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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review
 Tanvir Bell, MD
 NDA 208464
 Vemlidy (Tenofovir Alafenamide)

CLINICAL REVIEW

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Review Completion Date	October 7, 2016
Established Name	Tenofovir Alafenamide
(Proposed) Trade Name	Vemlidy™
Applicant	Gilead
Formulation(s)	Tablet
Dosing Regimen	25 mg tablet orally (po) once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of chronic hepatitis B in adults
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Recommended Indication(s)/Population(s) (if applicable)	Treatment of chronic hepatitis B in adults with compensated liver disease

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The current application requests approval of Tenofovir Alafenamide (TAF) for treatment of Chronic Hepatitis B virus infection (CHB) in adults. This agent is a prodrug of tenofovir (TFV) a nucleotide analogue that interferes with Hepatitis B viral replication. Another tenofovir prodrug, tenofovir disoproxil fumarate (TDF), has been approved for treatment of CHB since 2008. The major difference between TDF and TAF relates to cellular uptake in target cells. TDF is not readily absorbed into target cells but rather delivers TFV across the digestive tract into the blood stream where TFV is generated from where it enters target cells. TAF is more readily absorbed in target cells where the active agent TFV-diphosphate is generated at higher concentration. This absorption differential permits TAF to be given at doses that are 90% lower than TDF. TAF was approved as a component of Genvoya® (NDA 207561), Descovy® (NDA 208215), and Odefsey® (NDA 208351) for treatment of HIV in 2015 and 2016, respectively.

A single drug dosage of TAF (Vemlidy™) 25 mg was studied for treatment of CHB in this NDA application. Treatment for CHB is life-long for most subjects, and this application submitted early 48 week study data from the two studies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Forty eight week data from the two Phase 3 trials included in this application provide substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of TAF for treatment of in adults for CHB with compensated liver disease. Study GS-US-302-0108 evaluated Hepatitis B e antigen (HBeAg) negative subjects, while Study GS-US-302-0110 evaluated HBeAg positive subjects. Primary efficacy was measured by virologic response with HBV DNA < 29 IU/mL; and Study 108 TAF treatment results showed HBV DNA < 29 IU/mL of 94%; while Study 110 TAF treatment results showed virologic response with HBV DNA < 29 IU/mL of 64%. These efficacy rates were non-inferior to that seen with TDF at 48 weeks.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tenofovir alafenamide (TAF) is recommended for treatment of adults with Chronic Hepatitis B (CHB). TAF and Tenofovir Disoproxil Fumarate (TDF) are both prodrugs of Tenofovir (TFV), and TAF is more readily absorbed in target cells than TDF and results in less serum exposure to tenofovir. Higher serum tenofovir exposures from TDF may be associated with decreased bone mineral density (BMD) and renal proximal tubular dysfunction. TDF has been approved since 2008 for treatment of CHB and is among the preferred therapy for treatment of CHB. TAF as components of combination pills for treatment of HIV has been approved since 2015. This application supports the approval of TAF for the treatment of CHB in adults with compensated liver disease because of demonstrated efficacy that is non-inferior to TDF.

Two on-going randomized, active-controlled, Phase 3 trials conducted in Hepatitis B e Antigen (HBeAg)-negative and HBeAg-positive subjects with CHB with 48 week data were presented for this NDA application. HBeAg positive patients differ in higher viral loads burden, which often takes years to achieve viral suppression. Efficacy rates by HBV DNA <29 IU/mL were comparable between TAF and TDF with 93-94% in HBeAg negative subjects and 64-67% in HBeAg positive subjects. Hepatitis B surface antigen (HBsAg) loss and HBeAg seroconversion are serologic outcomes used in treatment decisions, and in these 48 week trials rates these rates were low and comparable between treatment arms, less than 1% and 10%, respectively. Across the trials, TAF out performed TDF with respect to ALT normalization, regardless of the upper limit of normal value used. In the face of ongoing viral replication, the relevance of this finding is unknown. Lower response rates were seen in TAF treated subjects with high baseline viral load above 8 log₁₀ IU/ml in HBeAg-positive subjects and in HBeAg-positive cirrhotics.

Some improvements in bone safety were seen in these studies, but concern for symptomatic amylase increase was identified. BMD declines of 5% or greater at the lumbar spine were experienced by 6% of TAF subjects and 20% of TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 3.2% of TAF subjects and 5.7% of TDF subjects. However, the long-term clinical relevance of these changes is not clear. Renal laboratory abnormalities were observed in a similar proportion of subjects treated with TAF and TDF. No proximal tubular dysfunction occurred in either treatment arms. Until additional renal safety information becomes available, renal warnings will be maintained in labeling. A small number of subjects had amylase elevations with adverse events associated with pancreatitis, and one subject had recurrent AEs associated with elevated amylase with rechallenge with TAF. Two subjects switched to alternative CHB treatment. This potential safety signal will be described in the label. Hepatic flares, a known entity that occurs in hepatitis treatment, occurred in approximately 2% and were not associated with HBeAg loss or hepatotoxicity. TAF was associated with less favorable changes in lipid levels, as is seen in HIV treatment trials with TAF.

Treatment for CHB is often prolonged. Efficacy at 96 and 144 week will be important for assessing outcomes and if TAF will offer any specific efficacy benefits compared to TDF. TAF and TDF demonstrated similar efficacy and overall safe side effect profile in 48 week data. The safety benefit of TAF for less BMD loss and differences in renal outcomes need to be monitored and assessed with more data. In addition, lipid changes favoring TDF are important considerations for CHB treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Chronic hepatitis B infection (CHB) causes inflammation of the liver that can lead to long term health problems or death. • Globally it is estimated that 240 million people are infected with HBV with an estimated 700,000 to 1.4 million persons having CHB in the United States (US). • HBV prevalence exists globally with the highest in Africa and Asia. • Hepatitis B e antigen (HBeAg) positive disease is more virulent with high viral loads and increased infectivity than HBeAg negative disease. • Sustained HBV DNA suppression is a goal of therapy. This may lead to Hepatitis B Surface Antigen (HBsAg) loss, ALT normalization, and improvement in liver histology. HBeAb seroconversion is an important outcome in HBeAg positive patients, which leads to less infectivity. • Current candidates for treatment are patients who are in the immune-active phase, where HBV DNA \geq 20,000 IU/mL and have elevated ALT. • There are at least eight known genotypes A, B, C, D, E, F, G, and H. Genotypes C and D are associated with higher progression rates to liver fibrosis. • Potential consequences of untreated CHB are cirrhosis, liver failure, hepatocellular cancer (HCC), or death. 	<p>If untreated, chronic CHB infection is a life-threatening condition, one that affects a large population. Potential consequences of untreated CHB are cirrhosis, liver failure, hepatocellular cancer (HCC), or death. HBV infection is a significant public health concern.</p>
Current Treatment Options	<ul style="list-style-type: none"> • There are six approved therapies for CHB. • The current standard of care is tenofovir disoproxil fumarate (TDF) or adefovir as monotherapy. • TDF works against all HBV genotypes. Genotype D has lower response rates to TDF. • HBV therapy is often lifelong unless HBsAg seroconversion occurs. • TDF has been associated with bone toxicity and renal toxicity. 	<p>The HBV treatment armamentarium would benefit from an option that may mitigate treatment side effects.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons															
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> The efficacy was established in two Phase 3 clinical trials with a total of 866 subjects with 48 week data presented. TAF and TDF are prodrugs of Tenofovir (TFV). TAF produces less serum exposure TFV. The primary efficacy endpoint was HBV DNA < 29 IU/mL. As displayed in the table below, efficacy for TAF was 94% in HBeAg negative subjects and 64% in HBeAg positive subjects at 48 weeks. <table border="1" data-bbox="331 623 1318 748"> <thead> <tr> <th></th> <th colspan="2">108</th> <th colspan="2">110</th> </tr> <tr> <th></th> <th>TAF</th> <th>TDF</th> <th>TAF</th> <th>TDF</th> </tr> </thead> <tbody> <tr> <td>HBV DNA <29 IU/mL</td> <td>94%</td> <td>93%</td> <td>64%</td> <td>67%</td> </tr> </tbody> </table> <ul style="list-style-type: none"> HBsAg loss occurred in <1% of subjects of TAF and TDF. HBeAg seroconversion occurred in 10% of subjects on TAF and TDF. ALT normalization occurred with both TAF and TDF, but differences favoring TAF were observed. Bone mineral density (BMD) decreased by -0.6% in TAF compared with -2.4% in TDF at the lumbar spine and -0.6% compared to -2.0%, respectively, at the femoral neck. Clinically relevant renal parameter changes were not observed in these studies where subjects with high baseline creatinine were enrolled. Biomarkers of renal function had greater decreases with TAF but the significance of these parameters is uncertain. 		108		110			TAF	TDF	TAF	TDF	HBV DNA <29 IU/mL	94%	93%	64%	67%	<p>TAF was non-inferior to TDF in comparing efficacy at 48 weeks.</p> <p>Data from longer treatment duration will be forthcoming for better evaluation of efficacy parameters and differences between TAF and TDF.</p>
	108		110														
	TAF	TDF	TAF	TDF													
HBV DNA <29 IU/mL	94%	93%	64%	67%													
<p><u>Risk</u></p>	<ul style="list-style-type: none"> The safety database for TAF includes the two aforementioned clinical trials and is considered adequate. Furthermore, the safety of TAF is augmented by evaluation of TAF as components in Genvoya®, Descovy®, and Odefsey® in HIV-infected individuals. Nasopharyngitis, upper respiratory tract infection, headache, abdominal pain, fatigue, cough, nausea, and back pain were the most common adverse drug effects that occurred. Increases in amylase levels accompanied by symptoms such as nausea, low back pain, abdominal tenderness, biliary pancreatitis, and pancreatitis 	<p>TAF demonstrated an overall favorable safety profile.</p>															

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>occurred. One subject experienced a positive rechallenge. In two subjects, alternative CHB therapy was needed due to increased amylase levels.</p> <ul style="list-style-type: none"> • Hepatic flares occurred in up to 2% of subjects. • TAF can cause less favorable lipid consequences than TDF with mean increase in LDL of 6 mg/dL on TAF compared to decreased LDL by 11 mg/dL on TDF. Total cholesterol did not change with TAF, but decreased 25 mg/dL on TDF. • Post-hoc analyses showed that subjects with higher baseline HBV DNA above 8 log₁₀ IU/mL did poorer on TAF compared with TDF in HBeAg positive subjects. • Cirrhotics did less well on TAF in Study 110 with 64% efficacy in TAF arm and 67% efficacy in TDF arm. 	<p>Lower efficacy results in subpopulations of viral load >8 log₁₀ IU/mL for HBeAg subjects and cirrhosis will be described in the label.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • Although no significant safety signals were detected in this review, the TAF prescribing information will include safety information contained in the current TDF label, even if the events occurred rarely in the TAF trials: <ul style="list-style-type: none"> ○ Though no cases of new or worsening renal impairment occurred in these Phase 3 trials, Section 5 of the TAF label will include a warning regarding new and worsening renal impairment. ○ Though less declines of BMD occurred in Phase 3 trials with TAF compared with TDF, late presentation of osteomalacia has been described for TDF. Further, the consequence of these changes is uncertain. • Section 5 will also include warning for lactic acidosis per class labeling. • Section 5 will include warning of severe hepatomegaly with steatosis and post treatment severe acute exacerbation of Hepatitis B. 	<p>Safety concerns associated with TAF are adequately addressed in product labeling.</p>

2 Therapeutic Context

Analysis of Condition

Chronic Hepatitis B (CHB) is a serious liver infection caused by the Hepatitis B virus (HBV). Globally it is estimated that 240 million people are infected with HBV with an estimated 700,000 to 1.4 million persons having CHB in the United States. Varying prevalence exists globally with the highest in Africa and Asia.

There are at least eight known genotypes A, B, C, D, E, F, G, and H. The genotypes generally follow geographic distributions and are related to disease progression. Genotypes B and C are common in Asia and are associated with higher levels of alanine aminotransferase (ALT) when compared to other genotypes (Sanbul 2014) and genotypes C and D are associated with higher progression rates to liver fibrosis.

Three phases of CHB have been identified. The immune-tolerant phase is seen primarily in children infected at birth born to HBV-infected mothers. In this phase, HBV is nonpathogenic and these patients are positive for Hepatitis B e Antigen (HBeAg), have high levels of HBV DNA, normal aminotransaminase levels, and minimal pathology on liver biopsy. Most of these patients will move into the immune-active phase during childhood to early adulthood. This phase is characterized by high HBV DNA levels $\geq 20,000$ IU/mL, elevated ALT levels with moderate-to-severe inflammation, or fibrosis in the liver. The transition to immune-inactive phase among adults is $\sim 12\%$ per year (Terrault et al., 2015). The third phase of CHB is the inactive carrier phase, in which patients become HBeAg negative, HBV DNA falls to <200 IU/mL, and aminotransferase levels become closer to normal. Patients in the immune active phase are candidates for treatment.

Potential consequences of untreated CHB are cirrhosis, liver failure, hepatocellular cancer (HCC), or death. Untreated adults with CHB have a cumulative 5-year incidence of cirrhosis of 8-20% and the risk of HCC is 2%-5% (Terrault et al., 2015). CHB contributes to 786,000 deaths annually. Viral host factors that contribute to cirrhosis and HCC include prolonged time to HBeAg seroconversion, development of HBeAg-negative CHB, genotype C infection, and elevated ALT levels (Terrault et al, 2015). The goal of therapy is to achieve loss of Hepatitis B surface Antigen (HBsAg) with conversion to Hepatitis B surface Antibody. However, this occurs either spontaneously or with treatment in $<2\%$ of patients per year. Treatment of CHB with nucleos(t)ide analogues or interferon results in HBV DNA suppression, which is associated with normalization of serum ALT levels, loss of Hepatitis B core Antigen (HBcAg) and improvement of liver histology. Successful suppression of HBV DNA (with or without HBsAg loss) is associated with a significant reduction in long-term liver-related morbidity

and mortality. There is no cure for CHB. The current recommendation is that nucleos(t)ide therapy be continued until there has been loss of HBsAg with conversion to anti-HBsAg, which can require decades of treatment.

2.2. Analysis of Current Treatment Options

There are currently six products approved for treatment of CHB in the US: Pegasys® (pegylated interferon alfa-2a), Epivir-HBV® (lamivudine, 3TC), Hepsera® (adefovir dipivoxil, ADV), Barracluide® (entecavir, ETV), Tyzeka® (telbivudine, LdT), and Viread® (TDF). Pegasys®, pegylated interferon alfa-2a, and PegIntron®, pegylated interferon alfa-2b, are immunostimulatory agents. Pegasys® is approved for adults, while PegIntron® is approved for children. Side effects of pegylated interferon include flu-like symptoms, mood disturbances, cytopenias, and autoimmune disorders in adults. The other five treatment options are nucleos(t)ide analogues and are listed with selected attributable characteristics in the Table 1 below.

Historically, clinical trial efficacy was determined by improvement in liver histology that was obtained by liver biopsy specimens. Liver biopsies usually represent only ~50,000th of the liver and are associated with morbidity (bleeding and infection) and in rare cases mortality. In its place, HBV DNA has emerged as a surrogate marker for efficacy. Most of the recently approved treatments used HBV DNA to support their anti-viral activity. The lower limit of quantification (LLOQ) has changed and become more sensitive over time. For example, when adefovir was approved, the LLOQ was <1000 copies/mL. With the development of more sensitive assays, the LLOQ currently used in clinical trials is <29 IU/mL.

Table 1: Characteristics of nucleos(t)ide analogues for treatment of CHB

Drug	Year of Approval	Dosing	Efficacy Information HBV DNA LLOQ at 48 or 52 weeks	Important safety and tolerability issues
Lamivudine	1998	100 mg po daily	36%-72%	Pancreatitis, Lactic acidosis
Telbivudine	2006	600 mg po daily	60%-88%	Creatinine kinase elevations and myopathy, Peripheral neuropathy, Lactic acidosis
Entecavir	2005	0.5 or 1.0 mg po daily	67%-90%	Lactic acidosis
Adefovir	2002	10 mg po daily	71%	Acute renal failure, Fanconi syndrome, Nephrogenic diabetes insipidus, Lactic acidosis
Tenofovir	2008	300 mg po daily	76%-93%*	Nephropathy, Fanconi syndrome, Osteomalacia, Lactic acidosis

(Adapted from Terrault, et. al., 2015)

*HBV DNA < 400 copies/mL

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tenofovir alafenamide (TAF) is approved as a component of multiple fixed-dose combinations for treatment of HIV-1 infection: Genvoya® (cobicistat/elvitegravir/emtricitabine/TAF), Descovy® (emtricitabine/TAF) and Odefsey® (emtricitabine/TAF/rilpivirine). Importantly, the TFV exposures at a 25 mg dose when given alone are consistent with TAF exposures generated with the TAF 10 mg when coadministered with cobicistat currently approved for HIV infection.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 115,561 for TAF for treatment of chronic CHB was submitted on July 30, 2012. The IND opening study, GS-9883-US-120-0104, was 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 CHB infection. Based on pre-clinical data and the results of Study 0104, the Applicant submitted protocols for two Phase 3 studies (GS-US-320-0108 and GS-US-320-0110) in June 2013. At the time of protocol submission, the Division agreed that the 25 mg dose of TAF was reasonable and to utilize TDF as the active comparator. A pre-NDA interaction (written responses only) occurred in December 2015, and NDA 208464 was submitted on January 11, 2016.

(b) (4)
The protocol for Study GS-US-320-1092 “A randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of Tenofovir Alafenamide (TAF) in adolescents with chronic Hepatitis B Virus infection” was submitted in March 2016 with an amendment in April 2016.

3.3. Foreign Regulatory Actions and Marketing History

TAF is not currently marketed in foreign countries.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Four sites (two in Study GS-US-320-0108 and two in Study GS-US-320-0110) were selected for clinical inspection. These sites were selected primarily on their relatively high enrollment. All four were ex-US sites. The sites were:

- Site #3076. Study 108. PI; Wan-Long Cuang; Kaohsiung Medical University Hospital; Kaohsinung, Taiwan. This site had 31 subjects screened and 16 randomized.
- Site #2757. Study 108. PI: Henry Lik Yen Chan; Prince of Wales Hospital, New Territories, Hong Kong. This site had 38 subjects screened and 24 randomized.
- Site #5691. Study 110. PI: Man Fung Yuen; Queen Mary Hospital. Hong Kong. This site had 79 subjects screened, 44 subjects randomized, and five discontinued.
- Site #02826. Study 110. PI: Scott Fung; Toronto General Hospital. Toronto, Ontario, Canada. This site had 33 subjects screened, 27 randomized, and three

discontinued.

(b) (4)

OSI review was completed and none of the above site inspections indicated serious deviations/findings that would affect the validity or reliability of the submitted data.

4.2. Product Quality

Vemlidy™ tablets are yellow, round, film-coated, debossed with “GSI” on one side and “25” on the other side. Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. It should be stored below 30 °C (86 °F).

4.3. Clinical Microbiology

Please refer to Dr. Sung Rhee’s Review for detailed assessment. Key findings are summarized below.

Antiviral Activity in Cell Culture

The antiviral activity of tenofovir alafenamide was assessed in a transient transfection assay using HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC₅₀ (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC₅₀ value of 86.6 nM. The CC₅₀ (50% cytotoxicity concentration) values in HepG2 cells were greater than 44,400 nM. In cell culture combination antiviral activity studies of tenofovir with the HBV nucleoside reverse transcriptase inhibitors (NRTIs) entecavir, lamivudine, and telbivudine, no antagonistic activity was observed.

Resistance in Clinical Trials

In a pooled analysis of treatment-naïve and treatment-experienced subjects receiving TAF in Studies 108 and 110, genotypic resistance analysis was performed on paired baseline and on-treatment HBV isolates for subjects who either experienced virologic breakthrough (2 consecutive visits with HBV DNA greater than or equal to 69 IU/mL [400 copies/mL] after having been less than 69 IU/mL, or 1.0-log₁₀ or greater increase in HBV DNA from nadir) through Week 48, or had HBV DNA greater than or equal to 69 IU/mL at early discontinuation at or after Week 24. Treatment-emergent amino acid substitutions in the HBV reverse transcriptase domain, all occurring at polymorphic positions, were observed in some HBV isolates evaluated (5/20) from these subjects; however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to TAF.

Cross-Resistance

The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing substitutions associated with HBV NRTI resistance in a transient transfection assay using HepG2 cells. HBV isolates expressing the lamivudine resistance-associated substitutions rtM204V/I (\pm rtL180M \pm rtV173L) and expressing the entecavir resistance-associated substitutions rtT184G, rtS202G, or rtM250V in the presence of rtL180M and rtM204V showed less than 2-fold reduced susceptibility (within the inter-assay variability) to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir also remained largely susceptible to tenofovir alafenamide (less than 2-fold changes in EC₅₀ values); however, the HBV isolate expressing the rtA181V plus rtN236T double substitutions exhibited reduced susceptibility (3.7-fold) to tenofovir alafenamide. The clinical relevance of these substitutions is not known.

Nonclinical Virology

TAF and TDF have a similar resistance profile in cell culture and in clinical trials.

4.4. **Nonclinical Pharmacology/Toxicology**

Please refer to Dr. Claudia Wrzesinski's Pharmacology Toxicology review for more details.

Per agreement with the FDA carcinogenicity studies and a perinatal and postnatal study have not been conducted for TAF registration due to the rapid conversion of TAF to TFV resulting in a lack of TAF exposure in rats and TgRasH2 mice. At the high tenofovir dose in female mice carcinogenicity studies, liver adenomas were increased at tenofovir exposures approximately 167 times those observed after TAF administration in humans. In rats, the study was negative for carcinogenic findings.

The principle target organs of toxicity in animals following oral administration of TAF were the kidney (karyomegaly, tubular degeneration/regeneration), bone (reduction in bone mineral density and mineral content, changes in bone turnover markers and in related hormones), and eye (posterior uveitis in dogs). Chronic administration of TAF led to a dose dependent slight to moderate renal cortical tubular degeneration/regeneration and karyomegaly in the dog as well as renal karyomegaly in the rat. Renal and bone toxicity findings correlate with the known clinical toxicities for TFV.

Minimal to slight infiltration of mononuclear cells of the posterior uvea of dogs was seen in the high dose group with similar severity after 3 and 9 month administration of TAF. Reversibility of the uveitis was seen after a 3 month recovery period. Ocular findings were not seen with TAF in any other animal model (mouse, rat, and monkey) and were not seen with Viread (TDF, prodrug of TFV). At the NOAEL for eye toxicity, the systemic TAF exposure in dogs was lower than in humans; therefore, no safety

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margins were established. The systemic exposure for TFV was 4 times higher than the exposures seen in humans. In clinical trials monitoring for ocular symptoms was included and if necessary followed by an ophthalmological exam, no safety signals were reported for the Genvoya application.

TAF use in women during pregnancy has not been evaluated. TAF is not mutagenic or teratogenic. Preclinical studies using TAF conducted in rats and rabbits did not demonstrate any adverse embryo-fetal effects were observed. TAF is rapidly converted to TDF and TDF doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 14 times higher than the exposures in humans at the recommended daily 25 mg dose of TAF. The TAF NOAEL for reproductive and early embryonic toxicity was 160 mg/kg/day.

4.5. **Clinical Pharmacology**

This section provides a brief summary of the clinical pharmacology of E/C/F/TAF. Please refer to the FDA Clinical Pharmacology Reviews by Dr. Mario Sampson for additional information. Twelve TAF studies were included in the population PK dataset, including studies in healthy volunteers (n=6), HBV-infected subjects (n=2), HIV-infected subjects (n=2), and renal impairment (n=1). This data was flawed by low level TAF concentrations, goodness-of-fit plots overpredicted exposures at low observed concentrations and underpredicted exposures at high observed TAF concentrations.

4.5.1. **Mechanism of Action**

Tenofovir Alafenamide: After cellular entry, TAF is metabolized to its active metabolite, tenofovir-diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain-termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

4.5.2. **Pharmacodynamics**

In the Phase 1b study, GS-US-320-0101, which has completed enrollment, 4 doses (8, 25, 40, and 120 mg) of TAF monotherapy, and TDF 300 mg were evaluated in 51 treatment naïve CHB subjects. To date, all subjects have completed the 28-day dosing period. Preliminary results demonstrate that TAF when given in doses over a range of 8 to 120 mg results in similar HBV DNA declines over 28 days. HBV DNA suppression with TAF is comparable to that of TDF 300 mg. No increased rates of viral suppression were observed with doses of TAF greater than 25mg.

Reviewer comments: Although study GS-US-320-0101 indicated essentially equivalent antiviral activity of the 8 mg and 25 mg dosage, (b) (4) it is likely that the 25 mg dose will have a higher barrier to the development of resistance.

No clinically relevant PK differences due to race and gender have been observed.

In a thorough QT/QTc study TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval.

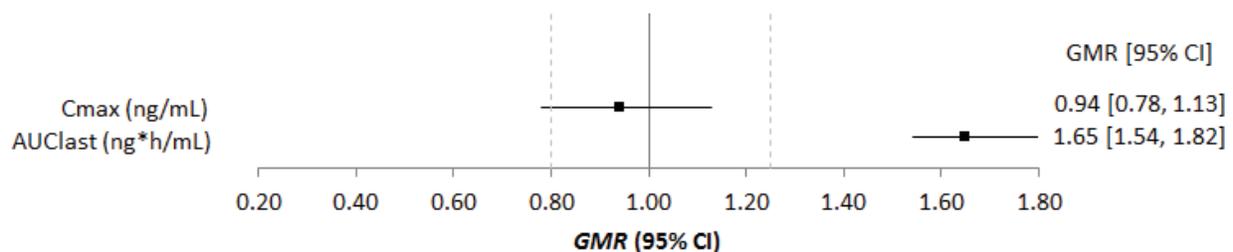
4.5.3. Pharmacokinetics

Review of pharmacokinetic data revealed the following key findings that influence labeling. Contributing rationale is provided in the lower bullet points.

Food effect

- TAF should be taken with food
 - TAF in these Phase 3 studies was given with food.
 - In a single-dose, crossover study evaluating TAF PK under fasted versus fed (high-fat meal) conditions (n=40), TAF exposures were ~40% lower in the fasted state relative to fed state.

Figure 1: TAF exposures changes in food effect study 320-1382.



GMR = geometric mean ratio (fed/fasted); CI = confidence interval.

Source: Mario Sampson, PharmD, clinical pharmacology reviewer

Significant Drug-Drug Interactions

- In coadministration with carbamazepine, 2 tablet of 25 mg of TAF should be given, (b) (4)
 - Carbamazepine (CBZ) is a CYP3A4 and Pgp inducer; TAF is a substrate of Pgp. When coadministered with CBZ, TAF (administered as emtricitabine [FTC, F]/TAF) AUC was reduced 55%.
- Coadministration of with oxcarbazepine or phenobarbital is not recommended.
 - (b) (4)

- (b) (4)
- Coadministration with rifabutin, rifampin, or rifapentine is not recommended.
 - *Same rationale as above regarding CYP3A and Pgp.*

Dosage in patients with renal impairment

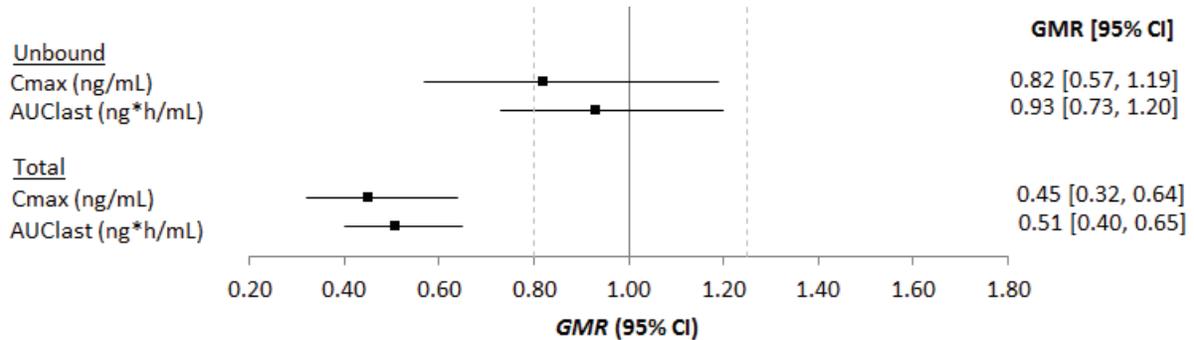
- Further consideration is needed to provide recommended dosing adjustment in subjects with End Stage Renal Disease (ESRD). (b) (4)

- (b) (4)
- In subjects with severe renal impairment versus normal renal function, TAF and TFV exposures were ~2- and ~6-fold higher, respectively in the Genvoya® application. Genvoya® is approved for use in patients with CrCl \geq 30 mL/min. No dosage adjustment is needed in this population.

Dosage in patients with hepatic impairment

- No dosage adjustment is needed in subjects with mild hepatic impairment, and use of TAF in subjects with moderate to severe hepatic impairment is not recommended.
 - A single dose PK study (TAF administered with a moderate-fat meal) was conducted in subjects with severe hepatic impairment (n=10) and matched controls (n=10). In subjects with severe hepatic impairment relative to those with normal hepatic function, total TAF exposures were ~50% lower while unbound TAF exposures were not significantly changed (See Figure below). TFV C_{max} and AUC were 10% and 37% lower in subjects with severe hepatic impairment, respectively. One issue with this study is that a similar food effect must be assumed in both groups and that the exposure differences between the groups are due to different hepatic function.
 - Subjects with compensated liver disease were included in Studies 108 and 110. These subjects were most likely Child-Pugh A Score.
 - Agency Clinical Pharmacologists do not think that unaltered plasma total or unbound exposures are sufficient to support efficacious use in decompensated patients.

Figure 2: Total and Unbound TAF exposures in Subjects with Severe Hepatic Impairment Relative to Subjects with Normal Hepatic Function.



GMR = geometric mean ratio (severe hepatic impairment/normal hepatic function); CI = confidence interval.

Source: Mario Sampson, PharmD, clinical pharmacology reviewer

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

In conjunction with the Phase 1 dose-ranging study described above, the Applicant conducted two adequate and well controlled Phase 3 trials studies comparing TAF to currently approved TDF in HBeAg- and HBeAg+ subjects. Table 2 provides the outline of these trials in which 866 HBV-infected adults were treated with the TAF for 48 weeks.

