF 40-and 120-mg groups. At Day 29, median change from baseline in ALT was greatest for the TAF 25-mg group (−9.0 U/L) followed by the TAF 8-mg group (−2.5 U/L). The TDF group showed fluctuations in median change from baseline in ALT over the treatment period with a median change of 0 U/L at Day 29. During the 4 week follow up period, persistent slight declines in ALT were seen in the TAF 8- and 25-mg groups, while ALT levels remained relatively stable in the other two groups (40- and 120-mg). At the end of the study (follow-up week 8), the median change from baseline in ALT level in the TDF 300-mg group (−4.0 U/L) was comparable with the TAF 8- and 25-mg groups (−7.5 U/L and −5.5 U/L, respectively).

No discernible changes from baseline in quantitative HBsAg levels after 28 days of treatment were observed. The median change from baseline at day 29 was the following: 0.00 $\log_{10}$ IU/mL for TAF 8 and 25 mg, −0.02 $\log_{10}$ IU/mL for TAF 40 and 120 mg, and 0.04 $\log_{10}$ IU/mL for TDF 300 mg.

Although allowed by protocol, the majority of subjects did not receive oral anti-HBV therapy during the follow-up period of the study. Overall, 10 of 10 subjects (100%) in the TAF 8-mg group, 9 of 10 (90%) subjects in the 25-mg group, 10 of 11 subjects (91%) in the TAF 40-mg group, 8 of 10 subjects (80%) in the TAF 120-mg group, and all 10 subjects (100%) in the TDF 300-mg group elected not to receive oral antiviral therapy. Four subjects elected to receive antiviral therapy during the follow-up phase of the study. One subject (Subject PPD in the TAF 25-mg group and 2 subjects (Subject PPD and Subject PPD in the TAF 120-mg group initiated treatment with entecavir on Study Day 29. One subject (Subject PPD in the TAF 40-mg group initiated treatment with entecavir on Study Day 56. The median HBV DNA levels at Day 29 for subjects who did not receive

oral anti-HBV therapy are 3.98, 3.45, 2.12, 1.69, and 1.74 log_{10} IU/mL in the TAF 8-, 25-, 40-, 120- mg and TDF 300-mg groups, respectively. By the end of the study, follow-up Week 8, median HBV DNA levels had returned toward baseline levels. The median changes from Day 29 at follow-up Week 8 for subjects who did not have oral anti-HBV therapy during the follow-up period in the TAF 8-, 25-, and 120-mg groups (2.25, 2.24, and 2.17 log_{10} IU/mL, respectively) was comparable to the median change in subjects from the TDF 300-mg group (2.21 log_{10} IU/mL). The TAF 120-mg group showed a lag in the smallest increase in HBV DNA levels from Day 29 until follow-up Week 6; however, from follow-up Week 6 to follow up Week 8, the levels in this group increased to values comparable to the other groups, including the TDF group.

Pharmacokinetic Results: At the dose of TAF 25 mg, mean TFV exposure (AUC_{inf}) was reduced by 92% in comparison with TDF 300 mg. The TAF dose of 25 mg was selected as it is consistent with exposures seen in the HIV program (GS-US-120-0104, GS-120-1101) and offers the greatest opportunity to demonstrate non-inferior efficacy to TDF 300 mg in Phase 3 studies. Furthermore, the incremental reduction in TFV exposure with TAF 8 mg compared with TAF 25 mg was only 5% and was not expected to offer an important safety advantage over TAF 25 mg.

Safety Results: All 51 randomized subjects completed treatment and 50 of 51 subjects completed the study. One subject, Subject PPD from the TAF 120-mg group, missed the Day 29 visit; however, the subject's drug accountability record and treatment completion CRF page indicated this subject had completed the study treatment. The mean exposure time for subjects in TAF 8, 25, 40 mg, and TDF 300 mg was 28 days. The mean exposure time for subjects in TAF 120-mg group was 27.4 days since Subject PPD missed the Day 29 visit as described previously.

Similar frequencies of AEs occurred while receiving TAF 8 mg (7 of 10 subjects [70.0%]), TAF 25 mg (6 of 10 subjects [60.0%]), TAF 40 mg (6 of 11 subjects [54.5%]), TAF 120 mg (8 of 10 subjects [80.0%]), and TDF 300 mg (5 of 10 subjects [50.0%]). All AEs reported were Grade 1 or Grade 2 in severity. No Grade 3 or Grade 4 AEs were reported. Adverse events reported by the Investigator as treatment related were also Grade 1 or Grade 2 in severity. No serious adverse events (SAEs), deaths, pregnancies, or AEs leading to the interruption of study drug or discontinuation were reported.