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Table 2: Listing of Clinical Studies

Trial Identity	Trial Design	Regimen ^a	Treatment Duration ^b	Efficacy Endpoint	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
GS-US-320-0108	Phase 3, Randomized, double-blind study	TAF 25 mg TDF 300 mg	96 W double-blind then 48 W OLE (Submitted 48 W data)	HBV DNA < 29 IU/mL	TAF: 285 TDF: 140 Total: 426	Treatment naïve and experienced CHB HBeAg –	105 centers 17 countries
GS-US-320-0108	Phase 3, Randomized, double-blind study	TAF 25 mg TDF 300 mg	96 W double-blind then 48 W OLE (Submitted 48 W data)	HBV DNA < 29 IU/mL	TAF: 581 TDF: 292 Total: 873	Treatment naïve and experienced CHB HBeAg +	161 centers 19 countries
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							
GS-US-320-0101	Phase 1b, randomized, open-label, active controlled study	TAF: 8, 25, 40, and 120 mg; TDF 300 mg	28 days	n/a	TAF: 41 TDF: 10 Total: 51	Treatment naïve CHB	12 centers 5 countries

^a all doses are per oral (po)

^bW=Weeks, OLE=open label extension

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5.2. Review Strategy

Dr. Tanvir Bell is the primary clinical reviewer for clinical trials associated with this NDA and reviewed the data from the Pivotal trials GS-US-320-0108 and GS-US-320-0110. Additionally, statistical and virology reviewers collaborated extensively during the review process, and a number of analyses included in this review. Please review the analyses performed by Dr. Fraser Smith, statistical reviewer, and Dr. Sung Rhee, virology reviewer. In addition, there were significant interactions with the clinical pharmacology, pharmacometrics, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

The JumpStart service provided by the Computational Science Center (CSC) in the Center for Drug Evaluation and Research (CDER) was utilized to assess data fitness and to provide exploratory safety analyses for Study 0108 and Study 110. Clinical trial data were independently analyzed in JReview and Empirica study.

Consultation was requested from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to gain expert opinion and recommendations regarding interpretation of comparative bone mineral density imaging and bone marker laboratory values between TAF and TDF. The pertinent findings, comments, and recommendations from the consult review are incorporated in this document. Please refer to the consult review by Dr. Stephen Voss for further details.

Consultation was also requested from the Division of Cardiovascular and Renal Products (DCRP) relating to the interpretation of renal effects of TAF compared to TDF. Assistance was sought for interpretation proteinuria, glycosuria, and markers of proximal tubular dysfunction. The key points are incorporated in this review. Please refer to the consult review by Dr. Kimberly Smith for further details.

Consultation was requested from the Division of Transplantation and Ophthalmology (DTOP) regarding interpretation of ocular findings among recipients of TAF compared to TDF. Assistance with suggestions for future surveillance was also requested. The key points are incorporated into this review. Please refer to the consult review of Dr. William Boyd for further details.

6 Review of Relevant Individual Trials Used to Support Efficacy

Study 108

6.1.1. Study Design

Overview and Objective

Study 0108 is an ongoing randomized, double-blind, non-inferiority study that compares the antiviral activity of TAF 25 mg QD versus TDF 300 mg QD in subjects with HBe antigen negative chronic hepatitis B.

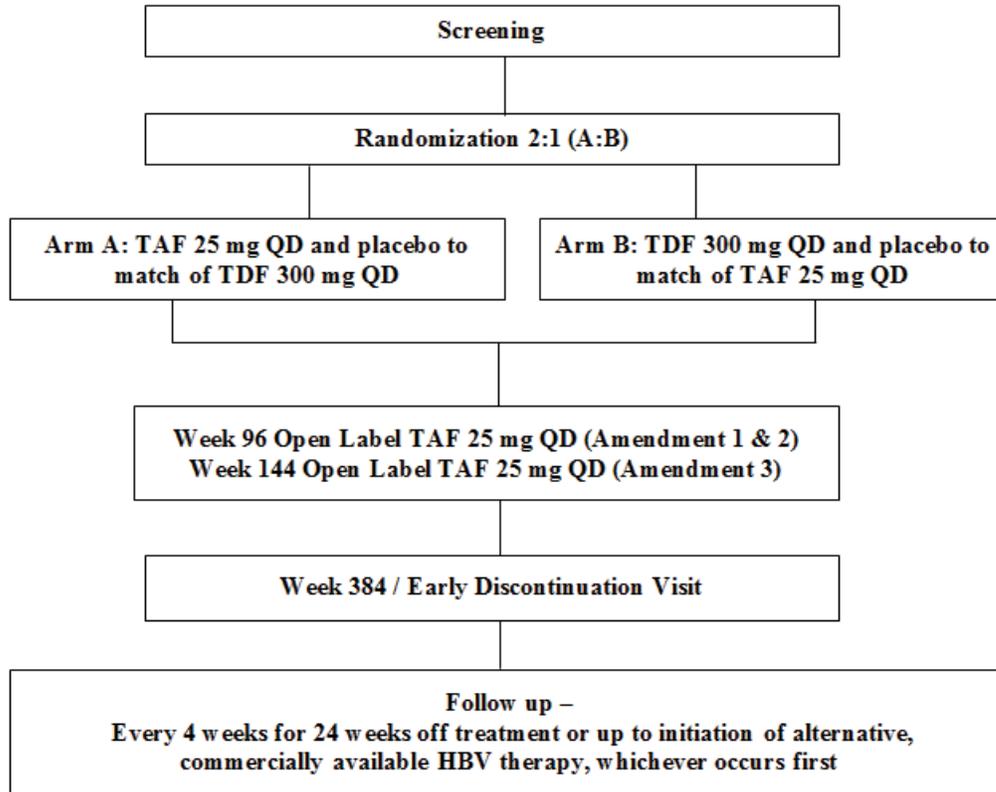
Trial Design

At entry, subjects were randomized in a 2:1 ratio (TAF: TDF) stratified by plasma HBV DNA level ($< 7 \log_{10}$ IU/mL, $\geq 7 \log_{10}$ IU/mL to $< 8 \log_{10}$ IU/mL, $\geq 8 \log_{10}$ IU/mL) and oral antiviral treatment status (treatment naïve vs. treatment experienced). Subjects were randomized using a centralized randomization procedure via an Interactive Voice Response System (IVRS). The figure below depicts the study schema as provided by the Applicant.

Treatment Arm A: 285 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD

Treatment Arm B: 140 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD

Figure 3. Study Schema for Study 108



Source: Applicant's Protocol Amendment 3 Submission

The duration of double-blind treatment was originally set at 48 weeks, which was then extended to 96 weeks, and more recently to 144 weeks. All subjects who complete double-blind treatment are eligible for participation in an open label TAF 25 mg QD extension period (through Week 384).

Subjects who permanently discontinued study drug (either prematurely or at the end of study [Week 384]) are to be followed every 4 weeks for 24 weeks off treatment or until initiation of alternative, commercially available, standard of care HBV therapy, whichever occurs first.

Subjects with HBsAg loss with confirmed seroconversion to anti-HBs were allowed to discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion to anti-HBs prior to Week 48 were not permitted to discontinue study drug prior to the Week 48 visit. Subjects who discontinued study drug for confirmed seroconversion to anti-HBs are to be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule through Week 144. Discontinuation of study drug for subjects experiencing

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HBsAg loss with confirmed seroconversion and who had known bridging fibrosis or cirrhosis was to be considered on a case-by-case basis.

An external, independent, multidisciplinary Data Monitoring Committee (DMC) was empanelled to review study progress and safety.

The trial began on September 12, 2013, and is ongoing. The trial is being conducted at 105 centers across Australia (5), Canada (11), France (2), Hong Kong (4), India (10), Italy (4), Japan (11), New Zealand (1), Poland (4), Romania (5), Russia (10), Spain (1), South Korea (10), Taiwan (5), Turkey (5), United Kingdom (3), and the U.S. (14). Data cut off for NDA submission was September 24, 2015 (last subject observation for primary endpoint).

Key inclusion criteria included the following:

1. Documented evidence of chronic HBV infection (e.g. HBsAg positive for more than 6 months)
2. HBeAg-negative, chronic hepatitis B with all of the following:
 - o HBeAg negative and HBeAb positive at Screening
 - o Screening HBV DNA $\geq 2 \times 10^4$ IU/mL
 - o Screening serum ALT level > 60 U/L (males) or > 38 U/L (females) and $\leq 10 \times$ ULN (by central laboratory range)
3. Treatment naïve subjects (defined as < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue, including TDF or TAF), **OR** treatment experienced subjects (defined as previous treatment ≥ 12 weeks with adefovir dipivoxil, and/or nucleoside analogues [lamivudine, clevudine, telbivudine, or entecavir]) will be eligible for enrollment. Treatment experienced subjects receiving oral antiviral treatment at Screening must continue their treatment regimen until the time of randomization, when it will be discontinued.
4. Any previous treatment with interferon (pegylated or non-pegylated) must have ended at least 6 months prior to the baseline visit.
5. Estimated creatinine clearance (CrCl) ≥ 60 mL/min (using the Cockcroft-Gault (CG) method)

Key exclusion criteria included any history of and current evidence of clinical hepatic decompensation or evidence of hepatocellular carcinoma (e.g. α -fetoprotein > 50 ng/mL or as evidenced by recent ultrasound or other standard of care measure). Subjects were excluded if they had treatment with TAF or TDF for > 12 weeks. Subjects were also excluded for laboratory evidence of hemoglobin < 10 g/dL, absolute neutrophil

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count $< 750/\text{mm}^3$, platelets $\leq 50,000/\text{mm}^3$, AST or ALT $> 10\times$ ULN, total bilirubin $> 2.5\times$ ULN, albumin < 3.0 mg/dL, or INR $> 1.5\times$ ULN.

Reviewer comment: Cirrhosis was defined in the case report form by a variety of ways including liver biopsy, transient elastography, Fibro/Test/FibroSure, APRI, or other methodology including imaging. Subjects were to have compensated liver disease, but a clear definition of what defined “compensated” was not provided.

Study Endpoints

In the original protocol, the primary efficacy endpoint was the proportion of subjects with complete viral suppression (HBV DNA < 69 IU/mL). A protocol amendment, based on FDA recommendations, lowered the level to < 29 IU/mL, which was the lower limit of quantitation of the polymerase chain reaction (PCR) assay (Roche COBAS® Taqman® HBV Test for Use with the High Pure System) proposed for use during the trial.

The secondary efficacy endpoints follow:

- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Weeks 96 and 144
- The proportion of subjects with plasma HBV DNA < 29 IU/mL (target not detected) at Weeks 48, 96, and 144
- The proportion of subjects with ALT normalization at Weeks 48, 96, and 144
- The proportion of subjects with HBsAg loss at Weeks 48, 96, and 144
- The proportion of subjects with HBsAg seroconversion to anti-HBs at Weeks 48, 96, and 144
- The change from baseline in fibrosis as assessed by FibroTest® at Weeks 48, 96, and 144
- The incidence of drug resistant mutations at Weeks 48, 96, and 144
- The change from baseline in \log_{10} (HBV DNA) (IU/mL) at Weeks 48, 96, and 144
- The change from baseline in \log_{10} (HBsAg) (IU/mL) at Weeks 48, 96, and 144
- The change from baseline in ALT at Weeks 48, 96, and 144

The safety objectives of the study follow:

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Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

- To compare the safety and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment naïve and treatment experienced subjects
- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the percent change from baseline in spine and hip BMD at Week 48
- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the change from baseline in CrCl by CG at Week 48

Statistical Analysis Plan

- **Sample Size and Power**

For Study 108, the Applicant calculated that a sample size of 130 for the TDF group and 260 for the TAF group would have 90% power to rule out the noninferiority margin of 10% at a 1-sided significance level of 0.025. This calculation assumed the expected difference (TAF – TDF) in proportion of subjects with HBV DNA < 29 IU/mL would be 0 and the proportion of subjects with HBV DNA < 29 IU/mL in the TDF group would be 91%. Sample size and power calculations were based on response rate of TDF for CHB treatment in HBeAg negative subjects observed in the TDF Phase 3 registrational trials (Marcellin et al., 2008).

- **Efficacy Analyses**

The primary efficacy endpoint was the proportion of subjects with HBV DNA <29 IU/mL at Week 48, and was conducted after all subjects had reached Week 48 or prematurely discontinued.

The statistical hypotheses for the primary endpoint follow:

- **Null hypothesis:** the TAF group (treatment group 1) is at least 10% worse than the TDF group (treatment group 2) with respect to the proportion of subjects with HBV DNA < 29 IU/mL at Week 48.
- **Alternative hypothesis:** the TAF group (treatment group 1) is less than 10% worse than the TDF group (treatment group 2) with respect to the proportion of subjects with HBV DNA < 29 IU/mL at Week 48.

The objective of the primary analysis was to assess the noninferiority of TAF compared to TDF using a 95% confidence interval (CI) approach, with a noninferiority margin of 10% using the full analysis set (FAS). The FAS includes all subjects who received at least one dose of study drug.

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The baseline stratum weighted difference in the proportion ($P1 - P2$) and its 95% CI was to be calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion, where stratification factors include baseline HBV DNA level ($< 7 \log_{10}$ IU/mL, $\geq 7 \log_{10}$ IU/mL to $< 8 \log_{10}$ IU/mL, $\geq 8 \log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced).

If noninferiority of TAF versus TDF was established, the lower bound of the same 95% CI was compared to 0; if the lower bound of the 95% CI was greater than 0, superiority of TAF over TDF would be established.

All the secondary efficacy endpoints involving proportions was analyzed using the same statistical method ($M = F$) applied to the analysis of the primary efficacy endpoint. P-value was calculated using the CMH test stratified by baseline HBV DNA and oral antiviral treatment TAF status, and the proportion difference between the 2 treatment groups and the associated 95% CI was calculated based on stratum-adjusted MH proportion. Sensitivity analyses was to be performed using the $M = E$ approach as well.

Resistance testing eligible subjects are those who remain viremic with HBV DNA ≥ 69 IU/mL (approximately 400 copies/mL) (1) at the end of each study year (e.g., Weeks 48 and 96) or (2) at the last on-treatment visit (only for those who discontinued treatment at/after Week 24 but before the end of each study year).

- **Safety Analyses**

For the Week 48 safety analysis, data were to be summarized for the double-blind phase only (i.e., up to Week 144) and p-value were calculated up to Week 48. All safety data at a minimum up to the Week 48 data-cut was included, and additionally, all safety data up to NDA submission and safety update report (SUR) submitted two months after was included.

Percentage change from baseline in hip BMD and spine BMD was 2 of the 4 key safety endpoints, and were to be summarized by treatment group and visit using descriptive statistics. Bone biomarkers include serum CTX, P1NP, PTH, OC, and bsAP. Baseline, postbaseline, change from baseline, and percentage change from baseline in bone biomarkers were to be summarized by treatment group and visit using descriptive statistics. Percentage change from baseline was compared between the 2 treatment groups using the Wilcoxon rank sum test. Fracture probabilities were to be assessed using FRAX®, a computer based algorithm developed by the World Health Organization (WHO; <http://www.shef.ac.uk/FRAX>).

Treatment-emergent confirmed renal abnormalities (confirmed increase from baseline in creatinine of at least 0.5 mg/dL or confirmed creatinine clearance by Cockcroft Gault (CG) below 50 mL/min or confirmed phosphorous < 2 mg/dL) were to be summarized

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for double-blind phase with statistical comparisons of the subject incidence rates between the 2 treatment groups performed using the Fisher's exact test. Changes from baseline in renal biomarkers including treatment-emergent proteinuria, urine protein to creatinine ratio (UPCR), urine albumin to creatinine ration (UACR), urine retinol binding protein (RPB), urine Beta-2 microglobulin, and fractional excretion of uric acid (FEUA) were evaluated.

Protocol Amendments

The following major amendments to the trials were proposed and agreed to by the Division:

- *The entry criteria for estimated glomerular filtration rate (eGFR) was lowered from ≥ 60 mL/min to ≥ 50 mL/min to be consistent with other trials being conducted with TAF for treatment of HIV-1 infection.*
- *The HBV DNA detection limit was changed from <69 IU/mL to <29 IU/mL. This plasma HBV DNA level represents the lower limit of quantitation of the polymerase chain reaction (PCR) assay employed (Roche COBAS®Taqman®HBV Test for Use with the High Pure System) proposed for use during the trial.*
- *The methods of ALT normalization described are by using the central lab normal values and AASLD criteria. Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years. During the conduct of the trial, the American Association for the Study of Liver Diseases (AASLD) recommended criteria of lower thresholds of ALT normalization: ALT <30 U/L for males and <19 U/L for females (Terrault, et al 2015). Both methods were to be used in the Applicant's evaluation.*
- *The blinded period was extended by one additional year (from Week 96 to Week 144)*
- *The open label period of the study was extended by 4 additional years (from Week 144 to Week 384)*

Another amendment provided for the inclusion of a subset of 150 subjects from China for additional safety information, and it was agreed that datasets were not required to be included in the NDA, but any required narratives were.

Reviewer comment: These protocol modifications did not have an impact on the interpretation of the overall conduct of the study or the results. The lower threshold of HBV DNA detection is consistent with improved technology and more applicable to current practice.

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Data Quality and Integrity: Sponsor's Assurance

The Applicant reviewed data to ensure completeness, consistency, and accuracy via edit checks and validation and check data using SAS® and Business Objects XI reporting tool. Data was also reviewed manually to ensure the electronic data matched the eCRF data. Data deficiencies were resolved electronically. Important protocol deviations were prespecified and documented during routine monitoring.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that clinical trials were conducted following Good Clinical Practice standards and considerations for the ethical treatment of human subjects and conducted under an IND application in according to ICH standards and 21CFR 312.20. The Applicant specifies that clinical trials not conducted under U.S. IND were conducted in compliance with the European Community Directive 2001/20/EC, as well as other local legislation.

Financial Disclosure

Eighteen investigators in Study 108 had financial interests/arrangements (see Section 13.2 in the Appendix for more information). The disclosed financial interests/arrangements did not appear to affect the approvability of this application.

Patient Disposition

There were 425 subjects randomized and treated in Study 108, and 94% completed 48 weeks of treatment. The Applicant's reasons for premature study drug discontinuations are shown in Table 3 and were similar across treatment arms.

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Table 3: Premature Study Drug Discontinuations for Study 108 by Applicant

	Study 108	
	TAF	TDF
Number randomized	285	141
Number treated	285	140
Number completed study drugs through week 48	269 (94%)	132 (94%)
Number discontinued study drug	12	7
-Adverse event	3	2
-Investigator discretion	1	0
-Withdrew consent	3	2
-Lost to follow-up	4	1
-Non-compliance	0	1
-Pregnancy	0	1
-Protocol specified criteria	1	0
-Death	0	0
-Lack of Efficacy	0	0

Two subjects discontinued the study due to consent withdrawn and were reclassified by this reviewer as discontinuations due to adverse events:

- Subject 0381-1218 in Study 0108 was initially classified as consent withdrawn. This 48 year-old male randomized to TAF discontinued study medication on day 17 due to Grade 3 insomnia, arthralgia, and head discomfort. The investigator considered these events related to study drug.
- Subject 2865-1138 in Study 0108 was initially classified as consent withdrawn. This 48 year-old female randomized to TAF discontinued study medication on day 11 due to rash and pruritus.

The above were determined by this reviewer to be possibly or probably related to study drug, and the table below aggregates these reclassifications with other reasons for premature study drug discontinuations.

Table 4: Premature Study Drug Discontinuations for Study 108 Reclassified by Reviewer

	Study 108	
	TAF	TDF
Number randomized	285	141
Number treated	285	140
Number completed study drugs through week 48	269 (94%)	132 (94%)
Number discontinued study drug	12	7
-Adverse event	5	2
-Investigator discretion	1	0
-Withdrew consent	1	2
-Lost to follow-up	4	1
-Non-compliance	0	1
-Pregnancy	0	1
-Protocol specified criteria	1	0
-Death	0	0
-Lack of Efficacy	0	0

Protocol Violations/Deviations

A total of 108 protocol deviations were reported for 81 subjects in Study 108. Protocol deviations occurred in similar proportions in the treatment arms. The majority of the deviations (13% overall) were for procedural violation followed by nonadherence to study drug (5% overall). Subjects with nonadherence to study drugs were counselled for improved adherence. Overdose occurred in 1% of subjects. All investigators of subjects with important protocol deviations were reinstructed regarding study procedures. Two subjects who had repeated nonadherence to drug, one in each arm, were not included in the per protocol analysis data set. None of these deviations affected the overall results for efficacy and safety of the 48 week data.

Table of Demographic Characteristics

The demographic and disease characteristics of subjects enrolled in Study 108 are displayed in the following table. Subjects in the trials were generally well matched across treatment arms with the majority being Asian males with Hepatitis B virus genotype C followed by genotypes B and D; all of which are found primarily in people of Asian descent.

The majority of subjects in Study 108 had baseline HBV DNA levels $<8 \log_{10}$ IU/mL.

Baseline renal function across treatment groups was comparable with most subjects entering the trials with normal creatinine clearance. Of note, in Study 108 there were substantially more subjects ≥ 50 years of age randomized to TDF, but there was no difference in baseline creatinine clearance levels between treatment groups.

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Approximately one-quarter of subjects had received prior nucleos(t)ide treatment and 11% had previously been treated with interferons. In the majority of subjects, the risk factor associated with HBV acquisition was unknown (68%), followed by vertical transmission (20%), then single percentages of IV drug use, contact with an infected individual, blood product transfusion, or other factors. Among those with data, 12% had evidence of cirrhosis either by biopsy or Fibrotest Score >0.75. The proportions of subjects in the trials with diabetes, hypertension, cardiovascular disease or hyperlipidemia were low (<10%) and comparable (data not shown).

Table 5. Demographic and Disease Characteristics for Study 108

	Study 108	
	TAF N=285	TDF N=140
Age (years)		
-Mean (SD)	45 (11.6)	48 (10.4)
-Median	46	50
-Min, Max	19, 80	25, 72
Age groups (%)		
-<50 years	176 (62)	69 (49)
-≥50 years	109 (38)	71 (51)
Sex (%)		
-Male	173 (61)	86 (61)
-Female	112 (39)	54 (39)
Race (%)		
-Asian	205 (72)	101 (72)
-Black/African American	5 (2)	3 (2%)
-Native Hawaiian/Pacific Islander	2 (1)	0
-White	71 (25)	35 (25)
-Other	2 (1)	1 (1)
Ethnicity		
-Hispanic/Latino	2 (1)	0
BMI (kg/m ²)		
-Mean (SD)	24.6 (4.04)	24.9 (3.81)
-Median	24.3	24.4
-Min, Max	15.2, 39.3	16.6, 36.9
HBV DNA (log ₁₀ IU/mL) and Categories		
-Mean (SD)	5.7 (1.34)	5.8 (1.32)
-<7	230 (81%)	116 (83%)
-≥7 - <8	42 (15%)	20 (14%)
-≥8	13 (5%)	4 (3%)
ALT (U/L) and Level		
-Mean (SD)	94 (88.3)	94 (80.0)
-Median	67	67

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-Min, Max	17, 720	9, 491
-≤ULN	49 (17)	19 (14)
->ULN – 5 x ULN	209 (73)	109 (78)
->5 – 10 x ULN	22 (8)	10 (7)
->10 x ULN	5 (2)	2 (1)
HBeAg Status (%)		
-Positive	2 (1)	2 (1)
-Negative	283 (99)	138 (99)
HBV Genotype (%)		
-A	15 (5)	6 (4)
-B	60 (21)	40 (29)
-C	115 (40)	47 (33)
-D	90 (32)	42 (30)
-E	5 (2)	2 (1)
-H	0	2 (1)
-Unknown	0	1 (1)
Previous Nucleos(t)ide Treatment (%)		
-Yes	60 (21)	31 (22)
-No	225 (79)	109 (78)
History of Cirrhosis (%)		
-Yes ¹	24 (11)	14 (12)
-No	195 (89)	99 (88)
-Indeterminate/Unknown	66	27
Fibrotest		
-N	280	282
-Mean (SD)	0.43 (0.22)	0.45 (0.23)
-Median	0.41	0.42
-Min, Max	0.05,0.97	0.04,0.97
eGFR by CG (mL/min)		
-Mean (SD)	104.7 (27.83)	100.3 (24.23)
-Median	99.6	98.4
-Min, Max	39.0, 214.2	59.4, 187.8
eGFR by CKD-EPI (mL/min/1.73m ²)		
-Mean (SD)	99.8 (14.97)	96.7 (13.48)
-Median	100.9	97.1
-Min, Max	46.4, 132.9	53.5, 122.3
Proteinuria by Urinalysis ² (%)		
-Grade 0	270 (95)	135 (96)
-Grade 1	13 (5)	5 (4)
-Grade 2	2 (1)	0
-Grade 3	0	0

¹ Cirrhosis was defined by liver biopsy, transient elastography, Fibro/Test/FibroSure, APRI, or other method including imaging

²By urine dipstick

Efficacy Results – Primary Endpoint

Overall, 268/285 (94%) achieved HBV DNA < 29 IU/mL in the TAF arm compared with 130/140 (93%) in the TDF arm after 48 weeks of treatment.

According to the Applicant’s analysis, the risk difference and 95% CI adjusted for baseline strata was 1.8% (95% CI -3.6%, 7.2%, p=0.47). The Agency biostatistician calculated the risk difference and 95% CI adjusted for baseline strata as 1.7% (95% CI -3.5% to 7.1%, p=0.51). The difference between the Applicant and Agency analyses was likely due to rounding. However, both analyses resulted in the conclusion that TAF was non-inferior to TDF. Superiority was not established.

Table 6: Summary of Primary Efficacy Analysis (Percentage of subjects with HBV DNA <29 IU/mL) at Week 48 for Study 108

Treatment Arm	TAF	TDF
	n/N	n/N
	%	%
Number and Percentage of Responders	268/285 94.0%	130/140 92.9%
Risk Difference and exact 95% CI (TAF – TDF)	+1.2% (-3.5% to +7.3%) p=0.68	
Risk Difference and 95% CI adjusted for baseline strata	+1.7% (-3.5% to +7.1%) p=0.51	

NI Margin= -10%

Source: Frasier Smith, PhD, statistical reviewer

Subgroup Analysis

In Study 108, the following subgroups were evaluated:

- Age (<50 versus ≥50 years);
- Sex (male versus female);
- Race (Asian versus non-Asian);
- Baseline HBV RNA level (< 7 log₁₀ IU/mL versus ≥7 log₁₀ IU/mL);
- Oral antiviral treatment status (treatment experienced versus treatment naive);
- Geographic Region (East Asia, Europe, North America);
- Study drug adherence (< 95% versus ≥ 95%);
- Genotype (A/D versus B/C)
- Baseline ALT by central lab normal range (≤ ULN versus > ULN)
- Baseline Fibrotest score (< 0.75 versus ≥ 0.75)

The rate of virologic success for subgroups of age, sex, race, antiviral treatment experience, geographic region, drug adherence, and baseline renal function were similar. Subpopulations with baseline factors of baseline viral load, treatment experience, HBV genotype, and cirrhosis were other areas explored by the Agency, and

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more details for these subgroups follow.

Baseline viral load

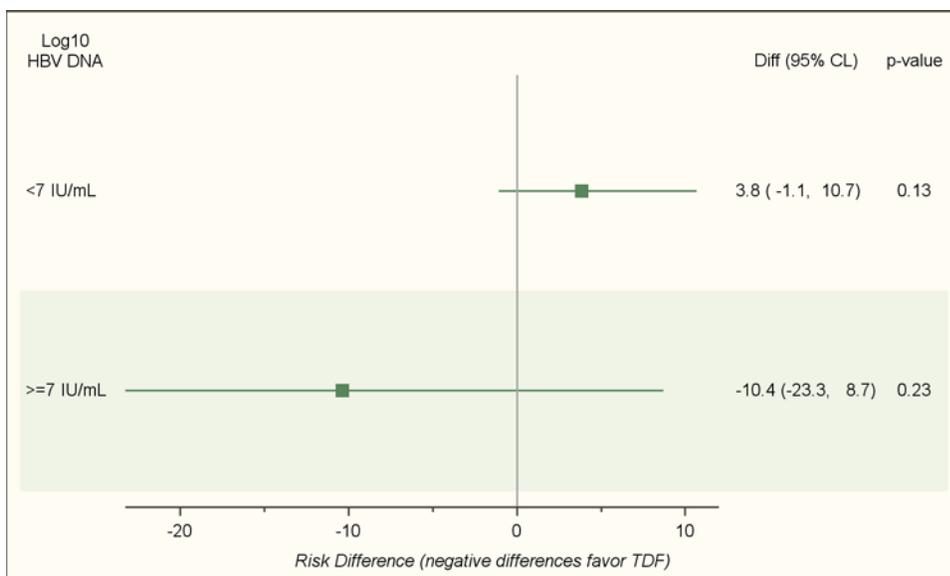
Subgroup analysis stratified by baseline viral load was performed and is shown in the following table. The results suggest that subjects with higher baseline viral loads ($\geq 7 \log_{10}$ IU/mL HBV DNA) had higher response rates with TDF compared to TAF, and the reverse trend was noted for subjects with baseline viral loads under $7 \log_{10}$ HBV DNA. However, the numbers of subjects in Study 108 with baseline viral loads under $7 \log_{10}$ HBV DNA were small, which may influence the ability to reach statistical significance and draw conclusions for this population. Zelen’s Interaction test showed a trend toward a difference that was not statistically significant ($p=0.086$). See Table 7 and Figure 4 below.

Table 7. Responses in HBV DNA < 29 IU/mL by Baseline Viral Load in Study 108

	TAF	TDF	Risk difference
<7 log ₁₀ HBV DNA	221/230 (96)	106/116 (92)	+3.8% 95% CI -1% to 11%, p=0.13
≥7 log ₁₀ HBV DNA	47/55 (85)	23/24 (96)	-10% 95% CI -23% to +9%, p=0.23

Source: Fraser Smith, PhD, statistical reviewer

Figure 4: Forest Plot of Risk Difference by Baseline Viral Load at Applicant Cut-offs in Study 108



Source: Agency statistical analyst with input from the statistics reviewer

Forest plots using other dichotomous cut-points in baseline viral loads are shown in Appendix 1. Numbers of subjects in the baseline viral load strata of $\geq 7 \log_{10}$ IU/mL to $< 8 \log_{10}$ IU/mL and $\geq 8 \log_{10}$ IU/mL were too small to provide any meaningful comparisons .

Treatment experience

The Applicant defined treatment naïve as oral antiviral treatment for less than 12 weeks, and treatment experienced as greater than 12 weeks of oral HBV treatment. Treatment naïve subjects had similar efficacy as treatment experienced subjects in HBeAg negative subjects in both arms. Treatment naïve subjects had a virologic suppression rate with TAF of 94% (212/225) and with TDF of 93% (102/110); whereas, treatment experienced subject had a response rate with TAF of 93% (56/60) and with TDF of 93% (28/30). Dr. Sung Rhee, the virology reviewer, used the definition of any NRTI treatment to evaluate if differences occurred with this definition and she found the rates of virologic suppression also to be similar (see Dr. Sung Rhee’s review for additional details).

HBV genotype

In general, across HBV genotypes in Study 108 had similar virologic suppression with response rates above 94%. Using Dr. Rhee’s definition of treatment experience, a small subset of TAF treated HBV Genotype C treatment experienced subjects had a higher virologic suppression of 97% (28/29) compared TDF treated HBV Genotype C treatment experienced subjects of 85% (11/13). In contrast, a small subset of TAF treated HBV Genotype D treatment experienced subjects had a lower virologic suppression of 88% (14/16) compared TDF treated HBV Genotype D treatment experienced subjects of 100% (10/10). The numbers in these two subgroups, HBV treatment experienced Genotype C or D, is small to be able to draw conclusion about differential efficacy.

Cirrhosis

Among cirrhotics by case report form, equal proportions (92%) achieved HBV DNA < 29 IU/mL in Study 108. Changes in fibrotest scores were small and comparable between the treatment groups.

Table 8: Proportion of Cirrhotics with HBV DNA < 29 IU/mL in Study 108

Treatment Arm n/N (%)	TAF	TDF
Cirrhotics*	22/24 (92%)	13/14 (93%)
Non-Cirrhotics	190/195 (97%)	92/99 (93%)
Unknown	56/66 (85%)	25/27 (93%)

* Cirrhosis was defined by liver biopsy, transient elastography, Fibro/Test/FibroSure, APRI, or other modality including imaging

Source: Adapted from Fraser Smith, PhD, statistical reviewer

Data Quality and Integrity – Reviewers’ Assessment

The applicant submitted the data that were well defined as were summary tables and figures in the clinical study report. There was generally good agreement between results obtained using independent analysis.

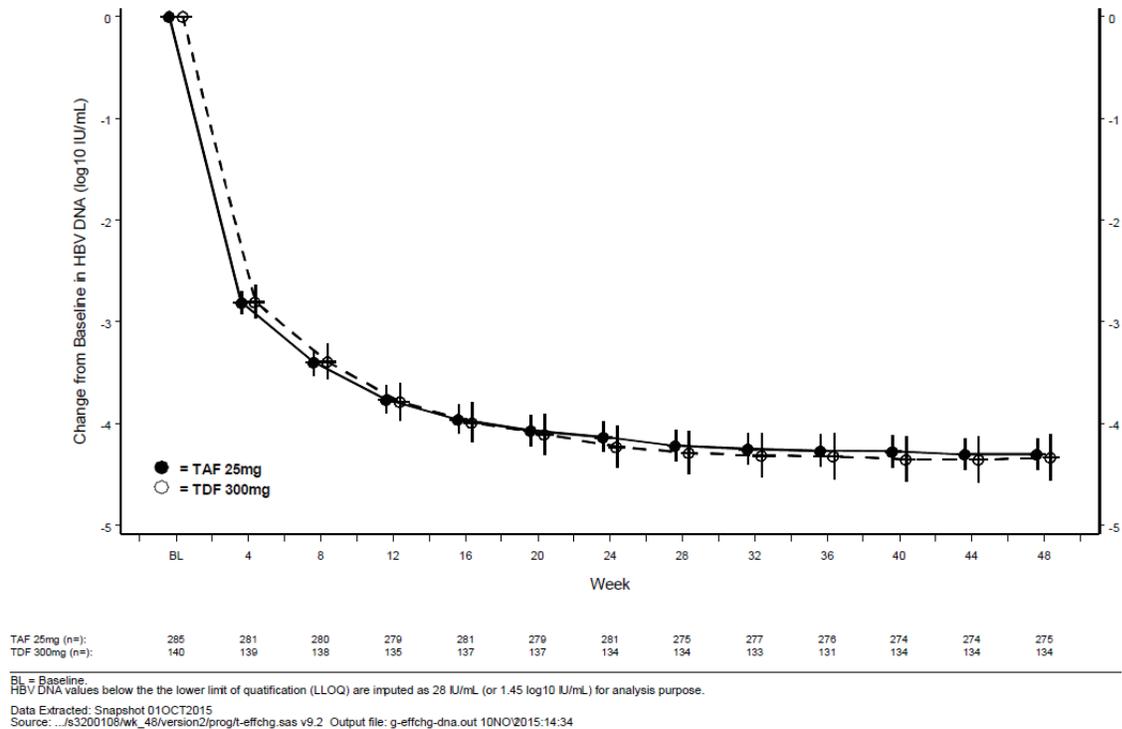
Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints evaluated by the Applicant are described above. The clinically relevant endpoints include change from baseline HBV DNA levels, normalization of ALT, change in fibrosis, Hepatitis B surface antigen loss, and viral resistance. Trajectory of HBV DNA changes from baseline (\log_{10} IU/mL, change in fibrosis, and viral resistance were similar in the TAF and TDF arms. Normalization of ALT was similar between the arms by central laboratory criteria; however, by ALT normalization by AASLD criteria was greater in the TAF versus TDF arm.

Similar declines in HBV DNA levels between the two groups occurred; without statistically significant differences (See Figure 5 below). The starting mean (SD) baseline HBV DNA levels 5.75 (1.341) \log_{10} IU/mL and 5.77 (1.321) \log_{10} IU/mL in the TAF and TDF arms, respectively. Mean (SD) changes from baseline were at Week 4 were -2.81 (0.945) \log_{10} IU/mL -2.80 (0.940) \log_{10} IU/mL in the TAF and TDF arms, respectively. Mean (SD) changes from baseline were at Week 24 were -4.13 (1.250) \log_{10} IU/mL and -4.23 (1.193) \log_{10} IU/mL in the TAF and TDF arms, respectively. The Virology reviewer evaluated Week 48 data and obtained a mean (SD) HBV DNA levels -4.29 (1.340) \log_{10} IU/mL and -4.26 (1.347) \log_{10} IU/mL in the TAF and TDF arms, respectively.

Figure 5: Change from Baseline in HBV DNA in Study 108

Figure 9–2. GS-US-320-0108: Mean and 95% CIs of Change from Baseline in HBV DNA (log₁₀ IU/mL) by Visit (Observed Data) (Full Analysis Set)



Source: Section 15.1, Figure 6

Source: Applicant's ISE

As described previously, two methods for assessing ALT normalization were used: central laboratory (lab) levels and levels set forth by the AASLD; the AASLD levels were more stringent than those of the central lab were. Regardless of the levels used, more subjects treated with TAF had normalized their ALT levels by Week 48 (see Table 9 below).

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Table 9. Study 108 Proportion of Subjects with Normalized ALT (With Baseline ALT > ULN) at Week 48, Missing=Failure

	TAF	TDF	TAF vs TDF	
			P-Value	Prop Diff (95% CI)
Normalized ALT (Central Lab)	196/236 (83%)	91/121 (75%)	0.076	8.0% (-1.3% to 17.2%)
Normalized ALT (AASLD)	137/276 (50%)	44/138 (32%)	<0.001	17.9% (8.0% to 27.7%)

Source: Applicant's Summary of Efficacy Section 15.1, Tables 23.1.1 and 23.2.1

No subjects in either group experienced HBsAg loss at Week 48.

Two subjects in each treatment arm qualified for population-based sequence analysis after up to 48 weeks to determine virologic resistance. The subjects in the TAF arm had no amino acid substitutions detected in HBV pol/RT. The subjects in the TDF arm were unable to be sequenced likely due to low HBV DNA.

Please refer to FDA Statistical and Virology Review for details of other analyses performed.

6.2. Study 110

6.2.1. Study Design

Overview and Objective

This is an ongoing randomized, double-blind, non-inferiority study to compare the antiviral activity of TAF 25 mg QD versus TDF 300 mg QD in subjects with chronic e antigen positive hepatitis B.

Trial Design

Subjects were randomized in a 2:1 ratio (A:B) to the treatment arms. Subjects were stratified by plasma HBV DNA level mL (< 8 log₁₀ IU/mL, ≥ 8 log₁₀ IU/mL) and oral antiviral treatment status (treatment naïve vs. treatment experienced). Subjects were randomized using a centralized randomization procedure via an Interactive Voice Response System (IVRS).

Treatment Arm A: 581 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD

Treatment Arm B: 292 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD

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As in Study 0108, the initial duration of double-blind treatment was 48 weeks, which was extended to 96 and then 144 weeks. All subjects who complete 144 weeks of treatment were eligible for participation in the open label TAF 25 mg QD extension period for an additional 48 weeks (through Week 192). See Figure 1 for study schema. Subjects who permanently discontinue study drug (either prematurely or at the end of study [Week 384]) will be followed every 4 weeks for 24 weeks off treatment or until initiation of alternative, commercially available, standard of care HBV therapy, whichever occurs first.

As in Study 0108, subjects with HBsAg loss with confirmed seroconversion to anti-HBs are to discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion to anti-HBs prior to Week 48 were not permitted to discontinue study drug prior to the Week 48 visit. Subjects who discontinue study drug for confirmed seroconversion to anti-HBs will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule through Week 144. Discontinuations of study drug for subjects experiencing HBsAg loss with confirmed seroconversion, who have known bridging fibrosis or cirrhosis, were to be considered on a case-by-case basis.

An external, independent, multidisciplinary Data Monitoring Committee (DMC) was empanelled to review study progress and safety.

The trial began on August 25, 2013 and is ongoing. The trial is being conducted at 161 centers across Australia (11), Bulgaria (4), Canada (12), France (4), Hong Kong (5), India (18), Italy (7), Japan (16), New Zealand (2), Poland (5), Romania (6), Russia (12), Singapore (3), Spain (2), South Korea (22), Taiwan (8), Turkey (5), United Kingdom (4), and the U.S. (15). Data cut off for NDA submission was November 6, 2015 (last subject observation for primary endpoint).

Key inclusion criteria included the following:

1. Documented evidence of chronic HBV infection (e.g. HBsAg positive for more than 6 months)
2. HBeAg-Positive, chronic hepatitis B with all of the following:
 - HBeAg positive at Screening
 - Screening HBV DNA $\geq 2 \times 10^4$ IU/mL
 - Screening serum ALT level > 60 U/L (males) or > 38 U/L (females) and $\leq 10 \times$ ULN (by central laboratory range)
3. Treatment naïve subjects (defined as < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue, including TDF or TAF), **OR** treatment experienced subjects (defined as previous treatment ≥ 12 weeks with adefovir dipivoxil, and/or nucleoside analogues [lamivudine, clevudine, telbivudine, or entecavir]) will be eligible for enrollment. Treatment experienced subjects

receiving oral antiviral treatment at Screening must continue their treatment regimen until the time of randomization, when it will be discontinued.

4. Any previous treatment with interferon (pegylated or non-pegylated) must have ended at least 6 months prior to the baseline visit.

Key exclusion criteria included any history of and current evidence of clinical hepatic decompensation and evidence of hepatocellular carcinoma (e.g. α -fetoprotein > 50 ng/mL or as evidenced by recent ultrasound or other standard of care measure). Subjects were also excluded if they had treatment with TAF or TDF for > 12 weeks.

Study Endpoints

The study endpoints were the same as in Study 0108, and are listed above. This study has an additional secondary efficacy endpoint of the proportion of subjects with HBeAg loss and seroconversion to HBeAb at Week 48.

Statistical Analysis Plan

- **Sample Size and Power**

For Study 0110, the Applicant proposed that a sample size of 288 for the TDF group and 576 for the TAF group would provide 84% power to rule out the noninferiority margin of 10% at a 1-sided significance level of 0.025, assuming the expected difference (TAF – TDF) in proportion of subjects with HBV DNA < 29 IU/mL is 0 and the proportion of subjects with HBV DNA < 29 IU/mL in the TDF group is 69%. Sample size and power calculations were based on response rate of TDF for CHB treatment in HBeAg positive subjects observed in the Phase 3 registrational trials.(Marcellin 2008).

- **Efficacy Analyses**

The primary efficacy endpoint was the proportion of subjects with HBV DNA <29 IU/mL at Week 48, and the primary efficacy analysis was conducted after all subjects had reached Week 48 or prematurely discontinued.

The statistical hypotheses for the primary endpoint follow:

- **Null hypothesis:** the TAF group (treatment group 1) is at least 10% worse than the TDF group (treatment group 2) with respect to the proportion of subjects with HBV DNA < 29 IU/mL at Week 48.
- **Alternative hypothesis:** the TAF group (treatment group 1) is less than 10% worse than the TDF group (treatment group 2) with respect to the proportion of subjects with HBV DNA < 29 IU/mL at Week 48.

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The objective of the primary analysis was to assess the noninferiority of TAF compared to TDF using a 95% confidence interval (CI) approach, with a noninferiority margin of 10% using the full analysis set (FAS). The FAS includes all subjects who received at least one dose of study drug.

The baseline stratum weighted difference in the proportion ($P1 - P2$) and its 95% CI was to be calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion, where stratification factors include baseline HBV DNA level ($< 8 \log_{10}$ IU/mL, $\geq 8 \log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced). For each level of subgroup factors, the difference in proportion between the 2 treatment groups and 95% CIs was computed based on the MH proportions adjusted by baseline HBV DNA level ($\geq 8 \log_{10}$ IU/mL vs $< 8 \log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced), if the factors were not defining the subgroups.

If noninferiority of TAF versus TDF was established, the lower bound of the same 95% CI would be compared to 0; if the lower bound of the 95% CI is greater than 0, superiority of TAF over TDF would be established. The baseline HBV DNA level ($< 8 \log_{10}$ IU/mL, $\geq 8 \log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive vs. treatment-experienced) stratum-stratified, 2-sided CMH test was to be used to assess superiority.

All the secondary efficacy endpoints involving proportions was analyzed using the same statistical method ($M = F$) applied to the analysis of the primary efficacy endpoint. P-value would be calculated using the CMH test stratified by baseline HBV DNA and oral antiviral treatment TAF status, and the proportion difference between the 2 treatment groups and the associated 95% CI was calculated based on stratum-adjusted MH proportion. Sensitivity analyses was to be performed using the $M = E$ approach as well.

Resistance testing eligible subjects are those who remain viremic with HBV DNA ≥ 69 IU/mL (approximately 400 copies/mL) (1) at the end of each study year (e.g., Weeks 48 and 96) or (2) at the last on-treatment visit (only for those who discontinued treatment at/after Week 24 but before the end of each study year).

- **Safety Analyses**

For the Week 48 safety analysis, data were to be summarized for the double-blind phase only (i.e., up to Week 144) and p-value were calculated up to Week 48. All safety data at a minimum up to the Week 48 data-cut was included, and additionally, all safety data up to NDA submission and SUR submitted two months after was included.

Percentage change from baseline in hip BMD and spine BMD were 2 of the 4 key safety endpoints, and were to be summarized by treatment group and visit using descriptive statistics. Bone biomarkers include serum CTX, P1NP, PTH, OC, and bsAP. Baseline,
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postbaseline, change from baseline, and percentage change from baseline in bone biomarkers were to be summarized by treatment group and visit using descriptive statistics. Percentage change from baseline was compared between the 2 treatment groups using the Wilcoxon rank sum test. Fracture probabilities were to be assessed using FRAX®, a computer based algorithm developed by the World Health Organization (WHO; <http://www.shef.ac.uk/FRAX>).

Treatment-emergent confirmed renal abnormalities (confirmed increase from baseline in creatinine of at least 0.5 mg/dL or confirmed CrCl by CG below 50 mL/min or confirmed phosphorous < 2 mg/dL) were to be summarized for double-blind phase with statistical comparisons of the subject incidence rates between the 2 treatment groups performed using the Fisher's exact test. Changes from baseline in renal biomarkers including treatment-emergent proteinuria, UPCR, UACR, RPB, urine Beta-2 microglobulin, and FEUA were to be analyzed.

Protocol Amendments

Study 110 was amended in a similar manner as Study 108 (see above).

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that clinical trials were conducted following Good Clinical Practice standards and considerations for the ethical treatment of human subjects and conducted under an IND application in according to ICH standards and 21CFR 312.20. The Applicant specifies that clinical trials not conducted under U.S. IND were conducted in compliance with the European Community Directive 2001/20/EC, as well as other local legislation.

Financial Disclosure

Twenty investigators in Study 110 had financial interests/arrangements (see Section 13.2 in the Appendix for more information). The disclosed financial interests/arrangements did not appear to affect the approvability of this application.

Patient Disposition

There were 875 subjects randomized and 873 were treated in Study 110, and 92% completed their assigned 48 weeks of randomized treatment. The reasons for premature study drug discontinuations are shown in Table 10 and were similar across treatment arms.

Table 10: Premature Study Drug Discontinuations for Study 110 by Applicant

	Study 110	
	TAF	TDF
Number randomized	582	293
Number treated	581	292
Number completed study drugs through week 48	537 (92%)	270 (92%)
Number discontinued DB* study drug	29	13
-Adverse event	6	3
-Investigator discretion	2	1
-Withdrew consent	11	5
-Lost to follow-up	2	2
-Non-compliance	2	1
-Pregnancy	2	1
-Protocol specified criteria	2	0
-Death	1	0
-Lack of Efficacy	1	0

*DB=double-blind

Fourteen subjects in the TAF group and eight in the TDF group completed double-blind therapy through Week 48 and entered open-label treatment.

The following subjects were reclassified by this reviewer as discontinuations due to adverse events in Study 110:

- Subject 2145-4641 was initially classified as consent withdrawn. This 59 year-old female randomized to TDF discontinued study medication on day 13 due to Grade 2 fatigue and insomnia. This subject was also uncomfortable with blood draws.
- Subject 4844-4697 was initially classified as consent withdrawn. This 33 year-old female randomized to the TDF arm discontinued study medication on day 442 due to occipital neuralgia and optic neuritis. This case is further reviewed in the SAE section 8.4.3.
- Subject 2757-4868 was initially classified as consent withdrawn. This 62 year-old male randomized to TAF discontinued study medication on day 9 due to Grade 2 dyspepsia, nausea, vomiting, and dizziness.
- Subject 4036-4555 was initially classified as consent withdrawn. This 42 year-old male randomized to TAF discontinued study medication on day 4 due to nausea and dizziness.

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- Subject 4058-4786 was initially classified as investigator discretion. This 49 year-old male randomized to TAF discontinued study medication on day 69 due to Grade 3 transaminitis.
- Subject 4058-5303 was initially classified as investigator discretion. This 52 year-old male randomized to TAF discontinued study medication on day 163 due to diarrhea.
- Subject 5685-4602 was initially classified as consent withdrawn. This 30 year-old male randomized to TDF discontinued study medication on day 81 due to abdominal pain and anxiety.
- Subject 8519-4599 was initially classified as investigator discretion. This 35 year-old male randomized to TAF discontinued study medication on day 211 due to Grade 3 basilar artery occlusion.

Of the above, all the events, with the exception of basilar artery occlusion, were determined by this reviewer to be possibly or probably related to study drug and the aggregation of this data resulted in the numbers of premature study drug discontinuations in the table below.

Table 11: Premature Study Drug Discontinuations for Study 110 by Reviewer

	Study 110	
	TAF	TDF
Number randomized	582	293
Number treated	581	292
Number completed study drugs through week 48	537 (92%)	270 (92%)
Number discontinued DB* study drug	29	13
-Adverse event	10	6
-Investigator discretion	2	1
-Withdrew consent	7	2
-Lost to follow-up	2	2
-Non-compliance	2	1
-Pregnancy	2	1
-Protocol specified criteria	2	0
-Death	1	0
-Lack of Efficacy	1	0

*DB=double-blind

Reviewer comment: The above reclassification increases the discontinued study drug due to AE to 2% (10 subjects) from 1% in the TAF arm and 2% (6 subjects) from 1% in TDF arm.

Protocol Violations/Deviations

A total of 265 protocol deviations were reported for 207 subjects in Study 110. Protocol deviations occurred in similar proportions in the treatment arms and study centers. The majority of the deviations were for procedural violation (16% overall) followed by nonadherence to the drug (5% overall). Subjects with nonadherence to study drugs were counselled for improved adherence. Overdose occurred in 3% of subjects in the TAF arm and 2% of subjects in the TDF arm. All investigators of subjects with important protocol deviations were reinstructed regarding study procedures. None of these deviations affected the overall results for efficacy and safety of the 48 week data.

Table of Demographic Characteristics

The demographic and disease characteristics of subjects enrolled in studies 0108 and 0110 are displayed in the following table. Subjects in the trials were generally well matched across treatment arms with the majority being Asian males with Hepatitis B virus genotype C followed by genotypes B and D.

The majority subjects in Study 0110 had significantly elevated baseline levels of HBV DNA $>8 \log_{10}$ U/mL, which is consistent with the known characteristics of HBeAg positive disease.

Median age in this study was matched at approximately 37 years old. Baseline renal function across treatment groups was comparable with most subjects entering the trials with normal creatinine clearance.

Approximately one-quarter of subjects had received prior nucleos(t)ide treatment and 11% had previously been treated with interferons. In the majority of subjects, the risk factor associated with HBV acquisition was unknown (68%), followed by vertical transmission (20%), then single percentages of IV drug use, contact with an infected individual, blood product transfusion, or other factors. Among those with data, 10% had evidence of cirrhosis either by biopsy and 5% of subjects had Fibrotest Score ≥ 0.75 . The proportions of subjects in the trials with diabetes, hypertension, cardiovascular disease or hyperlipidemia were low ($<10\%$) and comparable (data not shown).

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Table 12: Demographics and Disease Characteristics for Study 110

	Study 110	
	TAF N=581	TDF N=292
Age (years)		
-Mean (SD)	38 (11.0)	38 (11.7)
-Median	37	36
-Min, Max	18, 69	18, 68
Age groups (%)		
-<50 years	493 (85)	234 (80)
-≥50 years	88 (15)	58 (20)
Sex (%)		
-Male	371 (64)	189 (65)
-Female	210 (36)	103 (35)
Race (%)		
-Asian	482 (83)	232 (79)
-Black/African American	2 (<1)	3 (1)
-Native Hawaiian/Pacific Islander	1 (<1)	3 (1)
-White	96 (16)	53 (18)
-Other	0	1 (<1)
Ethnicity		
-Hispanic/Latino	4 (<1)	2 (<1)
BMI (kg/m ²)		
-Mean (SD)	23.8 (4.14)	24.1 (4.00)
-Median	23.5	23.8
-Min, Max	14.4, 44.5	16.7, 38.4
HBV DNA (log ₁₀ IU/mL) and Categories		
-Mean (SD)	7.6 (1.34)	7.6 (1.41)
-<7	150 (26%)	77 (26%)
-≥7 - <8	159 (27%)	73 (25%)
-≥8	272 (50%)	142 (49%)
ALT (U/L) and Level		
-Mean (SD)	117 (105.1)	125 (128.2)
-Median	85	86
-Min, Max	13, 1160	21, 872
-≤ULN	44 (8)	24 (8)
->ULN – 5 x ULN	470 (81)	225 (77)
->5 – 10 x ULN	56 (10)	30 (10)
->10 x ULN	11 (2)	13 (4.5)
HBeAg Status (%)		
-Positive	567 (98)	288 (99)
-Negative	14 (2)	4 (1)
HBV Genotype (%)		

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-A	39 (7)	25 (9)
-B	100 (17)	48 (16)
-C	303 (52)	152 (52)
-D	134 (23)	63 (22)
-E	2 (<1)	1 (<1)
-H	3 (<1)	2 (<1)
-Unknown	0	1 (<1)
Previous Nucleos(t)ide Treatment(%)		
-Yes	137 (24)	69 (24)
-No	444 (76)	223 (76)
History of Cirrhosis ¹ (%)		
-Yes	41 (10)	24 (11)
-No	376 (90)	189 (89)
-Indeterminate/Unknown	164	79
Fibrotest		
-N	566	282
-Mean (SD)	0.34 (0.23)	0.32 (0.23)
-Median	0.29	0.25
-Min, Max	0.04,0.98	0.03,0.99
Fibrotest (%)		
-≥ 0.75	21 (5)	20 (7)
-numbers who had fibrotest	566	288
eGFR by CG (mL/min)		
-Mean (SD)	113.7 (27.28)	112.5 (29.33)
-Median	108.6	109.2
-Min, Max	54.6, 235.8	39.6, 227.4
eGFR by CKD-EPI (mL/min/1.73m ²)		
-Mean (SD)	107.8 (14.57)	106.4 (15.10)
-Median	109.0	108.6
-Min, Max	45.4, 140.9	38.0, 136.8
Proteinuria by Urinalysis ² (%)		
-Grade 0	538 (93)	259 (89)
-Grade 1	40 (7)	31 (11)
-Grade 2	3 (<1)	2 (1)
-Grade 3	0	0

¹ Cirrhosis was defined by liver biopsy, transient elastography, Fibro/Test/FibroSure, APRI, or other method including imaging

² By urine dipstick

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was reported at over 99% and evenly matched between the treatment arms.

Efficacy Results - Primary Endpoint

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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The primary endpoint analysis demonstrated that TAF was non-inferior to TDF. Specifically, 371/581 (64%) achieved HBV DNA < 29 IU/mL in the TAF arm compared with 195/292 (67%) in the TDF arm. The risk difference and 95% CI adjusted for baseline strata was -3.5% (95% CI -9.7% to 2.6%, p=0.25) favoring TAF. Superiority was not established.

Table 13: Summary of Primary Efficacy Analysis (Percentage of Subjects with HBV DNA <29 IU/mL) at Week 48 Study 110

Treatment Arm	TAF	TDF
	n/N %	n/N %
Number and Percentage of Responders	371/581 63.9%	195/292 66.8%
Risk Difference and exact 95% CI (TAF – TDF)	-2.9% (-9.5% to +3.85%) p=0.40	
Risk Difference and 95% CI adjusted for baseline strata	-3.5% (-9.7% to +2.6%) p=0.26	

NI Margin= -10%

Source: Fraser Smith, PhD, statistical reviewer

The proportion who failed to achieve HBV DNA <29 by Week 48 were comparable between the arms with 183 (32%) versus 88 (30%) in the TAF versus TDF arms, respectively. The median HBV DNA among those who had not achieved HBV DNA <29 IU/mL by Week 48 in the TAF arm was 225 IU/mL comparable to 150 IU/mL in the TDF arm. Among the failures, only one subject in the TAF arm discontinued due to lack of efficacy in the versus none in the TDF arm. Fewer than 3% of subjects discontinued due to other reasons (3% in the TAF arm; 2% in the TDF arm). Two percent or fewer participants discontinued due to AE/Death in both arms. Less than one percent of subjects had missing data during window and were on study drug in each arm.

Subgroup Analysis

In study 110, the following subgroups were evaluated:

- Age (< 50 versus ≥ 50 years);
- Sex (male versus female);
- Race (Asian versus non-Asian);
- Baseline HBV RNA level (< 8 log₁₀ IU/mL versus ≥ 8 log₁₀ IU/mL);
- Oral antiviral treatment status (treatment experienced versus treatment naive);
- Geographic Region (East Asia, Europe, North America);
- Study drug adherence (< 95% versus ≥ 95%);
- Genotype (A/D versus B/C)
- Baseline ALT by central lab normal range (≤ ULN versus > ULN)
- Baseline Fibrotest score (< 0.75 versus ≥ 0.75)

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The rate of virologic success for subgroups of age, sex, race, antiviral treatment experience, geographic region, drug adherence, and baseline renal function were similar. Please refer to FDA Statistical Review for details of other analyses performed. Baseline renal function as a continuous variable was also evaluated and no significant difference was seen between the two treatment groups. Subpopulations with baseline factors of baseline viral load, treatment experience, HBV genotype, and cirrhosis were other areas explored by the Agency, and more details for these subgroups follow.

Baseline viral load

An analysis for the subgroups stratified by baseline viral load was conducted and is shown in Table 14.

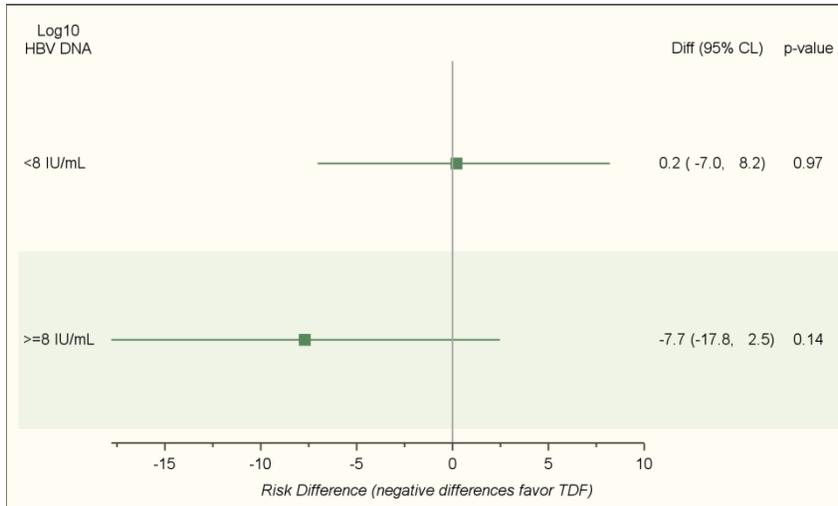
When the statistics reviewer used the same baseline HBV DNA strata that were used for Study 108 (ie. <7 and ≥ 7 \log_{10} IU/mL) the Zelen exact test for treatment by baseline interaction was statistically significant ($p=0.02$) due to the lack of homogeneity of treatment effect in the three baseline HBV DNA strata. While TAF appeared to be superior to TDF for subjects with low baseline viral loads ($p=0.049$), subjects in the two strata with baseline HBV DNA of at least 7 IU/mL had much higher observed response rates on TDF than on TAF.

Table 14. Response in HBV DNA < 29 IU/mL by Baseline Viral Load in Study 110

	TAF	TDF	Risk difference (TAF-TDF)
< 7 \log_{10} IU/mL	132/150 (88%)	60/77 (78%)	+10% 95% CI -+0.1% to +22%, p=0.049
7 to < 8 \log_{10} IU/mL	122/159 (77%)	66/73 (86%)	-10% 95% CI -20% to +2%, p=0.09
≥ 8 \log_{10} IU/mL	117/272 (43%)	72/142 (51%)	-8% 95% CI -18% to +2%, p=0.14

Source: Fraser Smith, PhD, statistical reviewer

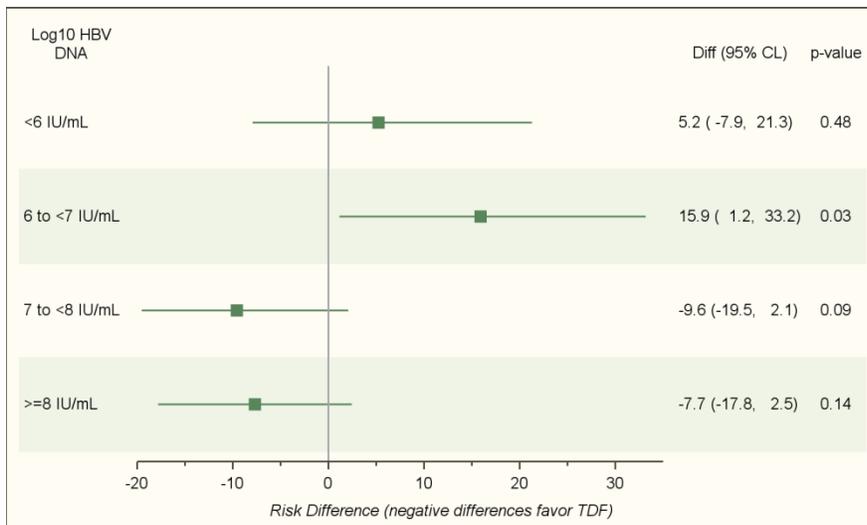
Figure 6: Forest Plot of Risk Difference in Efficacy by Viral Load Cut-offs of 8 log₁₀ IU/mL



Source: Agency statistical analyst with input from the statistics reviewer

The efficacy by baseline viral load in Study 110 was further dichotomized to <6 log₁₀ IU/mL, 6 to 7 log₁₀ IU/mL, 7 to 6 log₁₀ IU/mL, and ≥8 log₁₀ IU/mL; and the results are depicted in Figure 7 below. A numerically higher proportion of subjects in the TDF arm with baseline viral loads above 7 log₁₀ IU/mL achieved HBV DNA < 29 IU/mL.