The most frequently reported AEs (ie, those occurring in 2 or more subjects during any treatment) included headache (2 subjects [20.0%] in the TAF 8-mg group, 3 subjects [30.0%] each in the TAF 25-mg and TAF 120-mg groups); fatigue (2 subjects [18.2%] in the TAF 40-mg group and 3 subjects [30.0%] each in the TAF 8-mg and TAF 120-mg groups); nausea (2 subjects [20.0%] in the TAF 8-mg group); constipation (3 subjects [30.0%] in the TAF 8-mg group); cough (2 subjects [20.0%] in the TAF 40-mg group); and dizziness (2 subjects [20.0%] in the TDF 300-mg group). The remaining AEs occurred in 1 subject each receiving study treatment.

Eighteen of 51 subjects had an AE considered by the investigator to be study drug related; 2 of 10 subjects (20.0%) receiving TAF 8 mg, 4 of 10 subjects (40.0%) receiving TAF 25 mg, 3 of 11 subjects (27.3%) receiving TAF 40 mg, 4 of 10 subjects (40.0%)

receiving TAF 120 mg, and 5 of 10 subjects (50.0%) receiving TDF 300 mg. Nausea, reported in 5 subjects (2 subjects who received TAF 8 mg, 1 subject each who received 25 mg or 40 mg, and 1 subject who received TDF 300 mg), and fatigue, 3 subjects (1 subject each in TAF 40 and 120 mg, and TDF 300 mg) were the most frequently reported AEs considered study drug related by the investigator. Adverse events considered study drug related by the investigator that occurred in only 1 subject each included constipation, arthralgia, and loss of libido (TAF 8 mg); pain in extremity, abdominal distension, and change of bowel habit (TAF 25 mg); lethargy and somnolence (TAF 40 mg); sleep disorder, myalgia, influenza (TAF 120 mg); and dyspepsia, dysgeusia, otitis media, polyuria, increased appetite, and oropharyngeal pain (TDF 300 mg).

Most AEs experienced by subjects in all treatment groups were Grade 1 in severity. Grade 2 AEs were reported in 1 of 10 subjects (10.0%) receiving TAF 8 mg (Subject PPD [anxiety]), 1 of 10 subjects (10.0%) receiving TAF 25 mg (Subject PPD [headache]), 4 of 10 subjects (40.0%) receiving TAF 120 mg (Subject PPD [fatigue], Subject PPD [hypertension], Subject PPD [vomiting], and Subject PPD [influenza]), and 2 of 10 subjects (20.0%) receiving TDF 300 mg (Subject PPD [nausea] and Subject PPD [folliculitis]). Of these Grade 2 (moderate) AEs, none were considered serious and fatigue, nausea, vomiting, and influenza were considered by the investigator to be related to study drug.

The majority of treatment-emergent laboratory abnormalities were reported as Grade 1 or Grade 2 as the highest toxicity grade for a given parameter. Grade 3 treatment emergent laboratory abnormalities were reported in 3 of 11 subjects (27.3%) receiving TAF 40 mg (Subject PPD had Grade 3 elevated creatine kinase [2472 U/L] on Day 29, Subject PPD had Grade 3 glycosuria [+3] on Day 29, and Subject PPD had Grade 3 hematuria [+3] on Day 30), 2 of 10 subjects (20.0%) receiving TAF 120 mg (Subject PPD had Grade 3 ALT elevation on Day 43 [319 U/L] and Grade 3 ALT elevation [394 U/L] and AST elevation [190 U/L] on Day 58 during the off treatment follow-up period, and Subject PPD had Grade 3 amylase elevation on Day 8 [269 U/L] and Day 15 [224 U/L]). One of 10 subjects (10.0%) receiving TDF 300 mg (Subject PPD had Grade 3 amylase elevation on Day 8 [266 U/L] and Day 29 [230 U/L].

No subject experienced a Grade 4 treatment-emergent laboratory abnormality during this study.

A total of 7 subjects (1 subject receiving TAF 8 mg, 2 subjects receiving TAF 25 mg, 2 subjects receiving TAF 40 mg, 1 subject receiving TAF 120 mg, and 1 subject receiving TDF 300 mg) had Grade 1 increases in ALT and a total of 2 subjects (1 subject each in the TAF 40- and 120-mg group) had Grade 2 increases in ALT. One subject in the TAF 120-mg group (Subject PPD had a Grade 3 increase in ALT.

Subjects who received either TAF 8, 25, or 40 mg for 4 weeks consistently exhibited small increases from baseline in median LDL and cholesterol, whereas subjects in the TAF 120-mg group and TDF 300-mg group consistently exhibited small decreases in LDL and cholesterol at Day 29. Conversely, subjects in the TAF 8-, 25-, and 40-mg groups exhibited small but variable effects in HDL cholesterol at Day 29, while subjects in the TAF 120-mg and TDF 300-mg groups exhibited small decreases in HDL cholesterol at Day 29. In all treatment

groups, the cholesterol to HDL ratio remained essentially unchanged at Day 29. The median changes from baseline at Day 29 in triglycerides were decreased for all groups except for the TAF 40-mg group. Given these results, the impact of TAF and TDF on plasma lipid profiles over 4 weeks was not considered clinically relevant.