Figure 7: Forest Plot of Risk Difference in Efficacy by Baseline Viral Load in Study 110



Source: Agency statistical analyst with input from the statistics reviewer

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Treatment experience

Generally, across all genotypes, treatment experienced subjects did not do as well as treatment naïve subjects in both TAF and TDF with both the reproduced Applicant’s analysis and Agency Statistical analysis as shown in the table below. Treatment experienced subjects had a more favorable response with TAF compared with TDF (See Table 15 below).

Table 15: Virologic Suppression by Treatment Experience in Study 110

	TAF	TDF
Treatment naïve	302/444 (68%)	156/223 (70%)
Treatment experienced	69/137 (50%)	39/69 (57%)

HBV genotype

The same trend of treatment naïve subjects having higher rates of virologic suppression occurred in analysis by the Agency Virologist in HBV Non-D genotype versus HBV genotype D. Virologic suppression rates, as determined by Agency Virologist, in Non-D genotypes were 65-82% in treatment naïve subjects and 55-83% in treatment experienced subjects. In addition, worse response rates were seen in Genotype D in both TAF and TDF with 39-46%, regardless of treatment experience (See Dr. Sung Rhee’s review for more details).

Cirrhosis

Among cirrhotics, the TAF arm achieved slightly less HBV DNA <29 IU/mL at 63% than the TDF arm at 67% (see Table 16 below). These differences were not statistically significant. Again, changes in fibrotest scores were small and comparable between the treatment groups.

Table 16: Proportion of Cirrhotics with HBV DNA < 29 IU/mL in Study 110

Treatment Arm n/N (%)	TAF	TDF
Cirrhotics*	26/41 (63%)	16/24 (67%)
Non-Cirrhotics	245/376 (65%)	132/189 (70%)
Unknown	100/164 (61%)	47/79 (60%)

* Cirrhosis was defined by liver biopsy, transient elastography, Fibro/Test/FibroSure, APRI or imaging Analysis: Adapted from Dr. Fraser Smith, Agency Statistician

Data Quality and Integrity - Reviewers' Assessment

The applicant submitted the data that were well defined as were summary tables and figures in the clinical study report. There was generally good agreement between results obtained using independent analysis.

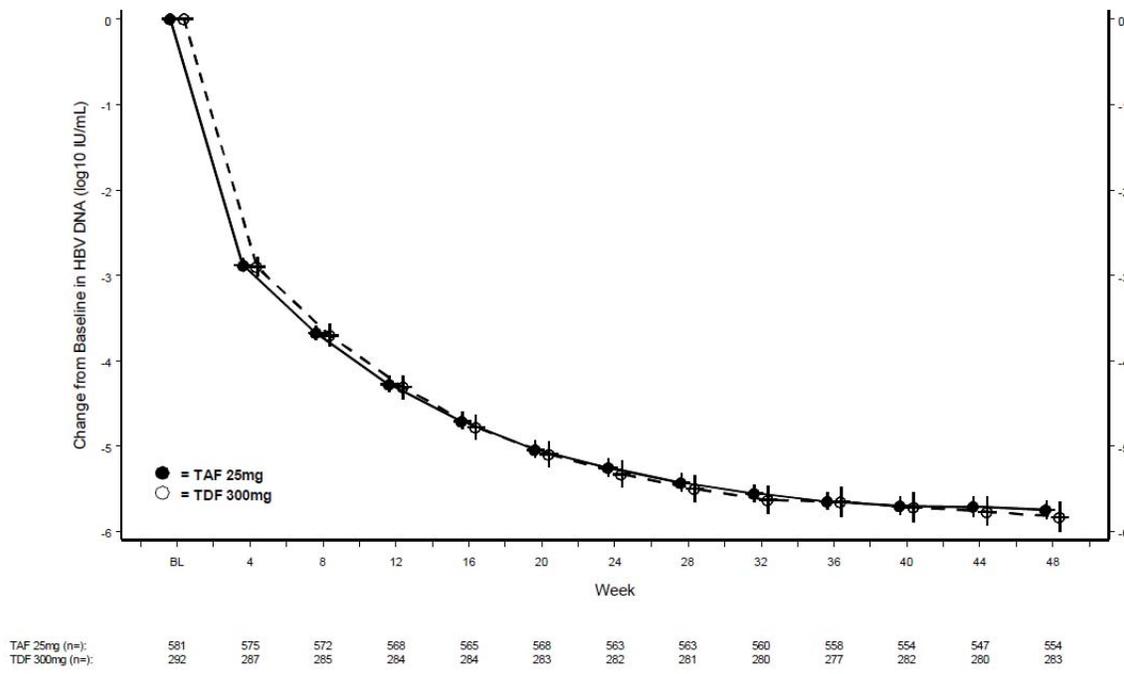
Efficacy Results - Secondary and other relevant endpoints

The secondary endpoints are described above. The clinically relevant endpoints include change from baseline HBV DNA levels, normalization of ALT, Hepatitis B surface antigen loss, Hepatitis B e antigen loss, antiviral treatment experience and viral resistance.

Similar declines in HBV DNA levels between the two groups occurred without statistically significant differences (See Figure 8 below). The starting mean (SD) baseline HBV DNA levels 7.59 (1.338) log₁₀ IU/mL and 7.62 (1.408) log₁₀ IU/mL in the TAF and TDF arms, respectively. Mean (SD) changes from baseline were at Week 4 were -2.88 (0.872) log₁₀ IU/mL -2.90 (0.953) log₁₀ IU/mL in the TAF and TDF arms, respectively. Mean (SD) changes from baseline were at Week 48 were -5.75 (1.310) log₁₀ IU/mL and -5.83 (1.427) log₁₀ IU/mL in the TAF and TDF arms, respectively.

Figure 8: Mean Change from Baseline of HBV DNA in Study 110

Figure 9-2. GS-US-320-0110: Mean and 95% CIs of Change from Baseline by Visit in HBV DNA (log₁₀ IU/mL) (Full Analysis Set)



BL = Baseline.
 HBV DNA values below the lower limit of quantification (LLOQ) are imputed as 28 IU/mL (or 1.45 log₁₀ IU/mL) for analysis purpose.
 Data Extracted: Snapshot 17NOV2015
 Source: ...s3200110/wk_48/version1/prog/t-effchg.sas v9.2 Output file: g-effchg-dna.out 19NOV2015:09:00

Source: Section 15.1, Figure 6

Source: Applicant's ISE

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As in Study 108, two methods for assessing ALT normalization were used: central lab levels and levels set forth by the AASLD. Regardless of the levels used, more subjects treated with TAF had normalized their ALT levels by Week 48 (see Table below).

Table 17. Study 110 Proportion of Subjects with Normalized ALT (With Baseline ALT > ULN) at Week 48, Missing=Failure

	TAF	TDF	TAF vs TDF	
			P-Value	Prop Diff (95% CI)
Normalized ALT (Central Lab)	384/537 (72%)	179/268 (67%)	0.018	4.6% (-2.3% to 11.4%)
Normalized ALT (AASLD)	257/572 (45%)	105/290 (36%)	<0.014	8.7% (1.8% to 15.6%)

Source: Applicant's Summary of Efficacy Section 15.1, Tables 23.1.1 and 23.2.1

Eighteen subjects in the TAF arm and 10 subjects in the TDF arm treatment arm qualified for population-based sequence analysis after up to 48 weeks to determine virologic resistance. Of these five subjects in the TAF arm and four subjects in the TDF arm had detectable treatment emergent HBV pol/RT substitutions. Conserved sites were defined as those positions where only one amino acid was found, or two amino acids was present and the prevalence of the minority amino acid was <1%; all other positions within the HBV rt domain were considered polymorphic sites (Kitrinis et al., 2014). None of the TAF-treatment failures was found to have conserved site substitutions, whereas two TDF-treatment failures had unique conserved site substitutions. The other identified patterns of resistance in both treatment groups were at polymorphic sites. No genotypic resistance pathways were identified.

Durability of Response and Persistence of Effect

This will be further assessed with results expected with 144 weeks of double-blind treatment.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Integration of the efficacy results from Study 108 and Study 110 is limited since the disease process is somewhat different in HBeAg negative and HBeAg positive patients. HBeAg positive disease has a higher viral load burden and more hepatic inflammation, and the serologic endpoint of HBeAg seroconversion is only measured in HBeAg positive disease.

7.1.1. Primary Endpoints

The primary efficacy endpoint for this application was the proportion of subjects with HBV DNA <29 IU/mL after 48 weeks of blinded treatment. In Study 108, 94% of TAF and 93% of TDF subjects achieved the primary endpoint. In Study 110, the proportions were 64% and 67% for the TAF and TDF groups, respectively. In each trial, TAF was non-inferior to TDF. Of note, the lower bound of the 95% confidence interval in Study 110 for comparing TAF to TDF was -9.8%, which was very close to the proposed lower bound for non-inferiority of -10%. In neither trial did TAF meet the superiority test. The overall lower antiviral response rate in HBeAg positive subjects of 64% subjects compared with 94% in HBeAg negative subjects is an expected outcome based on previous trials of approved nucleoside therapies.

7.1.2. Secondary and Other Endpoints

Prespecified secondary endpoints included ALT normalization, serologic responses, and resistance.

ALT normalization was assessed using a Central Lab and the AASLD cut-offs for normal values; the AASLD levels were lower and more stringent. Across the trials, TAF outperformed TAF with respect to ALT normalization regardless of the upper limit of normal value used. As with the primary endpoint, the rate of ALT normalization in Study 110 was relatively low: 45% for TAF and 36% for TDF. In the face of ongoing viral replication, the relevance of this finding is unknown. Hopefully more subjects will normalize their ALT levels with continued exposure to TAF and TDF as ALT is directly reflective of ongoing hepatic inflammation, which in the long-term is a primary driver for evolution of cirrhosis and development of HCC.

Consideration for stopping CHB therapy is made after HBV DNA suppression occurs and HBsAg seroconverts to HBsAb. No subjects in Study 108 and ~1% of subjects in Study 110 underwent HBsAg loss and conversion to HBsAb with no difference noted between treatments. In HBeAg patients, approximately 21% of subjects after 2-3 years of continuous nucleoside therapy experience seroconversion to HBeAb (Terrault et al., 2015). In Study 110, HBeAg seroconversion occurred in 10% of subjects in the TAF arm and 8% of subjects in the TDF arm in Study 110, which was not statistically different. Longer duration treatment and follow up of differences in rates of HBsAg loss and HBsAb production in both studies and HBeAg seroconversion in Study 110 may provide better comparison of treatment differences over time.

A total of 41 subjects with detectable HBV DNA at Week 48 were further evaluated for resistance based on the virology analysis plan, and no resistance-associated mutations were identified.

7.1.3. Subpopulations

There were no differences in TAF and TDF efficacy based on HBV genotype, age, race, or sex.

There was numeric, but not statistically significant trends in favor of treatment with TDF among subjects with high baseline viral load levels. Randomization was stratified on baseline viral load strata: <7 and ≥ 7 \log_{10} IU/mL in Study 108 and <7 , ≥ 7 to <8 , <8 and ≥ 8 \log_{10} IU/mL in Study 110. In Study 108, more subjects with baseline HBV DNA ≥ 7 \log_{10} IU/mL achieved HBV DNA suppression with TDF compared to TAF (96% versus 85%). Numeric, but not statistically significant, trends in favor of treatment with TDF among subjects with high baseline viral load levels were observed in both trials. Randomization was stratified on baseline viral load strata: <7 and ≥ 7 \log_{10} IU/mL in Study 108 and <7 , ≥ 7 to <8 , <8 and ≥ 8 \log_{10} IU/mL in Study 110. In Study 108, more subjects with baseline HBV DNA ≥ 7 \log_{10} IU/mL achieved HBV DNA suppression with TDF compared to TAF (96% versus 85%). In Study 110, 51% of TDF and 43% of TAF subjects with HBV DNA ≥ 8 \log_{10} IU/mL achieved the primary endpoint. This was due to an observed lack of homogeneity of the treatment effect in the baseline HBV DNA strata, which was a key baseline covariate used as a stratification variable at randomization.

Approximately 11% of study subjects had previously received treatment with a nucleoside analogue. Across both trials, treatment experienced subjects had lower rates of HBV DNA <29 IU/mL at Week 48: 22% for TAF compared to 27% for TDF. By comparison, treatment naïve subjects responded at rates between 73 and 79%.

The presence of cirrhosis was identified in case report forms by liver biopsy, transient elastography (FibroScan), Fibrotest, APRI, or other criteria. Cirrhosis was evaluated by case report form and the determination of cirrhosis was heterogeneous in these two studies. Approximately 11% of subjects were cirrhotic in both trials when excluding subjects with unknown cirrhosis status. Rates of efficacy in this small but important subpopulation were equivalent in Study 108 at about 92%; whereas in Study 110, TAF treated cirrhotics had a lower response at 63% than TDF treated cirrhotics at 67%.

7.1.4. Dose and Dose-Response

The Agency agreed with the dose of 25 mg evaluated in Studies 108 and 110. In the Phase 1b study, GS-US-320-0101 (also described in Section 4.5.2 above), results demonstrated that TAF when given in doses over a range of 8 to 120 mg results in similar HBV DNA declines over 28 days.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The steepest decrease in HBV DNA in HBeAg negative disease with both TAF and TDF

occur in approximately the first 4 weeks and is mostly maintained through week 48 as displayed in Figure 5, whereas, in HBeAg positive disease with higher viral loads the declines in HBV DNA are more gradual as displayed in Figure 8. HBV viral loads can take longer than 48 weeks to result in undetectable viral loads, and longer follow up of HBV DNA will better elucidate the primary efficacy difference between the two treatments. In contrast to the three to six months of treatment with multiple drugs currently needed for viral load suppression in HIV or HCV, treatment of CHB, which is monotherapy, often requires years of therapy to achieve viral suppression.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Patients with more severe hepatitis B liver disease and those with decompensated cirrhotics are important subpopulations not represented in these studies.

7.3. Integrated Assessment of Effectiveness

The efficacy results of the two trials reviewed in this NDA support the finding that TAF is effective for the treatment of CHB based on comparable rates of achieving HBV DNA <29 IU/mL after 48 weeks of treatment. With respect to ALT normalization, using the AASLD recommended stricter upper limit of normal values, more subjects treated with TAF achieved normal ALT levels during treatment. Trend data suggest that for subjects with high baseline viral load, cirrhosis, or with prior treatment experience responded better with TDF. Since the data is of short duration, it is unknown if this difference will translate into a clinically relevant benefit. However, TAF did not offer any treatment benefit for any population studied. Resistance to TFV is a rare occurrence and no resistance was observed in the current trials.

Along with HBV DNA suppression, seroconversion of HBsAg to HBsAb is an important outcome and can help with treatment cessation decisions. Spontaneous HBsAg loss in untreated patients occurs ~1% /year. It is noteworthy that active antiviral treatment with TAF or TDF did not increase this rate: <1% of subjects in both studies. Similarly, HBeAg seroconversion is an important prognostic marker and occurred in 10% of subjects in Study 110; again consistent with spontaneous seroconversion rates of 8-12%/year.

Inclusion in the label of responses by important secondary endpoints, such as response by baseline viral load and prior nucleoside experience, ALT normalization, serologic outcomes, and presence of cirrhosis is recommended to provide clinicians with a balanced overview of the efficacy of TAF.

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The trials are ongoing and 96 and 144 week data will be important for assessing outcomes and if TAF will offer any specific efficacy benefits compared to TDF.

8 Review of Safety

Safety Review Approach

Pivotal Phase 3 trials GS-US-320-0108 and GS-US-320-0110 were analyzed individually and included in the pooled safety population for the majority of safety analyses. Deaths, serious adverse events, and discontinuations due to adverse events occurring in any submitted Phase 2 or Phase 3 trials were reviewed and assessed for relatedness to study drugs.

Clinical trial data were independently analyzed in JReview and Empirica study. Any differences in findings by the FDA reviewer compared to the Applicant were relatively minor and attributable to variable methods of pooling and subgroup analyses. All of the safety assessments and conclusions are those of the FDA reviewer unless otherwise specified.

A thorough hepatic safety review was conducted, as it was the key to evaluate liver safety concerns in drugs that treat CHB. The pooled hepatic safety population included subjects who received TAF and TDF at the dosages and durations proposed for marketing.

Analysis of bone and renal events were performed in collaboration with DBRUP and DCRP since these were a major safety concern of these studies. Consultation with DTOP occurred to evaluate for posterior uveitis that was seen in preclinical dog models.

The Applicant submitted a Safety Update Report (SUR) two months after the original NDA submission. Deaths, SAEs, and discontinuations due to AEs reported in the SUR are included in the relevant safety sections.

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8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 18. Safety Population, Size, and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program for the indication under review N=866 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	TAF (n=866)	TDF (n=432)	Placebo (n=)
Normal Volunteers	N/A	N/A	0
Controlled trials conducted for this indication ²	866	432	0
All other than controlled trials conducted for this indication ³	N/A	N/A	N/A
Controlled trials conducted for other indications ⁴	0	0	0

¹ *study drug* means the drug being considered for approval.

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

1272 subjects have received at least one dose of TAF 25 mg in TAF clinical development program, of which 866 were in the two Phase 3 pivotal trials for treatment of CHB. The safety analysis population is the 'as treated' population, and includes all subjects who took at least one dose of TAF. In addition to the Phase 3 pivotal trials, 406 subjects received TAF single agent in Phase 1 studies, the majority of which were single dose studies. The safety data extrapolated from these single dose studies are limited and not aggregated in this review of safety data. The safety database for TAF is augmented by safety data from HIV-infected subjects in the Genvoya®, Descovy®, and Odefsey®. Since TAF is a prodrug of TDF, some safety data can be extrapolated from CHB and HIV-infected subjects on TDF containing regimens.

Table 19. Duration of Exposure

Number of patients exposed to the study drug: 866		
>=48 weeks	>=72 weeks	>=88 weeks or longer
N= 831 (96%)	N= 530 (61%)	N= 164 (19%)

8.2.2. Relevant characteristics of the safety population:

Please refer to Section 6.6.2 for additional details in the Demographic and Baseline Disease Characteristics. Further details follow:

- Age (years) 18-35 (n=491), 36-50 (n=505), 51-64 (n=281), ≥ 65 (n=21)
- The median age was approximately 40 years old.
- The racial demographic of this population was 70% Asian.
- Approximately 11% of subjects were cirrhotic by history or fibrotest and evenly matched between groups. The subjects in these studies mostly had mild disease from hepatitis B.
- In general, the subjects were predominantly treatment naïve at about 75%. About 25% had exposure to oral antiviral treatment, the most common being entecavir (about 12%), and about 12% had exposure to interferons.
- Subjects had a median Body Mass Index of about 24 kg/m³.
- Subjects in general had normal renal function with median creatinine clearance of approximately 105 mL/min
- Overall, about 3% had cardiovascular disease, 7% had diabetes mellitus, 12% had hypertension, and 9% had hyperlipidemia.

8.2.3. Adequacy of the safety database

The safety database for both products is comprehensive and adequate to assess safety of TAF for the proposed indication, dosage regimen, duration of treatment, and patient population. Submitted 48 week data over 866 subjects exposed to TAF is sufficient to characterize safety of product. Eight years of experience with for CHB (approved 2008) and 15 years of experience in HIV infection (approved 2001) provide safety information for TFV, the active component for TAF and TDF.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no identified issues regarding data integrity. For Phase 3 trials, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

The quality of the submission was adequate to perform most of the safety review for TAF. Jump Start service analyzed data fitness and found no major issues that would preclude performing a safety review.

8.3.2. Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), version 18.0 was used for AE coding. Adverse events were summarized by MedDRA System Organ Class and Preferred Term. A treatment-emergent AE was defined as any AE that began on or after the treatment start date up to 30 days after the treatment stop date. Our analysis utilized AEs 30 days after last dose, whereas, the Applicant evaluated AEs at last dose.

A serious adverse event (SAE) is any event that results in any one of the following outcomes: death; life-threatening AE; persistent or significant disability/incapacity; required in-patient hospitalization or prolonged hospitalization; congenital anomaly or birth defect; other important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

The Applicant provided guidelines for assessment of laboratory AEs. There were no identified issues with respect to recording, coding, and categorizing AEs. The Applicant categorized SAEs in accordance with standard, regulatory definitions. The applicant grouped by AEs in standard MedDRA hierarchy.

8.3.3. Routine Clinical Tests

Routine clinical evaluation and laboratory testing occurred at pre-specified regular intervals: four-week intervals for the first 48 weeks of the studies, and then eight-week intervals thereafter. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs and inspection of parameters including vital signs, physical examinations, 12-lead ECGs, standard laboratory safety tests, urine tests, and HBV DNA levels. DXA scans were done at screening and every 24 weeks. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

8.4. Safety Results

Deaths

Five on-treatment deaths have been reported thus far; two in Study 108 and three in Study 110, none of which were determined to be study drug related.

Two subjects, one in each trial died due to HCC.

- Subject 8519-1176 in Study 108 was a 51 year-old Asian male with CHB infection randomized to TDF blinded treatment that died due to hepatocellular carcinoma (HCC). This subject had a baseline alfa-fetoprotein level of 14.7 ng/mL. On Day 378, he had a CT abdomen that showed diffuse HCC reported as a Grade 3 SAE. The subject had further complications of pulmonary embolism, anemia, hyperkalemia, and leukocytosis and study drug was discontinued on Day 383. The subject died on Day 392.
- Subject 5691-5109 in study 110 was a 62 year-old Asian man with CHB who was on the TAF blinded arm of the study. On Day 35, he had a CT scan that showed a large hepatoma in the right lobe of the liver. Study drug was continued. The subject passed away on Day 93 with an autopsy confirmed cause of death of HCC.

Reviewer comment: These deaths were considered not to be related to study drug because HCC takes many years to manifest and can occur in subjects with CHB, even in the face of an antiviral response.

The other deaths were due to individual events of unrelated bronchopneumonia, multiorgan failure due to H1N1 influenza infection, and unexplained cardiorespiratory arrest.

- Subject 4037-1250 in Study 108 was a 55 year-old Caucasian female randomized to the TDF arm. On day 400, she presented with bilateral bronchopneumonia and died on Day 411 due to autopsy confirmed multiorgan dysfunction syndrome due to bilateral bronchopneumonia.
- Subject 9695-5213 in Study 110 was a 48 year-old Asian male randomized to the TDF arm. On day 446, he died at home and was cremated on the same day. "Possible (?) Cardiorespiratory Arrest" is listed as the cause of death.
- Subject 9695-5212 in Study 110 was a 55 year-old Asian female on the TAF arm. The subject was found comatose on Day 97 and during her hospitalization; she was septic with bilateral pneumonitis and in acute renal failure. Study drugs

were discontinued and she died on Day 99 due to sepsis, multi-organ failure, and cardio-pulmonary arrest secondary to H1N1 infection.

8.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

Two percent of subjects in both treatment groups (15/866 from TAF and 8/432 from TDF) discontinued study medication due to an adverse event through the first 48 weeks of the trials. This calculation includes the reclassified subjects described in Section 6.1.2 and 6.2.2 who either withdrew consent or discontinued due to investigator discretion as having an adverse event that drove the discontinuation decision.

Narratives were reviewed and the following subjects were discontinued due to an adverse event that was at least possibly related to study drug.

TAF Arms

- Subject 381-1218 was a 48 year-old (yo) male who discontinued study medication on Day 17 due to Grade 3 insomnia, arthralgia, and head discomfort. The investigator considered these events related to study drug.
- Subject 02865-1138 was a 48 yo Asian female who had Grade 2 (moderate) pruritus and Grade 1 (mild) maculopapular rash on Day 4 of TAF treatment. This event was thought to be related to study drug by the investigator. The subject was treated with oral cefuroxime. Study drug was stopped on Day 11, the event was considered resolved on Study day 42. Subject withdrew consent for participating in the study and did not complete treatment free follow-up.
- Subject 02757-4868 was a 62 yo Asian male with nausea, dyspepsia, and vomiting. The subject experienced these Grade 2 symptoms on Day 2 and the AEs resolved on Day 8, but the subject discontinued study drug on Day 9.
- Subject 04058-4786 was a 49 yo White male, HBeAg positive without cirrhosis with increased ALT. The subject had his ALT go from 83 U/L (Grade 1) at baseline to 498 U/L (Grade 4) at Day 57. His maximum was 601 U/L (Grade 4) at Day 66. All other LFTs were within normal range except GGT at Grade 1 elevation. Subject had study drug discontinued on Day 69. Last ALT was 645 U/L (Grade 4) at Day 71. The subjects HBV DNA had a good response going from >110,000,000 IU/mL at baseline to 378,000 IU/mL at Day 66.
- Subject 04036-4535 was a 42 yo White male with nausea and dizziness on Day 1 and discontinued drug on Day 4. The events resolved the same day the study drug was withdrawn. The investigator classified the events as not related to study drug. The subject withdrew consent on Day 32.
- Subject 01057-1043 was a 63 yo Asian male who started on TAF arm and on Day 287 had elevation amylase of 1036 U/L (Grade 4) and abdominal bloating that the investigator thought was study drug related. The amylase subsided after study drug was stopped and the adverse event resolved 14 days after stopping

study drug. Lipase and other LFTs were normal. The subject started entecavir per the site standard of care 14 days after study drug was stopped.

- Subject 04058-5303 was a 52 yo Hispanic male with ischemic cardiomyopathy who had increased lipase and diarrhea. On Day 114, the subject experienced lipase of 510 U/L (Grade 4) and amylase of 249 U/L (Grade 3). All other LFTs and PT were normal. The study drug was discontinued on Day 123 and the lipase and amylase decreased three days afterward to 121 U/L (Grade 1) and 121 U/L (Grade 1), respectively. The subject was rechallenged with the drug on Day 128 and had 521 U/L (Grade 4) elevation of lipase and 255 U/L (Grade 3) elevation of amylase. Subject did not complain of abdominal pain but did have diarrhea on Day 163 which resolved seven days later with drug cessation and both events were considered resolved on Day 174. The investigator considered both AEs of increased lipase and diarrhea were related to study drug. Subject was discontinued due to investigator's discretion.

TDF ARMS

- Subject 2145-4641 was a 59 yo female who discontinued study medication on day 13 due to Grade 2 fatigue and insomnia.
- Subject 02826-4561 was a 34 yo Asian male with nausea, dizziness, abdominal discomfort, dyspepsia, and fatigue. On Day 17, the subject had abdominal pain (Grade 1) dyspepsia (Grade 2), and fatigue (Grade 3). The events were considered study drug related and the study drug was discontinued on Day 18. The subject also had moderate oral herpes (Grade 2) on Day 17 and increased ALT 206 U/L (Grade 3) on Day 1. The ALT increase substantially to a maximum of 1644 U/L (Grade 4) on Day 17 but then decreased to 372 U/L (Grade 3) on Day 29. The increased ALT and AST was not determined to be related to study drug by the investigator; however, all events were resolved with dechallenge on Day 61.
- Subject 05730-5081 was a 32 yo Asian male with HBeAg positive, treatment naïve, without cirrhosis who had increased ALT. The subject had an ALT value of 674 U/L (Grade 4) on baseline and increased to 903 U/L on Day 24 (Grade 4). AST was 275 U/L (Grade 3) at baseline and increased at all times during double-blind period (range 295-350 U/L). All other liver-related parameters (alkaline phosphatase [ALP]; gamma-glutamyl transferase [GGT]; lactate dehydrogenase [LDH]; total, direct, and indirect bilirubin; and prothrombin time [PT] were within the normal range. No jaundice occurred. The adverse event of increased ALT was considered Grade 2 (moderate) in severity and not related to study drug. Study drug was discontinued on Day 26. His HBV DNA went from >110,000,000 IU/mL to 86,400 IU/mL (Day 15) at unscheduled visit and 15,000 at early study drug discontinuation visit. At follow-up Week 4 the HBV viral load was back to baseline high level of >110,000,000 IU/mL.

- Subject 05685-4602 was a 30 yo Asian male with h/o PUD and GERD who had increased upper abdominal pain which was labelled as Grade 1. The subject had a history of anxiety. The subject experienced upper abdominal pain on Day 18. Study drug was discontinued and the subject withdrew consent. The subject's HBV viral load went from >110,000,000 IU/mL to 405,000 on Day 25. On Day 25 subject's symptoms were continuing. His liver function tests and amylase were within normal limits.
- Subject 4844-4697, discontinued TDF on Day 337 due to optic neuritis and headache. This was a 33 yo Romanian female randomized to TDF. On approximately Day 215, she presented with optic neuritis. She was seen by neurologist and ophthalmologist and treated with non-steroidal anti-inflammatory drugs. On approximately Day 275, she was hospitalized and during the hospitalization, she was started on steroids. Steroids were tapered and her visual disorder improved on Day 333. Study drug was discontinued on Day 337.

Other events leading to discontinuation from the TAF (pancreatic cancer, HCC, death secondary to influenza, basilar artery occlusion) or TDF (HCC x 2, depressed mood/musculoskeletal chest pain) arms were determined not to be related to the study drugs.

8.4.3. Significant Adverse Event

The initial NDA application included 57 reports of non-fatal serious adverse event reports (SAEs): 33/866 (4%) among subjects randomized to TAF and 20/432 (5%) among those randomized to TDF. The safety update included an additional nine SAEs; seven in TAF recipients and two in TDF recipients. Three subjects had fatal outcomes due to their SAEs (see Deaths Section 8.4.1). No specific pattern of SAEs was observed in either treatment groups.

The narratives of each case were reviewed and only one event of headache and visual changes in a TDF subject (#048844-4697) were determined to be possibly related to study drug; this subject also discontinued study treatment (see Section 8.4.2 above). Of note, this case was reviewed by the Ophthalmologic consultant and determined the symptomatology was not consistent with uveitis.

Unrelated cellulitis occurred in three TDF subjects. All other SAEs occurred in two or less subjects in the arms and are as follows. In the TAF arms, the SAEs were adenocarcinoma of colon, anemia, anal abscess, angina pectoris, appendicitis, back pain, basilar artery occlusion, breast carcinoma in situ, bronchitis chronic, calculus ureteric, carcinoma of the pancreas, cervical radiculopathy, diarrhea infectious, dizziness, *Escherichia* bacteremia, *Escherichia* urinary tract infection, gastrointestinal submucosal tumor, hematuria, hand fracture, hypertension, hypoesthesia, hypoglycemia, intervertebral disc degeneration, left elbow trauma, ligament rupture, limb crushing injury, lobar pneumonia, malaria, meniscus injury, nasal septum deviation,

nephrolithiasis, pancreatitis, periodontitis, pneumonia, pyrexia, scrub typhus, spinal compression fracture, syncope, and vertigo/dizziness. In the TDF arms, the SAEs were abdominal pain upper, anemia, angina unstable, calculus urinary, cerebrospinal fluid leakage, dengue fever, epilepsy, hepatic fibrosis, hypoglycemia, inguinal hernia, leukocytosis, lower limb fracture, ovarian cyst, pulmonary embolism, pyelonephritis, spondylolisthesis, thymoma, transition cell carcinoma, traumatic clavicle fracture, and urinary tract infection.

Eight subjects (3 TAF, 5 TDF) were diagnosed with Hepatocellular Carcinoma during the reporting period; none were related to study drug.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Seventy-percent of subjects in the two pivotal trials experienced treatment emergent adverse events (TEAEs). The most frequently reported TEAEs, occurring in $\geq 5\%$ in any study are shown in Table 20. TEAEs considered related to study drug included abdominal distention, headache, fatigue and nausea in subjects treated with TAF, and nausea, fatigue, arthralgia, decreased appetite and headache in those treated with TDF.

(b) (4). According to the Guidance for Industry on Adverse Reaction Section of Labeling, the adverse reaction section should include adverse reactions where there is some basis to believe there is a causal relationship to the use of the drug including the adverse events that are consistent with the pharmacology of the drug. Therefore, we believe that adverse reaction profile for TAF should be consistent with TDF (VIREAD®), since both drugs contain tenofovir, and all adverse reactions reported in $\geq 5\%$ of subjects is recommended to be represented in the label.

Table 20: Common TEAEs

N (%)	Study 0108		Study 0110	
	TAF N=285	TDF N=140	TAF N=581	TDF N=292
Nasopharyngitis	30 (10.5)	15 (11)	56 (10)	16 (5.5)
Upper respiratory tract infection	35 (12)	10 (7)	51 (9)	22 (7.5)
Headache	40 (14)	14 (10)	42 (7)	22 (7.5)
Fatigue	16 (6)	9 (6)	33 (6)	14 (5)
Cough	18 (6)	8 (6)	37 (6)	19 (6.5)
Nausea	15 (5)	9 (6)	28 (5)	13 (4.5)
Diarrhea	8 (3)	2 (1)	27 (5)	15 (5)
Abdominal pain, upper	9 (3)	4 (3)	19 (3)	15 (5)

8.4.5. Laboratory Findings

In Phase 3 studies, clinical laboratory evaluations included assessment of hematologic, blood chemistry, and liver function parameters. Overall, 30% of subjects in the TAF arms and 27% of subjects in the TDF arms had at least one Grade 3 or 4 laboratory abnormality.

Hematology lab abnormalities

Taken individually, the incidence of Grade 3 or 4 abnormalities in hemoglobin, white blood cell count, lymphocytes, neutrophils, and platelets were low ($\leq 1\%$) and balanced between study arms. Of note, Grade 3 or 4 hematology-related abnormalities that occurred in $\geq 2\%$ of subjects were occult blood and urine erythrocytes. When further evaluated, the majority of these events occurred among women as shown in the Table 21 below, and these events were more likely to have been due to menstruation rather than organ pathology, such as cancer.

Table 21: Grade 3 or 4 Hemoglobin, Occult Blood, and Urine Erythrocyte Abnormalities in Integrated Trial Data.

Maximum Post Baseline Toxicity Grade	TAF	TDF
Hemoglobin	6/866 (1%)	0/432 (0%)
Occult Blood	59/866 (7%)	27/432 (6%)
Occult Blood Women	55/59 (93%)	22/27 (81%)
Urine Erythrocytes	56/866 (6%)	30/432 (7%)
Urine Erythrocytes Women	48/56 (86%)	27/30 (90%)

Clinical Lab Abnormalities

Clinical lab parameters that merit more detailed discussion include changes in liver function tests, changes in lipid parameters, amylase and lipase abnormalities, elevated serum glucose levels, and glycosuria and are described in subsequent sections. Taken individually, the incidence of Grade 3 or 4 abnormalities in sodium, potassium, magnesium and phosphorus were low ($\leq 1\%$) and balanced between study arms. Grade 3 or 4 creatinine kinase elevations were reported at a rate of 3% in both arms. The elevations of creatinine kinase occurred at a variety of time points, were not consistently present, and were not related to instances of rhabdomyolysis.

8.4.6. Vital Signs

There were no patterns of differences in vital signs, including median body weight, observed in any of the studies.

8.4.7. Electrocardiograms (ECGs)

One subject in each arm had treatment emergent clinically significant ECG changes at Week 48. One TAF treated subject with a history of coronary artery disease, angina, and coronary artery bypass graft performed at approximately Week 4 had a clinically significant ECG change of septal infarct. One TDF treated subject had sinus bradycardia that initially was deemed clinically significant but later changed to not clinically significant due to observed sinus bradycardia at baseline.

8.4.8. **QT**

The potential for TAF to cause QT prolongation was evaluated under IND 063737 in April 2013. The conclusion from the data submitted from a thorough QT study was that TAF does not lead to significant QTc prolongation effect. There were no events Study 108 or 110 related to QTc prolongation.

8.4.9. **Immunogenicity**

As TAF is a small molecule, immunogenicity issues were not anticipated and not specifically addressed during the clinical trials.

8.5. **Analysis of Submission-Specific Safety Issues**

8.5.1. **Bone Safety**

The bone toxicity of TDF has been appreciated for many years and has been observed in animal models and in humans. The exact mechanisms underlying decreased bone mineral density from TDF are not fully understood but are thought to involve the renal effects of the active antiviral tenofovir diphosphate (TFV) and to be proportional to its systemic exposure. TDF has been associated with enhanced BMD decline and nonpathologic fractures in HIV infected patients on TDF compared with other antiretrovirals. Bone safety data in trials with Genvoya® favor the TAF containing regimen (Genvoya®) over the TDF containing regimen (Stribild®) (See Dr. William Tauber's review in the Genvoya® NDA application for full details). Recently 96 week data has informed the decision to remove Warnings for Bone loss and demineralization from the label but retain pertinent information in the Adverse Reactions section of the label.

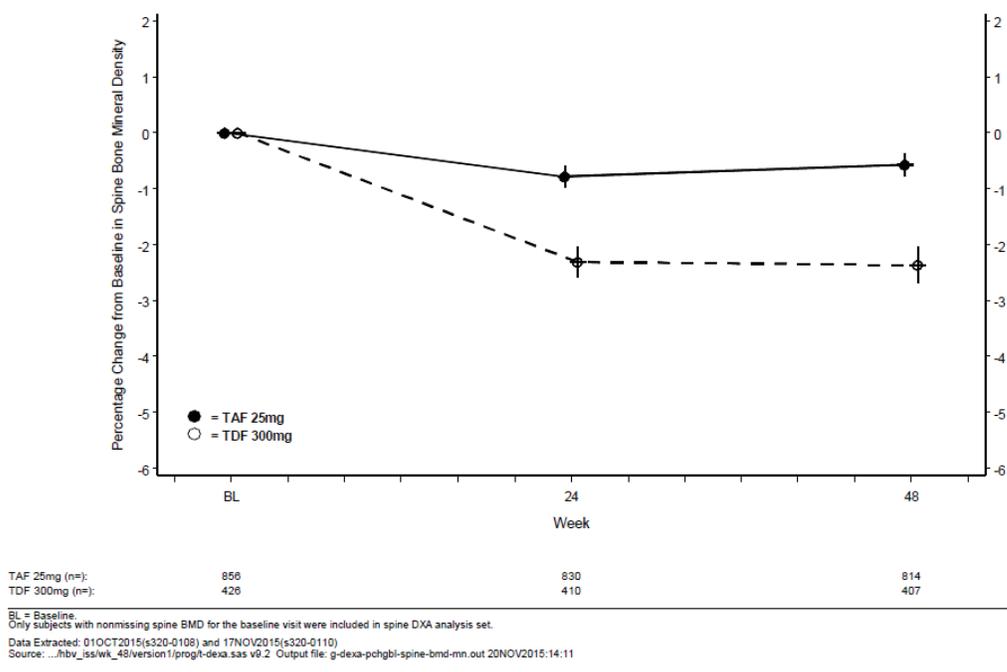
Changes in bone mineral density were a pre-specified safety endpoint. Associated with its 90% lower TFV systemic exposure, TAF is anticipated to have a more favorable bone toxicity profile. The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for the pooled analysis of Studies 108 and 110.

Overall, there were greater changes in subjects treated with TDF, but the clinical relevance of these changes is presently unknown as TDF-related osteopenia/osteoporosis can take many months to years to manifest.

Bone Mineral Density

Dual Energy X-ray Absorptiometry (DXA) scans of lumbar spine and hip were performed on all subjects at screening, every 24 weeks, and at early discontinuation if not done within the previous 12 weeks. At Week 48, mean spine BMD declined from baseline largely with TDF compared to TAF, 2.37% vs. 0.57% ($p < 0.001$), respectively (See Figure 9). In a smaller subset that completed evaluation at week 72, the changes were similar. (See Table 22 below).

Figure 9: Lumbar spine BMD changes mean (95% CI) by visit



Source: Applicant ISS, Figure 2

Table 22: Lumbar Spine BMD Changes

	TAF 25 mg (N=856)	TDF 300 mg (N=426)	TAF vs. TDF*	
			p-value	LSM difference (95% CI)
Baseline, n	856	426		
Mean BMD (g/cm ²)	1.056	1.052	0.67	
Week 24, n	830	410		
% change from BL, mean (SD)	-0.79 (2.64)	-2.31 (2.66)	<0.001	1.53 (1.21, 1.84)
Week 48, n	814	407		
% change from BL, mean (SD)	-0.57 (2.91)	-2.37 (3.21)	<0.001	1.80 (1.44, 2.16)
Week 72, n	192	93		
% change from BL, mean (SD)	-0.12 (3.00)	-2.28 (3.60)		
Week 96, n	16	9		
% change from BL, mean (SD)	-0.94 (2.20)	-3.26 (1.88)		

* p-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect
 Values represent observed data in all patients with nonmissing baseline spine DXA
 Source: ISS Table 23.2.2

Source: Dr. Steven Voss, DBRUP reviewer

At Week 48, the incidence of ≥5% decline in spine BMD was 6.3% among TAF recipients, and 20.4% among TDF recipients (p<0.001) as shown in the Table below.

Table 23: Categorical Changes in Lumbar Spine BMD Baseline to Week 48.

Category of % change from baseline	TAF 25 mg N=814* n (%)	TDF 300 mg N=407* n (%)
>0 (increase)	331 (40.7)	89 (21.9)
≥ -1.0 to ≤ 0	131 (16.1)	49 (12.0)
≥ -3.0 to < -1.0	193 (23.7)	114 (28.0)
≥ -5.0 to < -3.0	108 (13.3)	72 (17.7)
≥ -7.0 to < -5.0	45 (5.5)	50 (12.3)
≥ -10.0 to < -7.0	5 (0.6)	29 (7.1)
< -10.0	1 (0.1)	4 (1.0)

*subjects in Spine DXA analysis dataset (nonmissing baseline) and (observed) data at week 48
 Source: ISS Table 25.2, ADDEXA

Source: Dr. Steven Voss, DBRUP reviewer

Subgroup analysis lumbar spine BMD

Differences between TAF and TDF in spine BMD percentage changes at week 48 were generally consistent across subgroups of sex, age, race, and region (See Table 24 below). Additionally, the Applicant demonstrated that changes in BMD between the

arms were generally consistent in subjects with low and high baseline viral load (ISS Table 27). Small but greater differences were seen in East Asia than other regions of the world, and greater differences were seen in Asians than Non-Asians.

Table 24: Lumbar Spine BMD, Mean Percentage Change at Week 48 by Subgroups

	TAF 25 mg	TDF 300 mg
Sex		
Male (n=771)	-0.48	-2.07
Female (n=453)	-0.70	-2.90
Age		
< 50 years (n=919)	-0.43	-2.01
≥ 50 years (n=305)	-1.02	-3.22
Race		
Asian (n=970)	-0.53	-2.43
Non-Asian (n=255)	-0.68	-2.14
Region		
East Asia* (n=592)	-0.70	-3.01
Europe** (n=242)	-0.75	-2.08
North America*** (n=206)	-0.67	-1.75
U.S.A. (n=84)	-0.72	-2.12
Austral/NZ/India (n=184)	0.17	-1.15
*Hong Kong, Japan, Singapore, South Korea, Taiwan		
**Bulgaria, France, Italy, Poland, Romania, Russia, Spain, Turkey, UK		
***Canada, USA		
Source: ADDEXA		

Source: Dr. Steven Voss, DBRUP reviewer

Femoral neck BMD and total hip BMD changes also favored TAF over TDF. Week 48 results showed a decrease in femoral neck mean BMD of -0.16% in the TAF arm versus -1.86% in the TDF arm ($p < 0.001$) as shown in the table below. Through Week 48, the incidence of $\geq 7\%$ mean percentage decline in femoral neck BMD was 3% versus 6% in the TAF and TDF arms, respectively (see Table 25); whereas mean decline in the total hip BMD was $< 1\%$ versus 2% in the TAF and TDF arms, respectively. (See Table 26). Unlike the lumbar spine changes, the hip and femoral neck changes in favor of TAF appeared to be enhanced in the Week 72 data, but the number of subjects at that time point was only a fraction of those on study drug.

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 NDA 208464
 Vemlidy (Tenofovir Alafenamide)

Table 25: Femoral Neck BMD Changes

	TAF 25 mg (N=851)	TDF 300 mg (N=426)	TAF vs. TDF*	
			p-value	LSM difference (95% CI)
Baseline, n	851	426		
Mean BMD (g/cm ²)	0.956	0.952	0.69	
Week 24, n	822	405		
% change from BL, mean (SD)	-0.25 (1.87)	-1.06 (2.03)	<0.001	0.81 (0.58, 1.04)
Week 48, n	807	404		
% change from BL, mean (SD)	-0.16 (2.24)	-1.86 (2.45)	<0.001	1.70 (1.42, 1.97)
Week 72, n	190	93		
% change from BL, mean (SD)	-0.10 (2.09)	-2.34 (2.66)		
Week 96, n	16	9		
% change from BL, mean (SD)	0.02 (1.69)	-3.59 (2.11)		

* p-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect
 Values represent observed data in all patients with no missing baseline hip DXA
 Source: ISS Table 23.1.2

Source: Dr. Steven Voss, DBRUP reviewer

Table 26: Categorical Changes in Femoral Neck BMD Baseline to Week 48.

Category of % change from baseline	TAF 25 mg N=807* n (%)	TDF 300 mg N=404* n (%)
>0 (increase)	320 (39.7)	105 (26.0)
≥ -1.0 to ≤ 0	136 (16.9)	43 (10.6)
≥ -3.0 to < -1.0	200 (24.8)	107 (26.5)
≥ -5.0 to < -3.0	87 (10.8)	87 (21.5)
≥ -7.0 to < -5.0	38 (4.7)	39 (9.7)
≥ -10.0 to < -7.0	21 (2.6)	14 (3.5)
< -10.0	5 (0.6)	9 (2.2)

*subjects in Hip DXA analysis dataset (nonmissing baseline) and (observed) data at week 48
 Source: ADDEXA

Source: Dr. Steven Voss

Table 27: Categorical Changes in Total Hip BMD Baseline to Week 48.

Category of % change from baseline	TAF 25 mg N=807* n (%)	TDF 300 mg N=404* n (%)
>0 (increase)	383 (47.5)	83 (20.5)
≥ -1.0 to ≤ 0	148 (18.3)	67 (16.6)
≥ -3.0 to < -1.0	208 (25.8)	146 (36.1)
≥ -5.0 to < -3.0	58 (7.2)	79 (19.6)
≥ -7.0 to < -5.0	7 (0.9)	21 (5.2)
≥ -10.0 to < -7.0	3 (0.4)	5 (1.2)
< -10.0	0	3 (0.7)
*subjects in Hip DXA analysis dataset (nonmissing baseline) and (observed) data at week 48 Source: ISS Table 25.1, ADDEXA		

Source: Dr. Steven Voss

Reviewer comment: *The above data were reviewed by DBRUP. The DBRUP reviewer considers declines of ≥ 5% in lumbar spine and ≥ 7% in femoral neck BMD to represent potentially significant declines, taking into account the precision error of DXA at the lumbar spine. However, the reviewer was not able to determine the clinical relevance of these differences and longer duration data will be reviewed once it becomes available.*

Vitamin D levels

Baseline 25-OH-vitamin D was measured with baseline levels of approximately 18 in each of the treatment arms. There was no correlation between levels and spine BMD response at week 48. Further, a sensitivity analysis performed by the Applicant with 155 pts (116 TAF, 39 TDF) receiving vitamin D, calcium, and/or osteoporosis drugs found that BMD changes in a subset were similar to the overall study populations (ISS Request 7633 Table 4.3).

Bone Biomarkers

Serum markers of bone resorption (CTX) and formation (P1NP, BSAP, osteocalcin) demonstrated smaller median percentage decreases in TAF recipients than in the TDF recipients. TAF treatment resulted in less median percentage increases in PTH than TDF.

Table 28: Bone Biomarkers and PTH: Median Percentage Changes from Baseline

	TAF 25 mg (N=866)	TDF 300 mg (N=432)	p-value (TAF-TDF)
Serum CTX			
week 24	-4.8	29.9	<.001
week 48	-4.3	29.3	<.001
Serum PINP			
week 24	-6.1	18.9	<.001
week 48	-8.8	16.1	<.001
Serum BSAP			
week 24	-7.0	14.6	<.001
week 48	-12.4	7.5	<.001
Serum osteocalcin			
week 24	1.4	14.6	<.001
week 48	0.9	20.0	<.001
Serum PTH			
week 24	14.5	21.3	0.002
week 48	13.0	23.5	0.011
p-values are from the 2-sided Wilcoxon rank sum test to compare treatment groups Source: ISS, Tables 26.1 through 26.5			

Source: Dr. Steven Voss, DBRUP reviewer

Reviewer comments: The significance of these biomarker assessments as it relates to their risk of clinically significant tenofovir-induced bone toxicity is unclear.

Fractures

Less than one percent of subjects in either arm had reported fracture events (6/866 in TAF arm and 1/432 in TDF arm). Two of the fractures in the TAF arm, one traumatic fracture of the hand and one of the spine, occurred in subjects with non-drug related osteoporosis-range T scores. An incidental spinal compression fracture that may have been related to a previous motor vehicle accident was observed on a TAF treated subject with T score within normal range. The mean age in the pooled study was approximately 41 years old, where osteoporosis is less likely.

Reviewer comment: Fracture incidence was removed from the Genvoya® label recently as the observed fractures in the pivotal trials were mainly traumatic, and not fragility fractures. Based on a similar finding in this NDA, the addition of fracture data in the label is not necessary.

8.5.2. Renal Safety

A third key safety endpoint for the pooled analysis of Studies 108 and 110 were differences in changes in serum creatinine between TAF and TDF. Tenofovir exposures are thought to be related to the development of Fanconi syndrome and acute

and chronic renal failure. With TDF, the incidence of nephrotoxicity is severe enough to warrant discontinuation in TDF in about 1% of patients. Tenofovir alafenamide is believed to have lower impact on the renal proximal tubules due to its lowered serum tenofovir exposures.

For eligibility into Study 108 and 110 subjects were to have a CrCl by CG of ≥ 50 mL/min (reduced from ≥ 60 mL/min per Protocol Amendment 2), have no significant renal disease, and not be taking immunomodulators, nephrotoxic agents, or agents capable of modifying renal excretion. Baseline characteristics included an eGFR of approximately 100 mg/dL across treatment groups.

Differences in serum creatinine favoring TAF over TDF have been demonstrated in the data submitted in the Genvoya® application and this application. Beyond the small but statistically significant changes in serum creatinine and eGFR, the evidence for benefit is based upon non-validated laboratory testing results. (b) (4)

Renal Adverse Events

Two subjects in the TAF arms had renal AEs resulting in significant changes in creatinine, both of which were considered by the investigators as unrelated to TAF.

- Subject 02145-1077 died with H1N1 influenza and had acute renal failure prior to her death.
- Subject 02145-1007 had a history of diabetes and hypertension and had creatinine increase, which then returned to near baseline at Week 72.

There were no cases of renal function related adverse events attributed to study drug including SAEs, reports of proximal tubulopathy, or discontinuations of therapy for an AE. Other AEs Incident Rates by Dictionary Derived Terms are listed in Table 29, and all occurred in <1% of subjects.

Table 29. Renal and Urinary Adverse Events by Treatment Arm

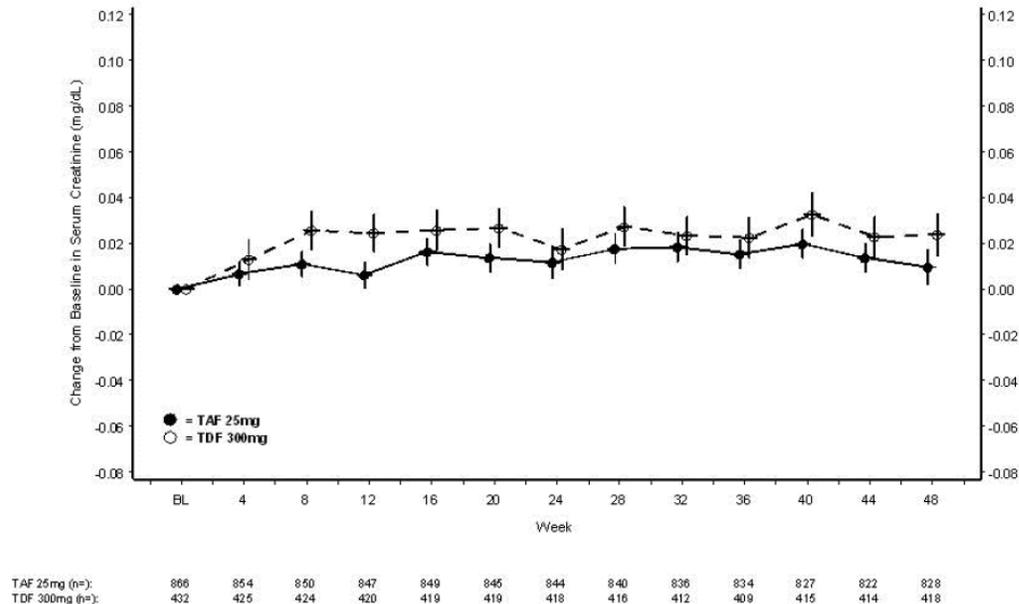
Dictionary Derived Term	TAF 25mg N=866	TDF 300mg N=432
Dysuria	12 (1%)	3 (1%)
Nephrolithiasis	8 (1%)	3 (1%)
Proteinuria	5 (1%)	3 (1%)
Hematuria	3 (0%)	2 (0%)
Renal cyst	5 (1%)	0 (0%)
Calculus ureteric	4 (0%)	0 (0%)
Renal colic	1 (0%)	1 (0%)
Calculus urinary	0 (0%)	2 (0%)
Hydronephrosis	1 (0%)	1 (0%)
Glycosuria	2 (0%)	0 (0%)
Urinary incontinence	2 (0%)	0 (0%)
Hypertonic bladder	1 (0%)	0 (0%)
Hydroureter	1 (0%)	0 (0%)
Renal impairment	1 (0%)	0 (0%)
Renal pain	1 (0%)	0 (0%)
Nocturia	1 (0%)	0 (0%)
Pollakiuria	1 (0%)	0 (0%)
Urinary straining	1 (0%)	0 (0%)
Urinary tract pain	1 (0%)	0 (0%)
Acute kidney injury	1 (0%)	0 (0%)

Review tool used: JReview

Changes in Laboratory Patterns

Serum creatinine levels remained fairly unchanged between the treatment arms (See Figure 10); although the small changes in serum creatinine were statistically significant, but unlikely clinically relevant, favoring TAF (0.01 mg/dL in TAF versus 0.03 mg/dL in TDF), in Study 110 (see Table 30). Hypophosphatemia can be an indicator of Fanconi syndrome, and serum phosphorus levels had small mean changes no greater than 0.1 mg/dL in either arm.

Figure 10: Change from Baseline in SCr (mg/dL) by Visit for ISS (observed data)



Source: Applicant, Summary of Clinical Safety Figure 3

Table 30: Change from Baseline in Serum Creatinine (SCr) at Week 48 by Study

	TAF		TDF		p-value
	n/N	SCr Change	n/N	SCr Change	
Study 108	275/285	0.01 (0.09)	135/140	0.02 (0.10)	0.32
Study 110	553/581	0.01 (0.12)	283/292	0.03 (0.09)	0.02

Source: Applicant, body of report 108 and 110, Table 55.2

Source: Dr. Kimberly Smith

Six subjects (1%) treated with TAF had graded serum creatinine abnormalities, five of which were isolated elevations. One subject (Subject 02145-1007 described above) had transient persistent elevation in creatinine likely due to hypertension and diabetes. No subject treated with TDF had graded serum creatinine abnormalities.

The Applicant assessed changes in proteinuria as another safety endpoint. Treatment emergent proteinuria occurred in five (1%) subjects in the TAF group and three (1%) subjects in the TDF group, all of which were grade 1.

Median changes in exploratory biomarkers of urine protein to creatinine ratio (UPCR), Urine albumin to creatinine ration (UACR), urine retinol binding protein (RBP), urine Beta-2 microglobulin, and fractional excretion of uric acid (FEUA) favored TAF over TDF (see Table 31 below, FEUA not listed). The significance of these biomarker

assessments as it relates to their risk of clinically significant tenofovir-induced renal toxicity is unclear.

Table 31: Renal Biomarkers at Week 48 in Safety Population

Parameter	Median Percentage Change (%) (Q1, Q3)		P-Value ^a
	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)	
UPCR (mg/g)	6.0 (-31.0, 57.6)	16.5 (-21.6, 72.4)	0.010
UACR (mg/g)	6.9 (-25.8, 46.7)	12.2 (-21.0, 63.5)	0.073
Urine RBP to Urine Creatinine Ratio (µg/g)	-0.3 (-23.2, 33.3)	25.1 (-7.9, 73.2)	< 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio (µg/g)	-3.5 (-34.3, 32.0)	37.9 (-4.6, 152.4)	< 0.001

UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio
 % Change = Change from baseline at a postbaseline visit/baseline × 100%.

a P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Source: Applicant ISS Table 22

Glycosuria

Normoglycemia glycosuria may be an indicator of proximal tubular dysfunction. Laboratory shift tables showed an imbalance in ≥ 3+ urine glucose between the arms with 5% in the TAF arm and 1% in the TDF arms (See Tables 32 and 33 below). Grade 1 and 2 abnormalities in glycosuria were evenly matched between the arms. Diabetics were evenly matched in the two treatment arms at 7%. Further evaluation of the trial data revealed, that the majority of the serum glucose elevations occurred in the setting of serum glucose ≥ 160 mg/dL (TAF 82% and TDF 78%), while the other subjects with glycosuria had hyperglycemia at other time points. Therefore, glycosuria in the TAF arms are not likely related to tubular dysfunction/tenofovir induced renal toxicity.

Table 32: The Sponsor’s Grading System for Glucose Levels

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hyperglycemia, fasting (mg/dL)	110-125	>125-250	>250-500	>500
Hyperglycemia, Nonfasting (mg/dL)	116-160	>160-250	> 250-500	>500
Glycosuria (Dipstick)	1+	2-3+	4+	N/A

Table 33: Treatment Emergent Abnormalities by Maximum Toxicity Grade in Serum Glucose and Urine Glucose Parameters

Parameter	Toxicity Grade	TAF 25mg (N=866)	TDF 300mg (N=432)
Fasting Glucose (mg/dL)	1	61 (7%)	33 (8%)
	2	42 (5%)	15 (3%)
	3	9 (1%)	0 (0%)
Glucose (mg/dL)	1	229 (26%)	129 (30%)
	2	87 (10%)	19 (4%)
	3	24 (3%)	6 (1%)
	4	1 (0%)	0 (0%)
Urine Glucose	1	12 (1%)	3 (1%)
	2	28 (3%)	16 (4%)
	3	39 (5%)	4 (1%)

Reviewer’s comment: Changes from baseline creatinine levels to Week 48 were small and clinically insignificant, in both treatment arms and renal adverse events were minimal. No cases of proximal tubule dysfunction were seen in this application, and increased Grade 3 glycosuria in the TAF arms is unlikely to be related to tubular dysfunction. Given that TAF is the prodrug to TDF and trials thus far have enrolled low risk subjects for renal failure (e.g. eGFR>50 mL/min), the consultant from DCRP agrees with the Division’s assessment that the label should still include warnings and precaution for “new onset or worsening renal impairment” and recommendations for monitoring. Discussions with the Applicant regarding the product label are in progress at this time.

(b) (4)

8.5.3. Serum Amylase and Pancreatitis

Amylase levels were evaluated at similar intervals as serum chemistry and liver function tests in Studies 108 and 110. Reflex lipase testing was to be performed in subjects with amylase > 1.5 X ULN, as lipase levels are more specific for pancreatitis. The Applicant’s definition of the graded abnormalities for amylase and lipase are provided in Table 34 below. In Study 108, the rate of Grade 3 and 4 amylase increases were greater in the TAF arm at 5% than 2% in the TDF arm, whereas, in Study 110, the rates were similar at 2% in each arm (See Table 35 below). The majority of subjects had asymptomatic isolated or intermittent amylase increases noted around Week 4 and reported as long as 48 weeks after initiation of treatment, and most did not have any changes to their study medication.