Glycosuria associated with Grade 2 elevated serum glucose was reported for 2 subjects. One subject (Subject PPD in the TAF 8-mg group experienced Grade 2 glycosuria (+2) on Day 29. The Grade 2 elevated serum glucose (193 mg/dL) for this subject resolved at the Week 6 follow-up visit. The second subject (Subject PPD [TAF 40-mg group]) also experienced Grade 3 glycosuria (+3) on Day 29; the Grade 2 elevated serum glucose (212 mg/dL) for this subject resolved at the Week 6 follow-up visit. This subject had a history of diabetes mellitus.

Throughout the study, median change from baseline in serum creatinine levels was lower or comparable in the TAF 8-, 25-, 40-, and 120-mg groups in comparison with the TDF 300-mg group. After 28 days of treatment, the median change (percent change) from baseline in the TAF 8-, 25-, 40-, and 120-mg groups were 0.01 (1.60%), 0.02 (1.66%), 0.03 (3.45%), and 0.00 (0.00%) mg/dL, respectively, whereas for the TDF 300-mg group it was 0.08 (9.82%). There was no difference in the change from baseline in creatinine levels between the 2 lowest dose groups (TAF 8- and 25-mg groups) and the high-dose group (TAF 120-mg group). No subjects had experienced a treatment-emergent graded serum creatinine abnormality during the study.

Creatinine clearance was calculated using both the Cockcroft-Gault method and the CKD-EPI equation. The CL_{cr} as calculated by the CKD-EPI equation was slightly lower than CL_{cr} calculated by Cockcroft-Gault method however, the overall trend was the same for both methods. After 4 weeks of dosing, there were smaller changes in CL_{cr} at Day 29 seen in subjects receiving TAF compared with TDF. Furthermore, there were no notable differences in CL_{cr} change among the 2 lowest dose groups (TAF 8 and 25 mg) and the highest TAF dose tested (TAF 120 mg). An early decline in CL_{cr}, similar to that observed in the TDF group was seen in the TAF 40-mg group; however, by Day 29 the change in CL_{cr} in this group was similar to the other TAF groups.

No subjects reported any AEs relating to bone or experienced any treatment-emergent bone related clinical laboratory abnormality. At baseline, there were no differences in median bsAP or serum alkaline phosphatase levels among treatment groups. Median change from baseline in bsAP was similar in the TAF 8-, 25-, and 120-mg groups whereas the median change in the TAF 40-mg group was comparable with the TDF 300-mg group. The serum alkaline phosphatase levels after 28 days of treatment were similar for the TAF 25-, 40-, and 120-mg groups whereas TAF 8-mg was comparable with the TDF 300-mg group.

No clinically relevant changes in vital signs measurements or ECG results were reported during this study. Ten subjects (1 subject each in the TAF 8-mg and 120-mg groups, 2 subjects each in the TAF 25-mg and 40-mg groups, and 4 subjects in the TDF 300-mg groups) had abnormal physical findings that were reported as AEs during the study. Of the 10 subjects, 9 subjects had abnormal physical findings that were considered Grade 1 AEs and 1 subject had a Grade 2 AE of folliculitis (Subject PPD Five of the 10 subjects had abnormal physical findings that were considered study drug related AEs.

CONCLUSIONS:

The conclusions of this Phase 1b randomized, open-label, active-controlled study of TAF monotherapy in subjects with CHB infection are as follows:

- Tenofovir alafenamide was safe and well tolerated. The safety profile for TAF did not differ among dose groups and was similar to that of TDF. Furthermore, at Day 29, declines in CLcr with TAF 25 mg were found to be smaller than those seen with TDF 300 mg.
- At the TAF doses studied, no differences were observed in HBV DNA declines among the TAF groups and in comparison with the TDF 300-mg group at Day 29.
- TAF exposures were dose proportional and linear on Day 1 over the dose range of 8-120 mg.
- At lower TAF doses (8 mg and 25 mg), substantial reductions in TFV exposures (≥ 92%) relative to TFV exposures with TDF 300 mg were observed. The reduced TFV exposure seen with TAF 25 mg in CHB subjects is comparable to the reduction seen in HIV infected subjects treated with TAF 25 mg as a standalone product. Furthermore, the reduction in TFV exposure with TAF 25 mg in CHB subjects is therapeutically consistent with that seen with TAF 10 mg when included in the E/C/F/TAF STR currently under evaluation in HIV infected subjects (due to an inhibitory drug interaction between TAF and cobicistat included in the STR).

These data support the selection of TAF 25 mg for future pivotal studies in subjects with CHB.