Table 34: The Applicant’s grading system for amylase and lipase levels

	Grade 1	Grade 2	Grade 3	Grade 4
Amylase	> 1-1.5 X ULN	> 1.5-2 X ULN	> 2-5 X ULN	>5 X ULN
Lipase	> 1-1.5 X ULN	> 1.5-3 X ULN	> 3-5 X ULN	>5 X ULN

Table 35: Treatment emergent Grade 3 and 4 Amylase and Lipase elevations

	Study 108 TAF N=285	Study 108 TDF N=140	Study 110 TAF N=581	Study 110 TDF N=292	Pooled Arm TAF N=866	Pooled Arm TDF N=432
Amylase						
Grade 3	13 (5%)	2 (1%)	9 (2%)	7 (2%)	22 (3%)	9 (2%)
Grade 4	1 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Grade 3&4	14 (5%)	3 (2%)	9 (2%)	7 (2%)	23 (3%)	10 (2%)
Lipase						
Grade 3	4 (1%)	0 (0%)	0 (0%)	1 (0%)	4 (0%)	1 (0%)
Grade 4	1 (0%)	1 (1%)	2 (0%)	2 (1%)	3 (1%)	3 (0%)
Grade 3&4	5 (2%)	1 (1%)	2 (0%)	3 (1%)	7 (1%)	4 (1%)

In the TAF arms, eight (8/866, 1%) subjects experienced 10 concurrent AEs, and two of these subjects discontinued TAF. These two subjects follow, and each had two AEs (in italics):

- Subject 04058-5303 had normal amylase at baseline. He had a Grade 3 amylase increase (249 U/L) with a Grade 4 lipase increase (510 U/L) on Day 114. Total cholesterol and triglycerides were within normal limits. Amylase and lipase decreased to Grade 1 within three days off treatment. On rechallenge five days after treatment stopped, the subject developed a Grade 3 amylase (255 U/L) and Grade 4 lipase, this time along with diarrhea. Study drug was discontinued; and amylase elevation, lipase elevation, and diarrhea resolved seven days later. These AEs of *elevated lipase* and *diarrhea* were considered study drug-related.
- Subject 01057-1043 had a Grade 3 amylase level of 305 U/L at baseline. On Day 287, he had a Grade 4 amylase increase (1036 U/L); serum lipase was within normal limits. The subject experienced an AE of *increased amylase*, which the investigator considered to be related to study drug, and Grade 1 *abdominal distension/bloating*, which the investigator assessed as not related to study drug. The event resolved 14 days after study drug was discontinued and the subject was treated with entecavir per standard of care at the study site. This reviewer reclassified this AE of abdominal distension as related to study drug.

Five additional subjects treated with TAF who had elevated amylase levels reported symptoms, such as nausea, low back pain, abdominal pain, abdominal tenderness,

biliary pancreatitis (SAE-unrelated), and pancreatitis; all had resolution of their symptoms with continued TAF. These subjects follow and each had one AE (in italics):

- Subject 04037-1249 had a Grade 1 amylase level of 143 U/L at baseline. At Week 8, he had Grade 3 amylase increase (276 U/L) with a Grade 3 lipase increase (431 U/L), and at Week 12, a Grade 2 amylase increase (183 U/L) with normal lipase. This subject had the AE of Grade 2 *pancreatitis* reported at week 12 that the investigator assessed as not related to study drug. This AE was reclassified by this reviewer as possibly related to study drug.
- Subject 01069-1159 had Grade 1 amylase increase at baseline (129 U/L) but after TAF initiation had many Grade 2-4 elevations from Week 4 to Week 32. She experienced Grade 1 lower *back pain* at Week 16 to Week 26. She also had confirmed Grade 4 elevation of lipase (1302 U/L) during Week 16 and Week 20 (654 U/mL). The amylase level normalized and back pain resolved while on TAF treatment with the addition of paracetamol. The Applicant's medical monitor assessed the back pain as potentially associated with pancreatitis, but the investigator assessed the back pain as not related to study drug. This reviewer agrees that this AE could be related to study drug.
- Subject 02757-4647 had a Grade 1 amylase elevation of 124 U/L. From Week 23 to Week 29, he experienced Grade 1 abdominal pain, with a Grade 3 amylase level of 332 U/L at Week 28. The *abdominal pain* then resolved at Week 44, at which time he had another single Grade 3 amylase elevation of 493 U/L without lipase elevation. The investigator classified this AE as not related to study drug, but this reviewer reclassified the AE as related to study drug.
- Subject 08599-5171 had Grade 2 amylase elevation of 184 U/L at baseline. This subject had recurrent Grade 3 amylase elevation without lipase elevation from Week 8 to Week 36 (maximum 220 U/L at Week 12), with AE of Grade 1 *nausea* at Week 14 that the investigator assessed as not related to study drug. This reviewer reclassified this case as related to study drug.
- Subject 05691-1421 had Grade 3 pancreatitis less likely related to TAF because the AE was *biliary pancreatitis* requiring hospitalization and broad-spectrum antibiotics (biliary pancreatitis event is in SAE Section 8.4.3). This amylase elevation and AE were not related to study drug.
- A sixth subject, Subject 02865-1023, had a Grade 2 amylase level of 194 U/L at baseline, with ALT of 148 mg/mL and HBV DNA of 9,270,000 IU/mL. At Week 4, he had AE of Grade 1 *abdominal tenderness* and Grade 3 amylase (207 U/L). Serum lipase was within normal limits, but ALT level was 790 (18.4X ULN) at this time point. At Day 35, his ALT was 80 (HBV DNA 13,400 IU/mL on Day 28). At Week 8, his amylase was back to his baseline at Grade 2 (181 U/L). This subject had many recurrent Grade 3 amylase increases during treatment including at Week 12 and up to Week 72. The investigator assessed these AEs as related to study drug. This reviewer agrees with the AE related to study drug, but the

subject's constellation of symptoms may be from a hepatic flare rather than pancreatitis.

No subjects treated with TDF with experienced Grade 3 or 4 elevated amylase levels had associated symptoms or discontinued treatment.

Because of the Agency's concern over increases in amylase with TAF in this NDA application, the Applicant and the OSE were queried about amylase increases and pancreatitis cases among TAF containing products in the post-marketing setting. Narrow SMQ for acute pancreatitis and PT for 'amylase increase' and 'amylase abnormal' through 7/18/16 were used, and both the Applicant and OSE identified one case of post-market pancreatitis in a subject who had severe abdominal pain 13 days after switching from Atripla® to Genvoya® for HIV treatment. The subject switched antiretroviral treatment back to Atripla® and was hospitalized subsequently for the development of pancreatic pseudocysts. This case was potentially confounded by other conditions that could have contributed to pancreatitis, including increases in triglycerides and concomitant medication of Lisinopril. In addition, if the subject had not switched from Atripla® to Genvoya®, the same symptoms might have occurred.

Reviewer Comment: Grade 3 or 4 elevations in serum amylase levels were observed in ~2% of subjects treated with the TAF-containing regimen Genvoya® for treatment of HIV-1 infection with <1% reporting associated symptoms; no subjects discontinued treatment due to amylase abnormalities. The frequency of Grade 3 or 4 amylase elevations and adverse reactions were similar in the current application; however, two subjects discontinued TAF due to symptomatic amylase increases. This finding raises concern that TAF may induce pancreatitis and will be included in Section 6 of the TAF label. In addition, OSE will be asked to monitor for post-marketing reports of pancreatitis.

8.5.4. Liver Function Abnormalities/Hepatotoxicity

There were two hepatic-related abnormalities of special interest: hepatic flares and hepatotoxicity. In the current trials, there were no cases of drug-induced liver injury observed, and ALT flares were infrequent and balanced between treatment groups. In the current trials, there were no cases of drug-induced liver injury observed, and ALT flares were infrequent and balanced between treatment groups.

Hepatic Laboratory Abnormalities

Among treated subjects, the mean baseline ALT was 94 U/L for both arms in Study 108, 117 U/L for the TAF arm, and 125 U/L for the TDF arm in Study 110. Following initiation of study medication, the ALT level in most subjects began to decrease consistent with reduction in viral load. On-treatment ALT elevations to ≥ 5 x ULN were comparable between the two treatment groups (See Table 36 below). There were few subjects who

experienced a combination of ALT and bilirubin elevations and one subject who experienced >10x ALT elevation with bilirubin elevation is discussed below. The majorities of the GGT elevations were Grade 1 and evenly matched at fewer than 8% across treatment groups (data not shown).

Table 36. Hepatic Laboratory Abnormalities in the Hepatic Safety Population: Worst Post-Baseline Toxicity Grade and Worse than Baseline*

Laboratory Parameter and Toxicity Grade N (%)	Study 108		Study 110	
	TAF (n=285)	TDF (n=140)	TAF (n=581)	TDF (n=292)
ALT				
Grade 1: 1.25 – 2.5 x ULN	14 (5)	7 (5)	35 (6)	24 (8)
Grade 2: >2.5 – 5 x ULN	15 (5)	9 (6)	58 (10)	46 (16)
Grade 3: >5 – 10 x ULN	3 (1)	3 (2)	48 (8)	24 (8)
Grade 4: >10x ULN	5 (2)	1 (1)	13 (2)	12 (4)
AST				
Grade 1: 1.25 – 2.5 x ULN	19 (7)	8 (6)	70 (12)	36 (12)
Grade 2: >2.5 – 5 x ULN	9 (3)	9 (6)	60 (10)	33 (11)
Grade 3: >5 – 10 x ULN	7 (2)	2 (1)	18 (3)	15 (5)
Grade 4: >10x ULN	1 (<1)	2 (1)	2 (<1)	3 (1)
ALP				
Grade 1: 1.25 – 2.5 x ULN	6 (2)	11 (8)	13 (2)	11 (4)
Grade 2: >2.5 – 5 x ULN	0	0	0	1 (<1)
Grade 3: >5 – 10 x ULN	0	0	0	0
Grade 4: >10x ULN	0	0	0	0
Total Bilirubin				
Grade 1: >1 – 1.5 x ULN	26 (9)	7 (5)	50 (9)	25 (9)
Grade 2: >1.5 – 2.5 x ULN	7 (2)	2 (1)	15 (3)	5 (2)
Grade 3: >2.5 – 5 x ULN	1 (<1)	0	1 (<1)	1 (<1)
Grade 4: >5 x ULN	1	0	0	0

*Numbers are similar to those obtained by Applicant.

Hepatic Flares

Following initiation of HBV antiviral therapy, the expectation is that as HBV viral titers decrease, inflammation will be lessened, and aminotransferase levels will normalize. On-treatment ALT elevations can indicate hepatotoxicity, or in some patients, an ALT flare may be observed during anti-HBV therapy that can be associated with HBeAg loss in HBeAg positive patients. An ALT flare for the purpose of this application was defined as an abrupt rise in ALT levels to 2x baseline or >10x ULN without associated symptoms that resolved with continued treatment. Hepatic flares are hypothesized to occur because of human leukocyte antigen-I restricted, cytotoxic T lymphocyte mediated immune response against HBV (Chang ML, 2014). This phenomenon is similar to Immune Reconstitution Syndrome (IRIS) in treatment of HIV infection.

In Study 108, 2% (5/285) in the TAF arm and no subjects in the TDF arm experienced ALT flares during the first four weeks of treatment. Increased ALT levels returned to near baseline levels by Week 8 with continued treatment. In two of the five TAF subjects, the ALT flares were reported as AEs for which the investigators assessed the event as unrelated to study drug. There was no off-treatment flares reported in this study.

In Study 110, all on-treatment hepatic flares occurred within the first 12 weeks of treatment. ALTs were within normal laboratory levels in those subjects that continued drug by Week 24. The incidence of treatment emergent hepatic flares was small, occurring in 1% in each arm (3/581 in TAF arm and 4/292 in TDF arm). One subject (04058-4786) on TAF had a baseline ALT of 122 U/L (Grade 1) and had an elevation of his ALT to 601 U/L (Grade 4) at Week 8. He had AE of Grade 1 macroglossia unrelated to study drug at 1 month and had the AE of ALT increased to 601 U/L at Week 8. TAF was stopped due to investigator discretion and the subject was started on alternative commercial therapy. The last ALT reported for this subject was 645 U/L at post-discontinuation week 4.

None of the hepatic flares was associated with hyperbilirubinemia, and no subject with a flare cleared HBeAg.

Of note, one subject who discontinued TDF experienced a post-treatment flare, which has been reported in patients that discontinue nucleoside-based CHB therapy:

- Subject 02826-4561 on TDF had a baseline ALT of 206 U/L (Grade 2) with AST 663 U/L (Grade 4) had a *nontreatment-emergent hepatic flare* according to the Applicant. The subject discontinued drug on Day 18 due to AEs of dyspepsia, fatigue, and abdominal discomfort. He then had an elevation of his ALT to 1644 U/L (Grade 4) at Week 4 along with a Grade 4 AST and Grade 1 bilirubin increase. This reviewer speculates ALT could have been elevated and not captured since laboratory tests were not done at the juncture of his symptoms. Therefore, this subject may have had unidentified hepatic flare.

Overview of Potential Drug-Induced Liver Injury and Hy's Law Cases

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e. aminotransferase elevation) accompanied by jaundice had a mortality of 10-50%. Hepatocellular injury sufficient to impair bilirubin excretion has been used by the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as an indicator of clinical concern for drug-induced liver injury includes the following: ALT or AST > 3x upper limit of normal (ULN), total bilirubin > 2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury).

Clinical Review
Tanvir Bell, MD
NDA 208464
Vemlidy (Tenofovir Alafenamide)

Due to a number of confounding factors, the appropriate application and interpretation of Hy's Law in the setting of treatment trials for CHB, in general, is unknown.

Eight subjects met the laboratory criteria for Hy's law; five (1%) in the TAF arms and one (<1%) in the TDF arms. The Applicant identified two additional cases in the TDF arms that had only total bilirubin increases without postbaseline increases in aminotransferase levels. This reviewer reclassified these as not meeting Hy's law. In most of these subjects, ALT and bilirubin elevations were transient, and study drug was continued with resolution. Only one TAF subject had an AE of ALT increased reported.

Reviewer assessment: TAF and TDF are used to treat a viral hepatic disease and often ALT and other tests of liver function improve. Hepatic flares may occur following institution of nucleoside therapy and were observed in these trials equally between TAF and TDF, but were not associated with clearance of HBsAg and HBeAg or hepatotoxicity. Review of other aminotransferase levels indicates no treatment-related DILI.

8.5.5. Serum Lipids

Elevations in serum lipids associated in subjects treated with a TAF-containing regimen were appreciated early in its development program. The first TAF containing regimen FDA approved for the treatment of HIV was Genvoya® (E/C/F/TAF), which was compared to Stribild® (E/C/F/TDF) in pivotal studies 292-0104/0111. Review of the Genvoya® application suggested that the TAF-containing regimen has a negative effect on serum lipid parameters, leading to greater increases in cholesterol and LDL levels.

The pooled analysis for Study 108 and 110 demonstrated a similar effect with significantly greater increases (or lower reductions) in total cholesterol, fasting cholesterol, fasting LDL, fasting HDL, and fasting triglycerides in subjects treated with TAF compared to TDF. In addition, the proportion of subjects with lipid values that reached at least Grade 3 was also greater among TAF-treated subjects. The difference between groups in median change from baseline was statistically significant at Week 48 for total cholesterol, direct LDL, HDL, and triglycerides ($p < 0.001$). The mechanism of action of this effect has not been elucidated.

The mean, median numerical change in values, and interquartile ranges from baseline for fasting lipid levels, and shifts in toxicity grades, are presented in the Tables below. There was no change in total cholesterol/HDL changes in either arm. Through 48 weeks, however, the proportion of subjects who instituted new lipid modifying agents was comparable across treatment groups at 2% (see Table 40). These changes in lipid parameters are considered clinically relevant and will be included in the label.

Table 37: Change from Baseline Fasting Lipid Levels

Change from Baseline (mg/dL)	Pooled TAF	Pooled TDF
Cholesterol (N)	772	394
Mean	0	-25
Median	-2	-24
Q1, Q3	(-17,17)	(-42,-6)
LDL (N)	772	394
Mean	6	-11
Median	4	-9
Q1, Q3	(-9,20)	(-25,5)
HDL (N)	771	394
Mean	-4	-10
Median	-3	-9
Q1, Q3	(-10,2)	(-17,-3)
Total cholesterol /HDL ratio (N)	771	394
Mean	0	0
Median	0	0
Q1, Q3	(0,1)	(0,0)
Triglycerides (N)	773	394
Mean	11	-10
Median	6	-7
Q1, Q3	(-13,26)	(-27,10)

The grading system used by the Sponsor to assess severity of elevations of fasting total cholesterol and LDL cholesterol is reproduced in the Table 38 below.

Table 38: The Sponsor’s grading system for fasting lipid levels

mg/dL	Grade 1	Grade 2	Grade 3	Grade 4
Hypercholesterolemia	200-239	>239-300	> 300	N/A
LDL Cholesterol	130-160	>160-190	>190	N/A
Triglycerides	N/A	500-750	>750-1200	>1200

The differences between the two products in the proportion of subjects with Grade 3 and 4 LDL cholesterol levels is striking with 4% in the TAF arm versus 0% in the TDF arm as seen in Table 39 below. The differences in all toxicity grades in fasting cholesterol and fasting LDL cholesterol is notable. No significant difference in toxicity grade changes in fasting triglycerides was seen in these trials.

Table 39: Shift Table Grade 3-4 Changes in Fasting Lipid Levels by Reviewer

mg/dL	Pooled TAF	Pooled TDF
Fasting Cholesterol		
All Grades	255 (30%)	36 (9%)
Grade 3 & 4	33 (4%)	0
Fasting LDL		
All Grades	216 (26%)	38 (8%)
Grade 3 & 4	33 (4%)	1 (0%)
Fasting Triglycerides		
All Grades	6 (1%)	0
Grade 3 & 4	1 (0%)	0

Total cholesterol and fasting LDL changes along with lipid modifying therapy at start of trial and at 48 weeks are compared between Study 108 and 110 and the findings from the Genvoya® trials and depicted in the Table 40 below. Data from studies 0104/0111 (treatment naïve HIV-1 infected adults) were provided in Dr. William Tauber's review of the Genvoya® NDA 207561. In the TAF studies, the changes in median total cholesterol and fasting LDL were less than in the Genvoya studies, but TDF alone appeared to be more protective of these parameters, as evidenced by greater reductions. In addition, compared to Genvoya®, the proportion of subjects who initiated a new lipid-modifying agent (statins, fibrates, and fish oil) was comparable across treatment arms.

Table 40: Change from baseline cholesterol and fasting LDL compared with Genvoya® trial 0104/0111 and lipid modifying therapy.

Change from Baseline (mg/dL)	Pooled TAF	Pooled TDF	Genvoya® 0104/0111
Total Cholesterol (N)	829	417	827
Mean			
Median	-2	-24	29
Q1, Q3	-2 (-17,16)	-23 (-41,-5)	31
Fasting LDL (N)	772	394	830
Mean	6	-11	14
Median	4	-9	16
Q1, Q3	(-9,20)	(-25,5)	
Lipid-modifying therapy baseline	5% (40)	4% (15)	4% (38)
Addition of Lipid-modifying therapy on treatment phase	2%	2%	3%

Of interest, Asians accounted for 70% of the HBV study population and they may require lower doses of statins due to differences in pharmacokinetics and tolerability compared to Caucasians (Liao, 2007), which may have influenced the low number of lipid lowering agents used in these trials. .

The current treatment of hyperlipidemia is evolving. The use of physician counseling and risk assessment is gaining more importance. Current guidelines from the American College of Cardiology/American Heart Association (Stone et al., 2014) suggest use of a risk calculator that inputs total cholesterol and HDL cholesterol along with other parameters. Clinicians when determining the need for therapy also use LDL values. Initiation of lipid-modifying agents may be needed when diet and exercise are not successful to reduce the risk of cardiovascular morbidity and mortality. CHB treatment with TAF will in most patients require long-duration administration, which could lead to the need for patients to initiate or change lipid-modifying therapy.

The trials are ongoing, and longer duration data may be helpful in quantifying and the requirements for lipid modifying agents.

8.5.6. **Ocular Safety**

In preclinical dog studies, posterior uveitis was detected at the highest doses studied at the 3 and 9 month period. Compared to TDF alone, there appeared to be a small increase in the incidence of symptoms suggestive of uveitis based on numerically higher levels of photophobia, visual blurring, decreased visual acuity, and vitreous floaters (2% for TAF versus 1% for TDF).

The ocular safety of TAF has been a concern based on observations of posterior uveitis in dogs. Because of this finding, the Applicant instituted increased vigilance for eye disorders including the institution of a substudy and investigator instruction and incorporation of specific language into the protocols and informed consents. There was one event of retinal detachment in a TAF recipient and one of uveitis in a TDF subject. A small fundoscopic substudy failed to identify any drug-related ocular toxicity. Overall, the numbers of events were too small to support a definitive conclusion; no future surveillance is suggested by DTOP.

Table 41: Ocular Events

	TAF N=866	TDF N=432
Selected Pooled Entities	21 (2%)	5 (1%)
Eye pain	5	1
Blurred vision	7	1
Decreased acuity	2	1
Photophobia	1	0
Dry eyes	4	1
Retinal detachment	1	0
Conjunctivitis/irritation	1	1
Optic neuritis	0	1

The Applicant enrolled 24 subjects (20 on TAF, 10 on TDF) into a substudy in which subjects underwent baseline and Week 48 fundoscopic exams. Across studies 108 and 110, 20 TAF subjects and 10 TDF subjects were enrolled into the substudy.

Among the 20 TAF subjects, 13 had normal baseline exams, and three had abnormalities observed at Week 24 or 48:

- Shift from normal to abnormal at Week 24 due to mild cup-to-disc ratio asymmetry; normal at Week 48
- Peripapillary atrophy in both eyes, mild cup-to-disc asymmetry both eyes
- Tilted optic discs in both eyes.

Of the seven with abnormal baseline exams, four remained abnormal at Week 48, and three were missing data.

Four TDF subjects had normal exams at baseline, Week 24 and Week 48. Five subjects had abnormalities identified at baseline that were unchanged at Weeks 24 or 48, and one subject had an abnormal exam at baseline and was found to normal at Weeks 24 and 48.

Reviewer comment: Dr. William Boyd from DTOP reviewed these data and concluded that one percent of adverse events could represent symptoms of uveitis, however there were no cases of uveitis per se. He recommended continued post-marketing vigilance.

8.5.7. Dental safety

In the Genvoya® NDA application, dental disorders, such as dental carries, dental abscess, and tooth extractions occurred in 11% of the Genvoya® treated subjects versus 9% in the Stribild® treated subjects. Consultation from the Division of Dermatology and Dental Products assessed that the numbers were too small to draw

any conclusions. This application revealed that dental disorders were reported in substantially fewer subjects: 20/866 (2%) in the TAF arms and 6/432 (1%) in the TDF arms. Based on these data, and the assessment of similar events in the Genvoya® application, it is unlikely that these dental disorders are related to treatment with TAF.

8.6. Safety Analyses by Demographic Subgroups

The TAF safety population was evaluated for differences in AEs by age <50 and ≥ 50, sex, and race (Asian vs. non-Asian) by this reviewer. These subgroups had generally consistent AE Preferred Terms and frequencies between the treatment groups.

8.7. Specific Safety Studies/Clinical Trials

There was no specific safety study conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Based on the available data from Phase 3 trials, there is no clinical evidence of carcinogenicity for TAF. Data submitted for the NDA application showed 13 subjects on TAF experienced an event within the SOC of Neoplasms, Benign, Malignant, and Unspecified, and no clustering of any particular neoplasm was noted. At time of this review, hepatocellular carcinoma occurred in three subjects on TAF and is a malignancy consistent with the patient population.

8.8.2. Human Reproduction and Pregnancy

Animal reproduction studies of TDF have failed to demonstrate risk to the fetus and there are no adequate and well-controlled studies in pregnant women. It is not expected for TAF to have increased risk to the fetus over TDF; however, data in humans is limited. TDF is one of the antivirals studied and recommended in pregnant women with CHB, but treatment is usually started at 28-32 weeks gestational age in pregnant women with CHB (Terrault et. al., 2015). Therefore, effects of TDF on organogenesis in vivo are limited.

Six pregnancies among female subjects were reported in the two Phase 3 pivotal trials all in Study 110, and no exposures were reported in lactating women. Five of the six pregnant subjects were on the TAF blinded arm. All pregnant subjects were between 30 to 42 years old (yo).

- Subject 9055-4727 was a 42 yo female subject on TAF blinded arm who was on study drug for nine months prior to expected date of pregnancy and discontinued after 11 months of study drug exposure when she informed the site of her pregnancy. The subject had an amniocentesis that revealed trisomy 21, and

then had an elective abortion. This event of Trisomy 21 was considered serious, medically significant, congenital anomaly judged by the investigator not related to study drug but rather to advanced maternal age.

- Subject 00342-4704 was a 36 yo female on the TAF blinded arm that was exposed to study drug for approximately seven months before becoming pregnant. Study drug was discontinued during the first trimester. No information is available about the outcome of her baby.
- Subject 2757-5072 was a 32 yo female on the TAF blinded arm for approximately 14 months prior to conception. Study drug was discontinued and the subject had an uncomplicated elective abortion about a month later.
- Subject 5552-4993 was a 30 yo female on the TAF blinded arm on study drug for approximately 14 months and had an elective abortion. Study drug was discontinued on the date of the elective abortion. The subject continued on blinded study drug.
- Subject 6330-4589 was a 32 yo female on the TAF blinded arm on study drug for eight months prior to pregnancy and discontinued study drug in the first trimester. The outcome of the pregnancy was a healthy boy.
- Subject 5691-4808 was a 31 yo female on the TDF blinded arm and reported pregnancy on Week 50 of study. The subject was removed from blinded study drug and placed on TDF. The outcome of the pregnancy was not reported.

Reviewer comment: There are insufficient human data on the use of TAF during pregnancy to inform a drug-associated risk of birth defects and miscarriage. From the few pregnancies reviewed herein, TAF did not appear to increase the risk of adverse pregnancy outcomes.

8.8.3. Pediatrics and Assessment of Effects on Growth

No studies in the pediatric population have been conducted. (b) (4)

(b) (4) A Proposed Pediatric Study Plan (PPSP) was submitted and reviewed by DAVP and the Pediatric Review Committee (PeRC). An agreed upon PSP dated June 19, 2014, proposes a program of formulation development, clinical pharmacology, and clinical trials. Final study reports will be submitted by March 2022.

An adolescent trial, GS-US-320-1092, is being conducted first for which the protocol and ICF have been reviewed by the Division before the filing of this review. PK parameters derived from adults and adolescents will inform dosing in younger pediatric patients from 2-12 years, who will be studied later. (b) (4)

(b) (4) A waiver was requested for children less than 2 years old since studies are impossible or highly impractical in a setting where subjects may not have CHB with infection > 6 months and with improvements in

perinatal transmission strategies such as passive immunization and hepatitis B immunoglobulin.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Limited clinical experience is available at doses higher than the therapeutic doses of TAF. If an overdose with TAF occurs, the patient must be monitored for evidence of toxicity, and should receive general supportive measures including close clinical assessment. TFV is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

Overdoses were reported in 2% of subjects in both treatment arms. Most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication and not associated with clinical symptoms or sequelae.

8.9. **Safety in the Postmarket Setting**

8.9.1. **Safety Concerns Identified Through Postmarket Experience**

To date no specific safety concerns have arisen from the postmarketing experience with Genvoya® or Viread®; both of which contain tenofovir.

8.9.2. **Expectations on Safety in the Postmarket Setting**

Increases in amylase and adverse events related to pancreatitis will need to be monitored in the postmarket setting as well as continued evaluation of ocular events

8.10. **Integrated Assessment of Safety**

The safety database providing up to 48 weeks of exposure to TAF in 866 HBV-infected subjects was considered to assess its short-term safety. There were no TAF-related deaths, SAEs, or discontinuations. The majority of subjects experienced an AE, and most was mild to moderate in severity. The most common TAF-associated AEs that occurred in $\geq 5\%$ of subjects were nasopharyngitis, upper respiratory tract infection, headache, abdominal pain, fatigue, cough, nausea, and back pain, which all occurred with comparable frequency to TDF.

Salient safety information includes:

Bone Safety: Preclinical and clinical data suggest that tenofovir diphosphate decreases bone mineral density. Since approval, the Viread® label has contained a Warning related to the potential for bone toxicity; this Warning has been carried through the labeling of all tenofovir-containing products. The Applicant proposed to remove this Warning from the TAF label. BMD decreased by -0.6% in TAF compared with -2.4% in TDF at the lumbar spine and -0.6% compared to -2.0% at the femoral neck with TAF

and TDF, respectively. BMD declines of 5% or greater at the lumbar spine were experienced by 6% of TAF subjects and 20% of TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 3.2% of TAF subjects and 5.7% of TDF subjects. There were no fractures related to reductions in BMD. The clinical relevance of these changes are not known. Further, data from other clinical trials and a recently published cohort study of over 7000 subjects with CHB treated with nucleosides for a median follow up of 4.9 years failed to identify a substantial increase in risk of fracture events over subjects with untreated CHB patients (Wong et al. 2015). Therefore, it will be recommended to remove the Warning and retain information about the observed changes in the the Adverse Reaction section language of the label.

Renal Laboratory Abnormalities: Although TAF and TDF are metabolized to the same active compound, TAF was anticipated to provide selected safety benefit related to less renal insufficiency over TDF. Numerous exploratory parameters to assess renal function (changes in creatinine, changes in creatinine clearance, and changes in serum phosphorous levels, UPCR, UACR, RPB, and FEUA) were included in the trials, and small differences were observed in some of these parameters, though the clinical significance of these changes is uncertain. There were no serious renal events and no subject had changes in renal function suggestive of Fanconi syndrome. Although the paper by Wong and colleagues (Wong, et al., 2015) failed to demonstrate a meaningful difference in renal function between treated and non-treated patients, it remains a possibility that differences were not appreciated due to the short duration of exposure. Both trials are ongoing, and longer duration data may demonstrate more clinically relevant differences. In the interim, the Warning related to renal toxicity will be retained in the TAF label and the clinical data included in Section 6.

Increased Amylase Levels: Increases in amylase levels accompanied by symptoms such as nausea, low back pain, abdominal tenderness, biliary pancreatitis, and pancreatitis were unexpected and not reported in prior studies of TAF-containing products. In most subjects, TAF was continued unchanged; however, two subjects discontinued treatment: one had a positive rechallenge when TAF was restarted and the other was placed on alternative HBV therapy. Due to the concern that treatment with TAF may cause clinical pancreatitis, this information will be included in the label.

Changes in Lipid Parameters: TAF can be more problematic for selected patients with lipid disease than TDF. Most notably, there was generally no change in mean total cholesterol, but LDL cholesterol levels increased a mean of 6 mg/dL from TAF compared; whereas, they decreased in the TDF group with cholesterol by 25 mg/dL and LDL by 11 mg/dL. Changes in lipid parameters, and requirements for lipid-lowering agents, may need to be considered when choosing TAF for treatment for CHB, and should be included in the adverse event section of the label.

Elevated Aminotransferase Levels: Aminotransferase elevations to >5 x ULN were reported in 8% of study subjects, and none were determined to be treatment-related

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hepatotoxicity. Hepatic flares are a known safety issue with hepatitis B treatment and were reported by 2% of subjects in Study 108 and 1% of subjects in Study 110. In many cases they resolve with continued treatment and in HBeAg positive patients can be associated with HBeAg loss; unfortunately, no subject with a hepatic flare in Study 110 cleared HBeAg.

Uveitis: Posterior uveitis was observed in preclinical dog studies with TAF. Symptoms that could represent uveitis were reported in 1% of subjects in both treatment groups; however, none was determined to be actual cases of uveitis.

9 Advisory Committee Meeting and Other External Consultations

Not Applicable

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted. The Applicant's proposals are summarized in the bullet points, while the Agency and this reviewer's labeling proposal and rationale are in bold and italic font.

-  (b) (4)

Lactic Acidosis/Severe Hepatomegaly with Steatosis was added to WARNING AND PRECAUTIONS, ADVERSE REACTIONS, and PATIENT COUNSELING INFORMATION. The Agency is including this information as it is class labeling for all nucleoside analogues.  (b) (5)



- The Applicant's proposed INDICATION AND USAGE statement read:

[TRADENAME] is a nucleoside analog HBV reverse transcriptase inhibitor and is

indicated for the treatment of chronic hepatitis B in adults.

This reviewer advises usage in treatment of CHB in adults with compensated liver disease. INDICATIONS AND USAGE section should identify the population to which the determination of substantial evidence is applicable and Studies 108 and 110 only evaluated subjects with compensated liver disease. Therefore, this reviewer recommends retaining “with compensated liver disease” in the indications statement, which is also consistent with the currently approved VIREAD® indications.

[Redacted]

(b) (4)

WARNINGS AND PRECAUTIONS for new onset or worsening of renal impairment is advised. This is currently present for all TDF and TAF containing products since Fanconi syndrome and acute renal failure can occur with tenofovir. In DOSAGE AND ADMINISTRATION, the Agency added that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be assessed before initiating VEMLIDY™ therapy and should be monitored during therapy in all patients. Changes in serum phosphorous and creatinine are more indicative of tenofovir-related renal toxicity and these are the most important clinically relevant and available parameters followed in routine clinical practice. In DOSAGE AND ADMINISTRATION Dosage in Patients with Renal Impairment subsection, the Agency added that VEMLIDY™ is not recommended in patients with end stage renal disease.

(b) (4)

[Redacted]

(b) (4)

- [Redacted]

(b) (4)

In the DOSAGE AND ADMINISTRATION section, this reviewer recommends change to dosage adjustment of VEMLIDY™ is required in patients with mild hepatic impairment. VEMLIDY™ is not recommended in patients with moderate or severe hepatic impairment. In USE IN SPECIFIC POPULATIONS and CLINICAL PHARMACOLOGY section, the Agency suggests use is in mild hepatic impairment (Child Pugh A). The safety and efficacy of VEMLIDY™ in patients with

moderate to severe hepatic impairment has not been established. VEMLIDY™ is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). Subjects with moderate or severe hepatic impairment were not enrolled in the Phase 3 studies. (b) (4)

- The Applicant proposed (b) (4)

The Agency recommends Vemlidy™ be given with food based on lower exposures seen in the fasted state.

- In the ADVERSE REACTIONS section, the Applicant proposed to place total hip BMD data in this label.

This reviewer and DBRUP suggest that femoral neck BMD data be included in the label to align representation among the labels for TAF containing products.

Adverse reaction table was updated to include the most common TAF-associated AEs that occurred in $\geq 5\%$ of subjects were (b) (4) (b) (4) headache, abdominal pain, fatigue, cough, nausea, and back pain, which all occurred with comparable frequency to TDF. According to the Guidance for Industry on Adverse Reaction Section of Labeling, the adverse reaction section should include adverse reactions where there is some basis to believe there is a causal relationship to the use of the drug including the adverse events that are consistent with the pharmacology of the drug.

- In the ADVERSE REACTIONS section, the Applicant listed 3% Grade 3-4 amylase elevations occurring from [TRADENAME].

Amylase and Lipase Elevations and Pancreatitis subsection was added by this reviewer with a description of adverse reactions related to pancreatitis seen in Studies 108 and 110. Adverse reactions and recurrent AEs with rechallenge were seen with VEMLIDY™ but not with the comparator, VIREAD®.

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- [Redacted] (b) (4)

This reviewer added a subsection describing serum lipid changes in a table. VIREAD® showed changes that are more favorable in lipid parameters than VEMLIDY™.

The following three changes were made to the DRUG INTERACTIONS section:

[Redacted] (b) (4)

The Agency recommends increasing dosage to two tablets daily as carbamazepine coadministration lowered TAF AUC by 55%.

[Redacted] (b) (4)

Coadministration of VEMLIDY™ with oxcarbazepine or phenobarbital is not recommended. Despite coregulation of CYP3A and Pgp, in mouse intestinal tissues not all CYP3A inducers were Pgp inducers. [Redacted] (b) (4)

[Redacted] (b) (4)

- The Applicant proposed [Redacted] (b) (4)

Coadministration of VEMLIDY™ with rifabutin, rifampin, or rifapentine is not recommended. [Redacted] (b) (4)

[Redacted] (b) (4)

- The Applicant proposed to include the table below in the CLINICAL TRIALS RESULTS section of the label.

Table (b) (4) HBV DNA (b) (4) at Week 48

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	[TRADENAME] (N=285)	(b) (4) (N=140)	[TRADENAME] (N=581)	(b) (4) (N=292)
HBV DNA <29 IU/mL	94%	93%	64%	67%
Treatment Difference ^b	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	2%	3%	31%	30%
No Virologic Data at Week 48	4%	4%	5%	3%

(b) (4)

A proposed table by the Agency included the following:

- 1) **Efficacy rates for cut-offs of 7 log₁₀ IU/mL were added for both studies and 8 log₁₀ IU/mL for Study 110. Efficacy information with these thresholds differed in favor of Vemlidy or Viread.**
- 2) **Data on treatment rates in naïve and treatment experienced rates were added. Subjects were stratified by this criterion in study. Lower responses were observed in treatment experienced subjects on Vemlidy in Study 110.**
- 3) **Subjects with no virologic data at Week 48 were aggregated. The information captured by small numbers provides little added information.**

Additionally, the agency proposed to add in text, response rates among subjects in Study 110 with baseline HBV DNA from 7 to <8 log₁₀ IU/mL and among cirrhotics. Cirrhotics are an important population of patients infected with CHB, but numbers of these subjects were small in Studies 108 and 110.

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing

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information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

10.3. **Nonprescription Labeling**

Not Applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No identified safety issues warrant consideration of REMS.

11.1. **Safety Issue(s) that Warrant Consideration of a REMS**

N/A

11.2. **Conditions of Use to Address Safety Issue(s)**

N/A

11.3. **Recommendations on REMS**

N/A

12 Postmarketing Requirements and Commitments

The following postmarketing requirement and commitments are in place to for the Applicant. Post-marketing requirements and commitments were still under discussion at the time this review was completed.

Post Marketing Requirements:

- Pediatric development plan is required.
- Perform genotypic (also phenotypic if qualified) resistance analysis of baseline virus samples from all HBeAg-positive NRTI-experienced subjects and of Week-48 virus samples from all evaluable subjects, regardless of their Week 96 virologic outcome.
- Phenotype Week-48 virus samples from Subjects 4296-5147 and 8758-5188 in the TAF group and Subjects 1507-4546 and 9035-4845 in the TDF group in Study GS-US-320-0110.
- Evaluate the anti-HBV activity of TAF in combination with sofosbuvir.

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- Sequence the baseline and Week 48 time-points (by population sequencing or NGS) for all subjects who had HBV DNA >69 IU/mL and provide a study report that includes resistance data analysis.
- Subjects 4296-4510, 5613-1163, and 9035-5187 had HBV DNA titers at the last PCR assessment that were >159 IU/mL, qualifying them for deep sequencing analysis. (b) (4) provide a study report that includes resistance data analysis and submit the fastq files and analyses for (b) (4).
- (b) (4) for subjects 8006-5282 and 8600-4558 who had HBV DNA titers at the last PCR assessment that were >159 IU/mL, (b) (4) provide a study report that includes resistance data analysis and submit the fastq files and analyses (b) (4).

Post Marketing Commitments: None

Appendices

13.1. References

Sunbul M. Hepatitis B virus genotypes: Global distribution and clinical importance. World J Gastroenterol 2014;20:5427-34.

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-83.

Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-55.

Kitrinos KM, Corsa A, Liu Y, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology 2014;59:434-42.

Liao JK. Safety and Efficacy of Statins in Asians. Am J Cardiol 2007;99:410-4.

Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:2889-934.

Wong GL, Tse YK, Wong VW, Yip TC, Tsoi KK, Chan HL. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: A cohort study of 53,500 subjects. Hepatology 2015;62:684-93.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): GS-US-320-0108 and GS-US-320-0110

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>1475</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>21</u>		

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If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>20</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>1</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

There were over 1400 investigators involved in the two pivotal studies, and 21 received payments from the Applicant in excess of \$25,000. Twenty-one investigators had form 3455 submitted, 17 of who participated in both studies and four who participated in only one of the studies. One investigator, (b) (6), had significant equity in Gilead with equity in Gilead of greater than \$50,000. There was one investigator, (b) (6), who was a Sub-Investigator in both studies, who left his job (b) (6), and began working for Gilead on (b) (6). His site enrolled (b) (6) subjects in Study (b) (6) and (b) (6) subjects in Study (b) (6). The low numbers of subjects at his site do not raise questions about the integrity of the data.

The total number of subjects in Study 0108 enrolled from investigators who received payments in excess of \$25,000 were 53/425 (12%). The total number of subjects in Study 0110 who enrolled from investigators who received payments in excess of \$25,000 or had equity of >\$50,000 was 90/873 (10%). The potential bias of clinical investigators from financial interests and arrangements were minimized by utilizing randomized study designs with no site enrolling numbers of subjects so high as to influence results. The primary endpoint for both covered studies was an objective laboratory endpoint of HBV DNA below the limit of quantification of an independent assay.

The following investigators who participated in both Study 0108 and 0110 hold financial interests required to be disclosed:

- (b) (6) received significant payments having total value in excess of \$25,000, other than payments for conducting clinical studies. The site enrolled (b) (6) subjects in Study 0108 and (b) (6) subjects in Study 0110.
- (b) (6) received significant payments having total value in excess of \$25,000, other than payments for conducting clinical studies. The site enrolled (b) (6) subjects in Study 0108 and (b) (6) subjects in Study 0110.
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- (b) (6) received significant payments having total value in excess of \$25,000, other than payments for conducting clinical studies. The site enrolled (b) (6) subjects in Study 0108 and (b) (6) subjects in Study 0110.

The following investigator who participated only in Study 0108 hold financial interests required to be disclosed:

- (b) (6) received significant payments having total value in excess of \$25,000, other than payments for conducting clinical studies. The site enrolled (b) (6) subject.

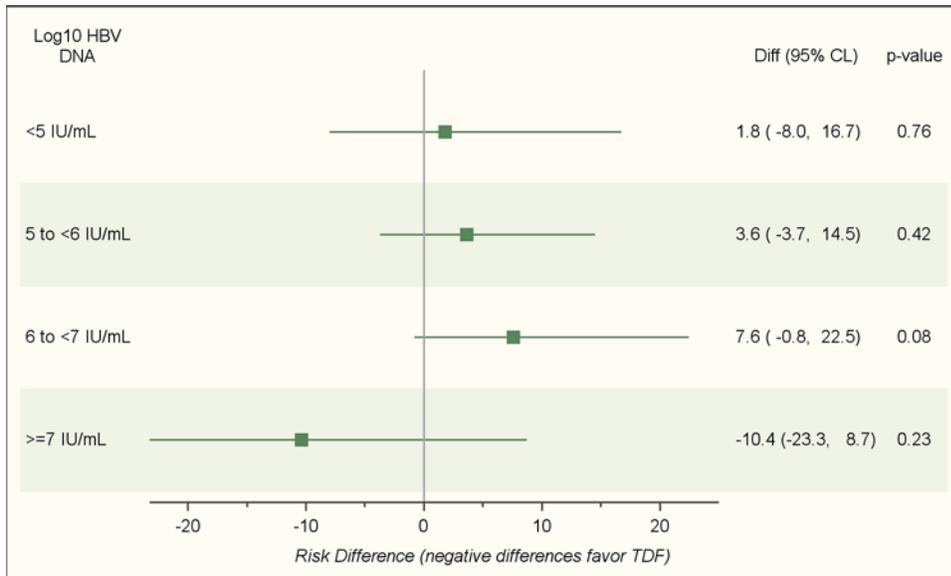
The following investigators who participated only in Study 0110 hold financial interests required to be disclosed:

- (b) (6) received significant payments having total value in excess of \$25,000, other than payments for conducting clinical studies. The site enrolled (b) (6) subjects.
- (b) (6) received significant payments having total value in excess of \$25,000, other than payments for conducting clinical studies. The site enrolled (b) (6) subject in Study 0110
- (b) (6) has equity in excess of \$50,000 in Gilead. The site enrolled (b) (6) subjects.

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as required in the guidance for industry *Financial Disclosure by Clinical Investigators*. In summary, the disclosed financial interests/arrangements did not appear to affect the approvability of this application.

13.3. **Appendix 1**

Figure 11: Efficacy by Baseline Viral Load in Study 108



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/s/

TANVIR K BELL
10/06/2016

RUSSELL D FLEISCHER
10/06/2016

Clinical Consultation

From: Stephen Voss MD, Clinical Reviewer DBRUP
Through: Theresa Kehoe MD, Clinical Team Leader DBRUP
Hylton Joffe MD, MMSc, Division Director DBRUP
To: Myung-Joo Patricia Hong, MS, SRPM, DAVP
Tanvir K Bell MD, Clinical Reviewer DAVP
Russell Fleischer MD, Clinical Team Leader DAVP
Subject: Vemlidy (tenofovir alafenamide, TAF), NDA 208464
for treatment of chronic hepatitis B, potential bone toxicity
DBRUP Tracking #: 164

Background

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir (TFV) which is approved to treat chronic HIV and HBV infection. The main safety concerns with TDF are bone and renal toxicities, which are believed to be linked via the mechanism of proximal renal tubule (PRT) dysfunction (Fanconi syndrome) with phosphate wasting, potentially resulting in osteomalacia.

Clinical trials of TDF-based multidrug regimens in HIV-infected adults demonstrated declines in bone mineral density (BMD) and increased serum levels of bone turnover markers and PTH. It is unknown to what extent such changes indicate an increased risk for clinically significant bone events, e.g. osteomalacia and/or fractures.

TDF is used as a single agent (Viread) to treat chronic hepatitis B (CHB) infection. Although the drug is highly effective in suppressing viral replication, HBsAg loss is unusual therefore treatment is generally long-term. Unlike the HIV trials of TDF, BMD and bone markers were not evaluated in the CHB pivotal trials. Literature reports suggest that TDF nephrotoxicity may be less common in HBV-monoinfected compared to HIV patients, possibly because of fewer comorbidities and co-medications. There were apparently no reports of bone toxicity in CHB until recently: a 40 y/o male who received TDF for 3 years for CHB developed osteomalacia, bone pain and multiple fractures in conjunction with Fanconi syndrome.¹

The sponsor (Gilead Sciences Inc.) is developing a second TFV prodrug, tenofovir alafenamide fumarate (TAF). Compared to TDF, TAF generates higher levels of the active moiety (TFV-diphosphate) within target cells (lymphocytes for HIV, hepatocytes for HBV), and is therefore given in smaller doses, with ~90% lower circulating levels of TFV and potentially improved renal and bone safety. The first TAF containing product was a fixed dose combination tablet (Genvoya, NDA 207561) approved in 2015 for treatment of HIV. That application included extensive bone- and renal-safety data, which consistently favored Genvoya over a similar combination product containing TDF (Stribild).

NDA 208464 was submitted on 1/11/16 for TAF monotherapy of CHB in adults. There are two ongoing phase 3 trials (#108, 110) evaluating the safety and efficacy of TAF 25 mg daily (Vemlidy) compared to active-control TDF 300 mg daily (Viread). The studies are conducted in 19 countries; most of the patients are Asian, reflecting global CHB prevalence patterns. The

primary study objective is to demonstrate non-inferiority in viral DNA suppression for TAF relative to TDF.

Patients are randomized (2:1 ratio) to TAF or TDF for 96 weeks of double blinded treatment; the initial 48 weeks' data, including BMD and bone biomarker data, are included in the NDA. DBRUP, which has consulted on TDF and TAF bone-safety data in the past, is asked to assist in interpretation of DXA and bone marker data with respect to the sponsor's claims and labeling, including the use of BMD cut points for significant bone loss in individual subjects.

Studies 108 and 110 enroll adults (age ≥ 18) with CHB (mono-infection), HBV DNA $\geq 2 \times 10^4$ IU/mL and ALT $>$ approx. 2x ULN, with or without previous CHB treatment. Among the exclusion criteria are decompensated liver disease; S/P transplant; renal disease (eGFR < 50 mL/min); current use of systemic corticosteroids or bisphosphonates; and evidence of bone disease e.g. osteomalacia or multiple fractures. The main difference between the two studies is the e-antigen status of patients (negative in study 108, positive in study 110).

Spine and hip BMD are key secondary safety endpoints, which these studies are adequately powered to evaluate. DXA scans of lumbar spine and hip are performed on all patients at the study sites at screening, every 24 weeks (± 14 days), and at early discontinuation if not done within the previous 12 weeks. Analysis of scans and coordination of quality control are performed by a central contracting DXA facility. Bone -related and other safety data from studies 108 and 110 are pooled for analysis and discussed in the ISS. There are no specific criteria for patient discontinuation related to BMD changes.

A total of 1298 patients were randomized in study 108 or 110 and received ≥ 1 dose of study medication (TAF 866, TDF 432). About 2/3 were e-antigen positive (study 110). Patients in the pooled studies had a mean age 41 y/o (range 18-80), 63% male, 79% Asian/20% white/2% others, 0.6% Hispanic, with median BMI 24.2 kg/m². By region, 47% of patients enrolled at centers in East Asia, 20% in Europe, 17% in North America and 16% in Australia, New Zealand or India. Baseline BMD was slightly below age/gender matched means, with lumbar spine mean Z-scores of -0.49 SD and -0.45 SD (TAF and TDF groups), and total hip mean Z-score of -0.29 SD (both groups). The 10-year fracture risk of patients at baseline (by FRAX algorithm) was low: 0.52% for hip fracture, and 2.74% for major osteoporotic fracture. Mean baseline 25-OH-vitamin D level was 18.4 and 18.7 ng/mL (TAF, TDF).

Among randomized/treated patients, about 95% remained in the studies at week 48, and 93-94% had both baseline and week 48 DXA data for analysis.

There were 13 patients (8 TAF, 5 TDF) who received osteoporosis medications (bisphosphonates or denosumab) during the studies.

Lumbar spine BMD

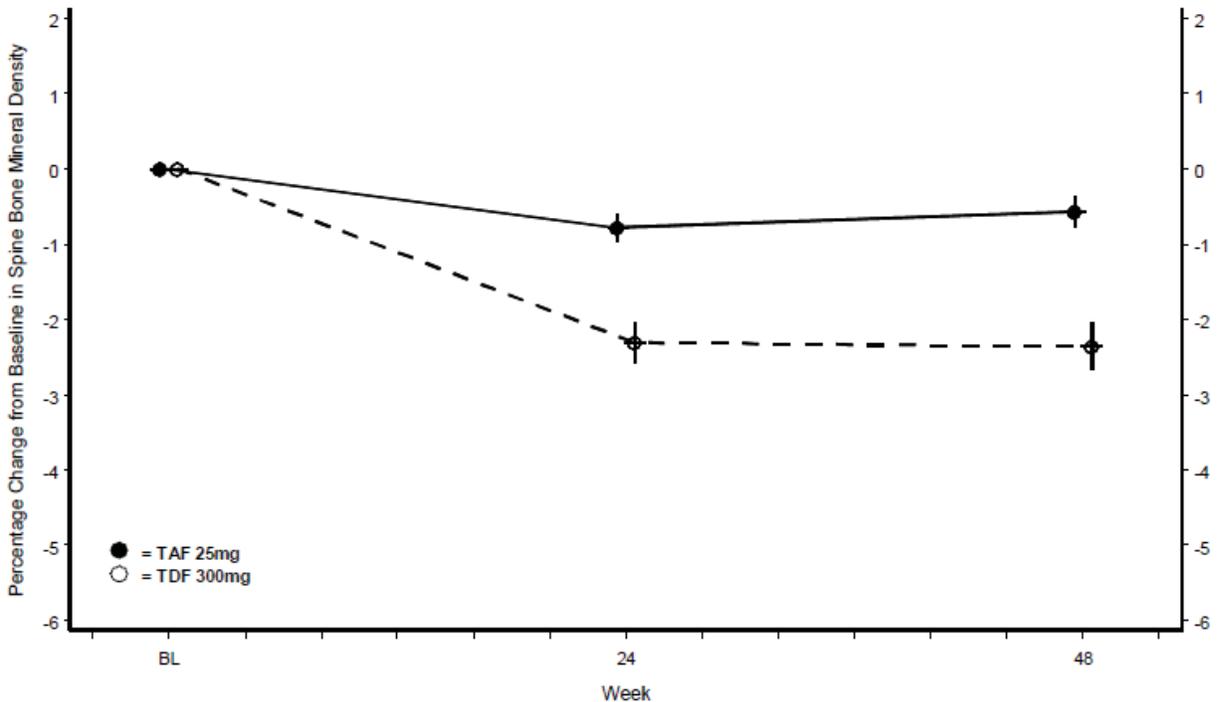
In combined studies 108/110 at week 48, the key secondary endpoint of mean spine BMD declined from baseline to a significantly greater extent with TDF compared to TAF (2.37% vs. 0.57%). Data at week 24 and (in a subset) at week 72 were similar.

Studies 108 and 110: Lumbar spine BMD changes (Spine DXA analysis set)

	TAF 25 mg (N=856)	TDF 300 mg (N=426)	TAF vs. TDF*	
			p-value	LSM difference (95% CI)
Baseline, n	856	426		
Mean BMD (g/cm ²)	1.056	1.052	0.67	
Week 24, n	830	410		
% change from BL, mean (SD)	-0.79 (2.64)	-2.31 (2.66)	<0.001	1.53 (1.21, 1.84)
Week 48, n	814	407		
% change from BL, mean (SD)	-0.57 (2.91)	-2.37 (3.21)	<0.001	1.80 (1.44, 2.16)
Week 72, n	192	93		
% change from BL, mean (SD)	-0.12 (3.00)	-2.28 (3.60)		
Week 96, n	16	9		
% change from BL, mean (SD)	-0.94 (2.20)	-3.26 (1.88)		

* p-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect
Values represent observed data in all patients with nonmissing baseline spine DXA
Source: ISS Table 23.2.2

**Studies 108 and 110: Lumbar spine BMD changes, mean (95% CI) by visit
(Observed data, Spine DXA analysis set)**



Source: ISS Figure 3.2.2

Analysis of week 48 data using LOCF imputation was very similar (ISS Table 23.2.1).

Reviewer comment: These data show that TDF monotherapy for CHB is associated with bone loss; previously, nearly all such BMD data involved TDF-containing multidrug regimens in HIV

patients. The smaller degree of bone loss with TAF compared to TDF in CHB patients is consistent with TAF/TDF differences in HIV patients (Genvoya vs. Stribild, studies 104/111).

Subgroups

TAF-TDF differences in spine BMD % changes at week 48 were generally consistent across subgroups of sex, age, race and region (table below). The Applicant showed that this also applied to subsets of patients with low and high baseline viral load (ISS Table 27).

Studies 108/110: Lumbar spine BMD, mean % change at week 48 by subgroups

	TAF 25 mg	TDF 300 mg
Sex		
Male (n=771)	-0.48	-2.07
Female (n=453)	-0.70	-2.90
Age		
< 50 years (n=919)	-0.43	-2.01
≥ 50 years (n=305)	-1.02	-3.22
Race		
Asian (n=970)	-0.53	-2.43
Non-Asian (n=255)	-0.68	-2.14
Region		
East Asia* (n=592)	-0.70	-3.01
Europe** (n=242)	-0.75	-2.08
North America*** (n=206)	-0.67	-1.75
U.S.A. (n=84)	-0.72	-2.12
Austral/NZ/India (n=184)	0.17	-1.15
*Hong Kong, Japan, Singapore, South Korea, Taiwan		
**Bulgaria, France, Italy, Poland, Romania, Russia, Spain, Turkey, UK		
***Canada, USA		
Source: ADDEXA		

25-OH-vitamin D was measured at baseline only; there was no correlation between levels and spine BMD response at week 48. There were 155 pts (116 TAF, 39 TDF) who were receiving vitamin D, calcium, and/or osteoporosis drugs during the study 108 or 110; a sensitivity analysis performed by the Applicant found that BMD changes in this subset were similar to the overall study populations (ISS Request 7633 Table 4.3).

Categorical changes in spine BMD

In studies 108/110 through week 48, the incidence of ≥5% decline in spine BMD was 6.3% among TAF recipients, and 20.4% among TDF recipients (p<0.001). The four patients with the largest week-48 declines (-14.6% in a TAF recipient; and -13.7%, -11.8% and -11.6% in TDF recipients) were all Asian women. The TAF recipient (ID# 0110-01065-4829) was a 34 y/o woman who also had week-48 BMD declines at total hip (-9.2%) and femoral neck (-14.4%). She had a low baseline 25-OHD level (6.4 ng/mL) which was treated with vitamin D and calcium, and no unusual changes in serum phosphate or bone turnover markers.

Studies 108/110: subjects with categorical changes in lumbar spine BMD from baseline at week 48

	TAF 25 mg	TDF 300 mg

Category of % change from baseline	N=814* n (%)	N=407* n (%)
>0 (increase)	331 (40.7)	89 (21.9)
≥ -1.0 to ≤ 0	131 (16.1)	49 (12.0)
≥ -3.0 to < -1.0	193 (23.7)	114 (28.0)
≥ -5.0 to < -3.0	108 (13.3)	72 (17.7)
≥ -7.0 to < -5.0	45 (5.5)	50 (12.3)
≥ -10.0 to < -7.0	5 (0.6)	29 (7.1)
< -10.0	1 (0.1)	4 (1.0)
*subjects in Spine DXA analysis dataset (nonmissing baseline) and (observed) data at week 48 Source: ISS Table 25.2, ADDEXA		

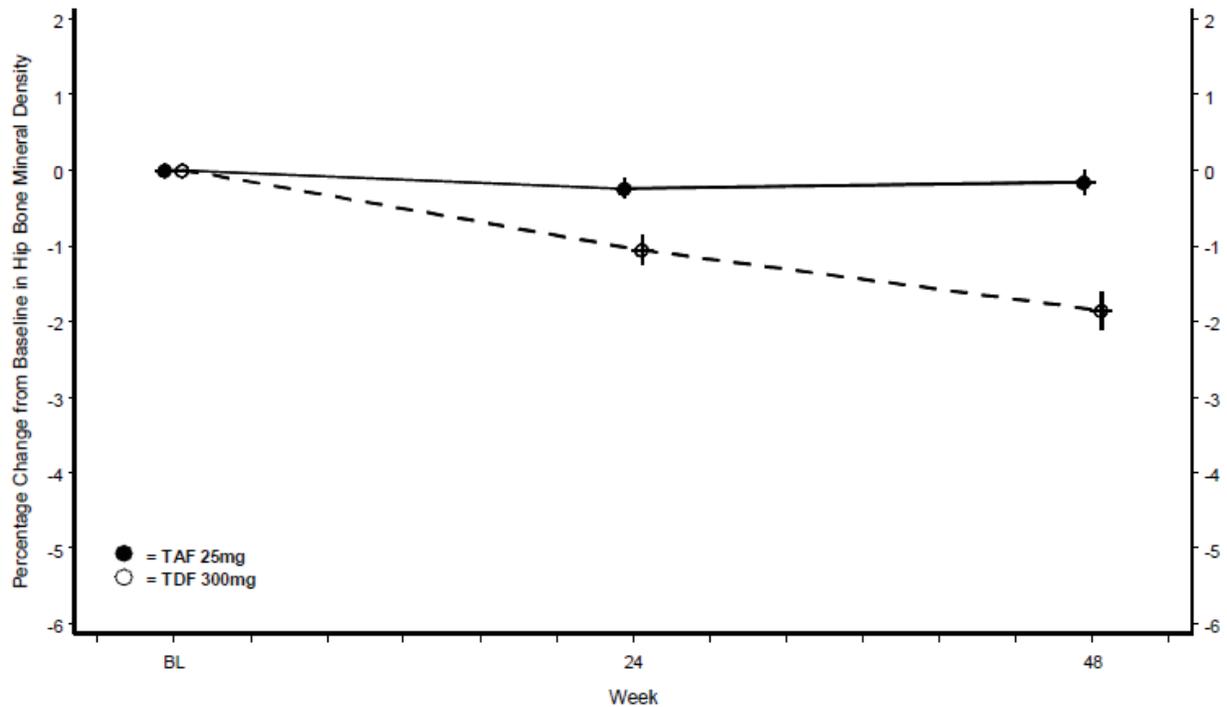
Total hip BMD

Total hip BMD, also a key secondary endpoint of studies 108 and 110, demonstrated a similar pattern of declines at weeks 24 and 48 with TDF, and much smaller declines with TAF.

Studies 108 and 110: Total hip BMD changes (Hip DXA analysis set)

	TAF 25 mg (N=851)	TDF 300 mg (N=426)	TAF vs. TDF*	
			p-value	LSM difference (95% CI)
Baseline, n	851	426		
Mean BMD (g/cm ²)	0.956	0.952	0.69	
Week 24, n	822	405		
% change from BL, mean (SD)	-0.25 (1.87)	-1.06 (2.03)	<0.001	0.81 (0.58, 1.04)
Week 48, n	807	404		
% change from BL, mean (SD)	-0.16 (2.24)	-1.86 (2.45)	<0.001	1.70 (1.42, 1.97)
Week 72, n	190	93		
% change from BL, mean (SD)	-0.10 (2.09)	-2.34 (2.66)		
Week 96, n	16	9		
% change from BL, mean (SD)	0.02 (1.69)	-3.59 (2.11)		
* p-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect Values represent observed data in all patients with nonmissing baseline hip DXA Source: ISS Table 23.1.2				

Studies 108 and 110: Total hip BMD changes, mean (95% CI) by visit (Observed data, Hip DXA analysis set)



Source: ISS Figure 3.2.1

Analysis of week 48 data using LOCF imputation was very similar (ISS Table 23.1.1). Patients receiving vitamin D, calcium and/or osteoporosis drugs had similar hip BMD changes to the overall populations (ISS Request 7633 Table 4.1).

Categorical changes in total hip BMD

In studies 108/110 through week 48, the incidence of $\geq 7\%$ decline in total hip BMD was 0.4% among TAF recipients, and 2.0% among TDF recipients ($p=0.005$). The largest individual declines were -9.3% among TAF patients and -15.3% among TDF patients.

Studies 108/110: subjects with categorical changes in total hip BMD from baseline at week 48

Category of % change from baseline	TAF 25 mg N=807* n (%)	TDF 300 mg N=404* n (%)
>0 (increase)	383 (47.5)	83 (20.5)
≥ -1.0 to ≤ 0	148 (18.3)	67 (16.6)
≥ -3.0 to < -1.0	208 (25.8)	146 (36.1)
≥ -5.0 to < -3.0	58 (7.2)	79 (19.6)
≥ -7.0 to < -5.0	7 (0.9)	21 (5.2)
≥ -10.0 to < -7.0	3 (0.4)	5 (1.2)
< -10.0	0	3 (0.7)

*subjects in Hip DXA analysis dataset (nonmissing baseline) and (observed) data at week 48

Source: ISS Table 25.1, ADDEXA

Femoral neck BMD

Femoral neck BMD changes in studies 108/110 were generally similar to total hip BMD:

Studies 108 and 110: Femoral neck BMD changes (Hip DXA analysis set)

	TAF 25 mg (N=851)	TDF 300 mg (N=426)	TAF-TDF Difference
Baseline, n	851	426	
Mean BMD (g/cm ²)	0.868	0.850	
Week 24, n	822	405	
% change from BL, mean (SD)	-0.59 (2.83)	-1.13 (3.10)	0.74
Week 48, n	814	409	
% change from BL, mean (SD)	-0.60 (3.19)	-2.00 (3.36)	1.40
Week 72, n	190	94	
% change from BL, mean (SD)	-0.48 (3.13)	-2.53 (3.66)	
Week 96, n	18	11	
% change from BL, mean (SD)	-0.53 (2.96)	-2.82 (3.53)	

Source: ADDEXA

Categorical changes in femoral neck BMD

Through week 48, the incidence of $\geq 7\%$ decline in total hip BMD was 3.2% among TAF recipients, and 5.7% among TDF recipients. The largest individual declines were -14.4% among TAF patients and -13.0% among TDF patients.

Studies 108/110: subjects with categorical changes in femoral neck BMD from baseline at week 48

Category of % change from baseline	TAF 25 mg N=807* n (%)	TDF 300 mg N=404* n (%)
>0 (increase)	320 (39.7)	105 (26.0)
≥ -1.0 to ≤ 0	136 (16.9)	43 (10.6)
≥ -3.0 to < -1.0	200 (24.8)	107 (26.5)
≥ -5.0 to < -3.0	87 (10.8)	87 (21.5)
≥ -7.0 to < -5.0	38 (4.7)	39 (9.7)
≥ -10.0 to < -7.0	21 (2.6)	14 (3.5)
< -10.0	5 (0.6)	9 (2.2)

*subjects in Hip DXA analysis dataset (nonmissing baseline) and (observed) data at week 48
Source: ADDEXA

Bone turnover markers

Consistent with previous studies of HIV patients, serum markers of bone resorption (CTX) and formation (P1NP, BSAP, osteocalcin) and PTH all increased from baseline in TDF treated patients. In contrast, TAF recipients had little change in markers and smaller increases in serum PTH.

Studies 108/110: Bone biomarkers and PTH: median % changes from baseline

	TAF 25 mg	TDF 300 mg	p-value
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	(N=866)	(N=432)	(TAF-TDF)
Serum CTX			
week 24	-4.8	29.9	<.001
week 48	-4.3	29.3	<.001
Serum PINP			
week 24	-6.1	18.9	<.001
week 48	-8.8	16.1	<.001
Serum BSAP			
week 24	-7.0	14.6	<.001
week 48	-12.4	7.5	<.001
Serum osteocalcin			
week 24	1.4	14.6	<.001
week 48	0.9	20.0	<.001
Serum PTH			
week 24	14.5	21.3	0.002
week 48	13.0	23.5	0.011
p-values are from the 2-sided Wilcoxon rank sum test to compare treatment groups Source: ISS, Tables 26.1 through 26.5			

Reviewer comment: *These changes are consistent with the BMD changes, as increased bone turnover and/or increased PTH, from a variety of causes, are frequently associated with bone loss.*

Fractures

Fracture events were reported for 6/866 subjects (0.7%) in the TAF group and 1/432 subjects (0.2%) in the TDF group (p=0.44). Six of the 7 fractures were associated with trauma; the other was a spinal compression fracture, found incidentally by CT scan, which may have been related to a previous auto accident (BMD was normal). Two of the other fractures (spine, hand) occurred in 69 y/o and 65 y/o patients with osteoporosis-range T-scores.

Studies 108/110: Fracture events

Group	Subject #	Age/sex	Study day	Skeletal site
TAF	0108-02145-1004	47/M Asian	585	Spinal compression L1, mild Incidental finding on CT for kidney stone, unknown age No trauma during study Auto accident and back pain before study Normal BMD Z-scores
TAF	0108-05552-1279	65/F Asian	349	Hand (5 th metacarpal) from a fall T-scores c/w osteoporosis: hip -2.6, spine -3.8
TAF	0108-00557-1400	37/F White	57	Tibia (skiing) Normal BMD Z-scores
TAF	0110-05685-4592	47/M Asian	127	Hand: open fracture of thumb, index finger Crush injury by machine Normal T-scores
TAF	0110-08705-4659	30/M	424	Hand (5 th metacarpal) Fell in a parking lot Normal BMD Z-scores
TAF	0110-08705-4819	69/M	457	Spinal compression fracture "C11-C12"

		Asian		Fell ~3 meters Baseline T-scores -3.06 spine, -0.66 hip
TDF	0110-05689-4657	49/M Asian	180	Closed fx tibia fibula Motorcycle accident Normal BMD Z-scores

Reviewer comment: *It is unlikely that any of these fractures were related to the study drugs.*

Discussion

In studies 108 and 110, CHB patients exhibited BMD declines at week 48 of treatment that were significantly smaller with TAF compared to TDF, at both lumbar spine and hip. The following table summarizes BMD changes at week 48 in studies 108/110 (patients with CHB) and studies 104/111 (patients with HIV). As shown, TAF-TDF differences were generally consistent, despite the markedly different patient populations (with different co-medications), and also different TAF doses (10 mg in Genvoya, vs. 25 mg).

CHB and HIV studies: BMD changes at week 48, TAF vs. TDF

	Studies 108/110 (CHB)		Studies 104/111 (HIV)	
	TAF 25 mg N=866	TDF 300 mg N=432	Genvoya* (TAF 10 mg) N=866	Stribild* (TDF 300 mg) N=867
Lumbar spine BMD				
Mean percent change	-0.57	-2.37	-1.29	-2.84
% of subjects with >10% decline	0.1	1.0	0.9	1.6
Total hip BMD				
Mean percent change	-0.16	-1.86	-0.66	-2.87
% of subjects with >10% decline	0	0.7	0.5	1.8
Femoral neck BMD				
Mean percent change	-0.60	-2.00	-1.68	-3.80
% of subjects with >10% decline	0.6	2.2	2.6	5.6

*fixed-dose combination products containing TAF or TDF as noted
Source: NDAs 207561 and 208464

Changes in bone turnover markers were also significantly less with TAF compared to TDF, as was the case with Genvoya vs. Stribild:

CHB and HIV studies: Bone turnover marker changes, TAF vs. TDF

	Studies 108/110 (CHB)		Studies 104/111 (HIV)	
	TAF 25 mg	TDF 300 mg	Genvoya* (TAF 10 mg)	Stribild* (TDF 300 mg)
Serum CTX				
Mean % change, week 24	-4.8	29.9	9.4	21.6
Mean % change, week 48	-4.3	29.3	8.8	20.8
Serum P1NP				
Mean % change, week 24	-6.1	18.9	16.5	57.6
Mean % change, week 48	-8.8	16.1	26.7	72.9

*fixed-dose combination products containing TAF or TDF as noted
Source: NDAs 207561 and 208464

Reviewer comment: *The smaller changes in BMD and bone markers in CHB compared to HIV patients overall, and particularly the minimal changes in CHB patients treated with TAF 25 mg, are reassuring. The limitations of the data are absence of an untreated control group, lack of longer term data and unclear relationship of such data to clinically significant endpoints such as osteomalacia or fractures.*

Labeling

Current labeling for TDF (Viread) includes, in addition to a Warning & Precaution regarding the risk for bone loss and osteomalacia, the following data:

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Trials Experience

Changes in Bone Mineral Density:

In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz ($-2.2\% \pm 3.9$) compared with subjects receiving stavudine + lamivudine + efavirenz ($-1.0\% \pm 4.6$) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups ($-2.8\% \pm 3.5$ in the VIREAD group vs. $-2.4\% \pm 4.5$ in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the VIREAD group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range.

(NOTE: the hip BMD data listed in this Viread label represent femoral neck BMD, rather than total hip BMD.)

For the TAF product Genvoya, labeling also includes a bone related W&P, and the following (which may be updated to week-96 data in a pending supplement):

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Bone Mineral Density Effects

Treatment Naïve Adults:

In the pooled analysis of Studies 104 and 111, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA) to compare the bone safety of TAF to that of TDF when administered as GENVOYA or STRIBILD, respectively. Mean BMD decreased from baseline to Week 48 -1.30% with GENVOYA compared to -2.86% with STRIBILD at the lumbar spine and -0.66%

compared to -2.95% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of GENVOYA subjects and 22% of STRIBILD subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of GENVOYA subjects and 19% of STRIBILD subjects. The long-term clinical significance of these BMD changes is not known.

Fractures (excluding fingers and toes) were reported in 7 (0.8%) subjects in the GENVOYA group and 12 (1.4%) subjects in the STRIBILD group through 48 weeks.

Reviewer comment: *The rationale for the thresholds in BMD decline of $\geq 5\%$ in lumbar spine BMD and $\geq 7\%$ in femoral neck BMD listed in these labels is that these levels are considered by DBRUP to represent potentially clinically significant declines, taking into account the precision error of DXA at these skeletal sites.*

The Applicant's proposal for TAF bone safety-related labeling is as follows:

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Bone Mineral Density (b) (4)

In a pooled analysis of Studies 108 and 110, bone mineral density (BMD) from baseline to Week 48 (b) (4) assessed by dual-energy X-ray absorptiometry (DXA) (b) (4)

(b) (4) -0.6% with [TRADENAME] compared to -2.4% with (b) (4) at the lumbar spine and -0.2% compared to -1.9% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 6% of [TRADENAME] subjects and 20% of (b) (4) subjects. BMD declines of 7% or greater at the (b) (4) were experienced by (b) (4)% of [TRADENAME] subjects and (4)% of (b) (4) subjects. The long-term clinical significance of these BMD changes is not known.

Reviewer comments:

To maintain consistency with the Viread and Genvoya labels, it would be more appropriate to use femoral neck (b) (4) data in the statement about $\geq 7\%$ BMD decline. By this reviewer's calculations the statement could be amended as follows:

*BMD declines of 7% or greater at the **femoral neck** (b) (4) were experienced by **3.** (b) (4) % of [TRADENAME] subjects and **5.7** (b) (4) % of (b) (4) subjects.*

Also to maintain consistency with Viread and Genvoya labels, inclusion of fracture data in section 6.1 could be considered, although the events in studies 108/110 (similar to most fracture events in other HIV and CHB studies) were generally trauma-related and relationship to treatment was doubtful. If such labeling is considered appropriate, the format should be consistent with Viread and Genvoya, with one of the events (a fractured thumb and finger) excluded:

Fractures (excluding fingers and toes) were reported in 5 (0.6%) subjects in the [TRADENAME] group and 1 (0.2%) subject in the VIREAD group through 48 weeks.

The Applicant proposes not to include a W&P for bone loss and mineralization defects as currently included in the Viread and Genvoya labels. This appears to be supported by current evidence. Nearly all reported cases of TDF-related osteomalacia in HIV patients have been associated with renal tubule toxicity, and literature indicates that CHB patients are probably at substantially lower risk compared to HIV patients. In this NDA, the number of patients with large (>10%) BMD decline in CHB patients treated with TAF 25 mg was very low in comparison to both Viread (in similar CHB patients) and Genvoya (in HIV patients, despite lower TAF dose of 10 mg in Genvoya). On the other hand, TDF-related osteomalacia typically presents after many months or years of treatment, so lifelong therapy of CHB with these drugs justifies long-term vigilance.

References

1. Magalhaes-Costa P et al, Fanconi syndrome and chronic renal failure in a chronic hepatitis B monoinfected patient treated with tenofovir, *Rev Esp Enferm Dig* 2015; 107: 512-514

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/s/

STEPHEN R VOSS
08/01/2016

THERESA E KEHOE
08/01/2016

HYLTON V JOFFE
08/01/2016

Medical Officer's Ophthalmology Consultation Review of NDA 208464

NDA 208464

Date of Document: 1/11/16
Date of Consultation: 6/7/16
Date of Review: 7/25/16

Applicant:

Gilead Sciences, Inc
333 Lakeside Drive
Foster City, CA 94404
Sara Snow, PharmD, MBA, Manager, Regulatory
Affairs
Tel 650-425-8310

Drug:

Vemlidy (tenofovir alafenamide)

Pharmacologic Category:

phosphonoamidate prodrug of tenofovir (2'-
deoxyadenosine monophosphate analogue)

Indication:

treatment of chronic hepatitis B in adults

Consultation Comments/Special Instructions:

The current NDA is for the use of Tenofovir Alafenamide (TAF) for use in Chronic Hepatitis B (CHB) infection. The NDA compared TAF to an active comparator of TDF that is currently approved for CHB. CHB treatment will potentially be lifelong for subjects. TAF differs from TDF in having better entry and concentration in target cells where the prodrug is converted to tenofovir diphosphate the active moiety. The improved target cell entry and concentration permits the administration of smaller doses of the TAF prodrug with lowered circulating TFV exposure. TAF at highest doses in dog preclinical studies lead to uveitis. TAF has been approved as part of the fixed dose combination (FDC) Genvoya under NDA 207561 for the treatment of HIV infection. About 7% of subjects on Genvoya had symptoms that were suggestive of uveitis. In the current NDA, there have been no reported cases of overt uveitis, but about 2% of subjects in the TAF arm and 1% of subjects in the TDF arm had symptoms that could be suggestive of uveitis. An ocular substudy was done with fundoscopic evaluations in which 30 subjects were to be enrolled.

Questions

1. Please assess eye symptoms and finding from this NDA and assist with interpretation of symptoms and findings.
2. Please assist with any suggestions for future surveillance.
3. Please assist with recommendations for labelling and post-marketing surveillance.

Background:

Gilead Sciences (Gilead) has submitted a new drug application for tenofovir alafenamide (TAF), a 25-mg tablet administered orally, for the treatment of chronic hepatitis B (CHB). The proposed indication for the TAF 25-mg tablet is for use once daily for the treatment of CHB in adults. The efficacy and safety of TAF 25 mg were evaluated in 2 Phase 3 studies in subjects with CHB

(Studies GS-US-320-0108 and GS-US-320-0110). Study GS-US-320-0108 evaluated TAF 25 mg once daily compared with TDF 300 mg once daily for 48 weeks in hepatitis B e antigen (HBeAg)-negative subjects with CHB. Study GS-US-320-0110 evaluated TAF 25 mg once daily compared with TDF 300 mg once daily for 48 weeks in HBeAg-positive subjects with CHB.

Table 1. Clinical Studies to Support Efficacy for the TAF Marketing Application

Study	Study Design	Treatment Regimen (Number of Subjects ^a)	Data Presented	CSR and Narrative Locations
GS-US-320-0108	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative subjects with CHB	TAF 25 mg once daily (N = 285) TDF 300 mg once daily (N = 140)	Week 48 efficacy, PK, and safety	CSR: GS-US-320-0108 Narrative: m2.7.3, Section 2.1
GS-US-320-0110	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive subjects with CHB	TAF 25 mg once daily (N = 581) TDF 300 mg once daily (N = 292)	Week 48 efficacy, PK, and safety	CSR: GS-US-320-0110 Narrative: m2.7.3, Section 2.2

^a Subjects included in the Safety Analysis Set (subjects who were randomized and received at least 1 dose of study drug). Source: GS-US-320-0108 Week 48 CSR, Section 15.1, Table 3 and GS-US-320-0110 Week 48 CSR, Section 15.1, Table 3

Per Module 2.7.4 Summary of Clinical Safety, Section 2.1.1.8.3. Ocular Safety:

In a 9-month toxicology study conducted in dogs, some animals administered with the highest dose of TAF (12-18 mg/kg) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation. This finding did not occur in animals given lower doses, and it has not occurred in other animal studies. This nonclinical finding has also not been observed in humans, where the dose is much lower, nor have there been reports of posterior uveitis in human clinical studies.

The protocols for GS-US-320-0108 and GS-US-320-0110 provided for a substudy to assess ophthalmologic findings, including fundoscopy, anytime during the screening period, but prior to the first dose of study drug, and at Weeks 24 and 48, at select sites (n = 30 per trial). In GS-US-320-0108, a total of 7 subjects participated in the ophthalmologic substudy (TAF 6 subjects; TDF 1 subject). In Study GS-US-320-0110, a total of 23 subjects participated in the ophthalmologic substudy (TAF 14 subjects; TDF 9 subject)

Ophthalmology Reviewer's Comments:

DTOP comments are limited to the ophthalmic evaluations for Studies GS-US-320-0108 and GS-US-320-0110. Tenofovir alafenamide (TAF) was the subject of two previous ophthalmology consultations: IND 115,561 dated 5/16/13, and IND 111,007 dated 9/2/14.

Study GS-US-320-0108 Interim Week 48 Clinical Study Report

Table 11–10 presents a summary of AEs in the eye disorders SOC. The incidence of eye disorders was similar for both treatment groups (TAF 4.6%, 13 subjects; TDF 5.7%, 8 subjects). One subject in the TAF group experienced an eye disorder AE considered related to study drugs by the investigator (Subject 06981-1389: Grade 1 vision blurred). All AEs in the eye disorders SOC were nonserious, and none resulted in discontinuation of study drugs.

Table 11–10. GS-US-320-0108: Summary of Adverse Events in the Eye Disorders System Organ Class (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term ^{a,b,c}	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)
Eye disorders	13 (4.6%)	8 (5.7%)
Vision blurred	4 (1.4%)	0
Dry eye	2 (0.7%)	0
Eye pain	2 (0.7%)	0
Conjunctival hyperaemia	0	1 (0.7%)
Corneal opacity	0	1 (0.7%)
Episcleritis	0	1 (0.7%)
Eye allergy	0	1 (0.7%)
Eye irritation	0	1 (0.7%)
Eye pruritus	0	1 (0.7%)
Eye swelling	0	1 (0.7%)
Eyelid dermatochalasis	1 (0.4%)	0
Eyelid function disorder	1 (0.4%)	0
Eyelid oedema	0	1 (0.7%)
Eyelid ptosis	1 (0.4%)	0
Lacrimation increased	1 (0.4%)	0
Ocular hyperaemia	0	1 (0.7%)
Photophobia	1 (0.4%)	0
Punctate keratitis	0	1 (0.7%)
Retinal degeneration	1 (0.4%)	0
Visual acuity reduced	0	1 (0.7%)
Vitreous detachment	1 (0.4%)	0
Vitreous floaters	0	1 (0.7%)

a Adverse events were mapped according to MedDRA Version 18.

b SOC were presented alphabetically, and PT was presented by decreasing order of the total frequencies.

c Multiple AEs were counted only once per subject for each SOC and PT, respectively.

Source: Section 15.1, Table 28

Five subjects (1.8%) in the TAF group and 2 subjects (1.4%) in the TDF group experienced AEs from the list of identified terms that could represent symptoms of uveitis (Table 39).

Table 39: Treatment-Emergent Potential Uveitis Events
Safety Analysis Set
Double-Blind Phase

	TAF 25mg (N=285)	TDF 300mg (N=140)	p-value
Potential Uveitis Events	5 (1.8%)	2 (1.4%)	1.00
Photophobia	1 (0.4%)	0	
Vision blurred	4 (1.4%)	0	
Visual acuity reduced	0	1 (0.7%)	
Vitreous floaters	0	1 (0.7%)	

All potential uveitis AEs were Grade 1, except for an AE of visual acuity reduced in the TDF group which was Grade 2. All potential uveitis AEs were nonserious, and none resulted in discontinuation of study drugs. Clinically, none of these AEs were considered representative of an actual clinical case of uveitis by the applicant. Of the 5 subjects in the TAF group, 4 had a potential uveitis AE of vision blurred; all were Grade 1, and for 2 of these cases, the events resolved without treatment. One subject in the TAF group experienced vision blurred coincident with nonserious AEs of nausea (Grade 1) and intermittent vomiting (Grade 2); the intermittent vomiting resolved after 7 months without treatment but vision blurred and nausea were ongoing.

Fundoscopy Examination Results (Ophthalmologic Substudy)

A total of 7 subjects participated in the ophthalmologic substudy (TAF 6 subjects; TDF 1 subject). No subject in the ophthalmologic substudy had fundoscopic findings consistent with uveitis based on the central evaluations of fundus photographs.

Ophthalmology Reviewer's Comments:

None of the Adverse Events in the Eye Disorders System Organ Class (Safety Analysis Set), Table 11, are serious events. No ocular adverse events resulted in discontinuation of study drugs.

Study GS-US-320-0110 Interim Week 48 Clinical Study Report

Table 11–10 presents a summary of AEs in the eye disorders SOC. The incidence of eye disorders was similar for both treatment groups (TAF 3.3%, 19 subjects; TDF 2.7%, 8 subjects). One subject in the TAF group experienced an eye disorder AE considered related to study drugs by the investigator (Subject 06960-5161: Grade 1 refraction disorder). One subject in the TAF group experienced an eye disorder SAE; Subject 01069-5193, a 42-year-old Asian male who had a nonserious AE of visual acuity reduced in the left eye and no prior trauma, experienced a Grade 2 SAE of retinal detachment in the right eye. The subject had peripheral lattice degeneration in both eyes. The subject was noted as recovering from the SAE of retinal

detachment following post-retinal detachment repair. No AEs in the eye disorders SOC resulted in discontinuation of study drugs.

Table 11–10. GS-US-320-0110: Summary of Adverse Events in the Eye Disorders System Organ Class (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term ^{a,b,c}	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)
Eye disorders	19 (3.3%)	8 (2.7%)
Eye pain	3 (0.5%)	1 (0.3%)
Vision blurred	3 (0.5%)	1 (0.3%)
Dry eye	2 (0.3%)	1 (0.3%)
Asthenopia	2 (0.3%)	0
Cataract	1 (0.2%)	1 (0.3%)
Eye pruritus	1 (0.2%)	1 (0.3%)
Visual acuity reduced	2 (0.3%)	0
Vitreous floaters	0	2 (0.7%)
Accommodation disorder	0	1 (0.3%)
Conjunctivitis allergic	1 (0.2%)	0
Dacryostenosis acquired	1 (0.2%)	0
Eye irritation	1 (0.2%)	0
Glaucoma	1 (0.2%)	0
Lacrimation increased	1 (0.2%)	0
Myopia	0	1 (0.3%)
Ocular hyperaemia	1 (0.2%)	0
Ocular icterus	1 (0.2%)	0
Refraction disorder	1 (0.2%)	0
Retinal detachment	1 (0.2%)	0
Retinopathy	0	1 (0.3%)
Ulcerative keratitis	1 (0.2%)	0
Vitreous opacities	1 (0.2%)	0

a Adverse events were mapped according to MedDRA Version 18.

b SOC were presented alphabetically, and PT was presented by decreasing order of the total frequencies.

c Multiple AEs were counted only once per subject for each SOC and PT, respectively.

Source: Section 15.1, Table 28

Adverse events from the list of identified terms that could represent symptoms of uveitis were reported for the same percentage of subjects in each treatment group (TAF 1.0%, 6 subjects; TDF 1.0%, 3 subjects). See Table 39.

Table 39: Treatment-Emergent Potential Uveitis Events
Safety Analysis Set
Double-Blind Phase

	TAF 25mg (N=581)	TDF 300mg (N=292)	p-value
Potential Uveitis Events	6 (1.0%)	3 (1.0%)	1.00
Vision blurred	3 (0.5%)	1 (0.3%)	
Visual acuity reduced	2 (0.3%)	0	
Vitreous floaters	0	2 (0.7%)	
Vitreous opacities	1 (0.2%)	0	

There was no subject with an AE of uveitis. All potential uveitis AEs were Grade 1, except for a Grade 2 AE of visual acuity reduced for 1 subject in the TAF group. All potential uveitis AEs were nonserious, and none resulted in discontinuation of study drugs. None of these AEs were considered representative of an actual clinical case of uveitis. Of the 6 subjects in the TAF group, 3 had a potential uveitis AE of vision blurred; all were Grade 1, 1 resolved without treatment and 2 were ongoing. Of the 3 subjects in the TDF group, 1 had a Grade 1 potential uveitis AE of vision blurred which was ongoing.

Fundoscopy Examination Results (Ophthalmologic Substudy)

A total of 23 subjects participated in the ophthalmologic substudy (TAF 14 subjects; TDF 9 subjects). No subject in the ophthalmologic substudy had fundoscopic findings consistent with uveitis based on the central evaluations of fundus photographs.

Ophthalmology Reviewer's Comments:

One subject in the TAF group experienced an eye disorder SAE; Subject 01069-5193, a 42-year-old Asian male who had a nonserious AE of visual acuity reduced in the left eye and no prior trauma, experienced a Grade 2 SAE of retinal detachment in the right eye. The subject had peripheral lattice degeneration in both eyes. No ocular adverse events resulted in discontinuation of study drugs.

Ophthalmology Reviewer Recommendations:

1. Please assess eye symptoms and finding from this NDA and assist with interpretation of symptoms and findings.

There are no reports of anterior or posterior uveitis in the new drug application for tenofovir alafenamide (TAF), a 25-mg tablet administered orally, for the treatment of chronic hepatitis B (CHB). The adverse event reports for eye disorder SOC for Studies GS-US-320-0108 and GS-US-320-0110 are generally nonserious and nonspecific with the exception of retinal detachment in a subject with a predisposing retinal anatomical abnormality. Blurred vision, while associated with uveitis, is not specific; blurred vision was not noted in these trials in association with photophobia or floaters or redness.

The ophthalmology subgroup examinations in the two trials, while limited in number and in the examinations performed, did not reveal fundoscopic findings consistent with uveitis based on the central evaluations of fundus photographs.

2. Please assist with any suggestions for future surveillance.

We have no specific suggestions for future surveillance other than the continued routine collection of adverse events.

3. Please assist with recommendations for labelling and post-marketing surveillance.

We have no specific suggestions for labelling and post-marketing surveillance other than the continued routine collection of adverse events.

William M. Boyd, M.D.
Clinical Team Leader
Division of Transplant and Ophthalmology Products

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/s/

WILLIAM M BOYD
08/01/2016

WILEY A CHAMBERS
08/01/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products**

Date: July 29, 2016
Drug Name: tenofovir alafenamide fumarate (TAF)
NDA: 207561 (Genvoya [elvitegravir/cobicistat/emtricitabine/TAF])
208464 (Vemlidy [TAF])
Applicant: Gilead Sciences, Inc.
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Myung-Joo Hong, Regulatory Project Manager, Division of Antiviral Products
Subject: Consult to review renal safety findings for TAF

Background

Tenofovir alafenamide fumarate (TAF) is a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir. TAF was initially approved on November 5, 2015 for the treatment of HIV-1 infection as one component of the four-drug, fixed-dose combination Genvoya under NDA 207561. Genvoya also includes elvitegravir (integrase inhibitor), cobicistat (pharmacokinetic enhancer for EVG), and emtricitabine (nucleoside reverse transcriptase inhibitor). On November 13, 2015, one week after initial approval, the Division of Antiviral Products (DAV) received efficacy supplements with data through Week 96 for the pivotal trials (GS-US-292-0104 and -0111; S-001) and through Week 72 for the renal safety study (GS-US-292-0112; S-002). On May 4, 2016, the applicant submitted a major amendment to S-002 containing data through Week 96 for the renal safety study. The applicant has also developed TAF for the treatment of chronic hepatitis B infection (CHB) and, on January 11, 2016, DAV received NDA 208464 with data for two pivotal trials for this indication (GS-US-320-0108 and -0110).

TAF is similar to the approved drug tenofovir disoproxil fumarate (TDF). Both TAF and TDF are prodrugs of tenofovir and are converted to the active moiety tenofovir diphosphate upon entry into target cells. TDF is known to cause renal toxicity including Fanconi Syndrome and acute and chronic renal failure. Although estimates vary, the incidence of nephrotoxicity severe enough to warrant discontinuation of TDF therapy is approximately 1% with <0.2% of patients experiencing severe renal failure. Nephrotoxicity often develops over a period of months but can also develop after years of therapy. As a result, labels for tenofovir prodrugs include a Warning and Precaution for “New onset or worsening renal impairment” and a recommendation to assess creatinine clearance, urine glucose, and urine protein before initiating treatment and periodically during treatment.

(b) (4)

During the initial NDA review for Genvoya, the Division of Cardiovascular and Renal Products (DCRP) was consulted regarding interpretation of the renal safety study (Study 112) and associated labeling (see reviews dated May 29, 2015 and October 1, 2015). Although no obvious safety signal was observed, we noted that the study size,

duration of follow-up, lack of a control arm, and nature of the population (e.g., 64% of patients had previously tolerated TDF) limited our ability to draw firm conclusions. Although no cases of Fanconi's syndrome were observed with TAF, Genvoya was ultimately approved with a label that included the renal Warning and Precaution and monitoring recommendations.

With the current submissions, the applicant has provided additional follow-up data for the two pivotal studies and the renal safety study for the HIV indication and data from two pivotal studies for the chronic hepatitis B indication. DAV has requested input from DCRP on the renal safety findings in these studies and the applicant's proposed labeling.

Materials Reviewed

NDA 207561

1. Interim Week 96 Clinical Study Reports for studies 104 and 111
2. Statistical analysis plans for the Week 96 interim analyses of studies 104 and 111 dated August 3, 2015
3. Interim Week 96 Clinical Study Report for study 112
4. Statistical analysis plan for the Week 96 interim analysis of study 112 dated January 11, 2016
5. Summary of Clinical Safety; Integrated Summary of Safety Tables, Figures, and Listings
6. Selective narratives
7. Current Genvoya prescribing information
8. Draft revised prescribing information submitted May 4, 2016

NDA 208464

1. Interim Week 48 Clinical Study Reports for studies GS-US-320-0108 and -0110
2. Protocols for studies GS-US-320-0108 and -0110 dated May 3, 2013 (Original) and amendments dated July 12, 2013 (Amendment 1), December 4, 2013 (Amendment 2)
3. Statistical analysis plans (SAP) for studies GS-US-320-0108 and -0110 Version 1.0 dated September 22, 2015
4. Summary of Clinical Safety; Integrated Summary of Safety Tables, Figures, and Listings
5. Selected narratives
6. Draft prescribing information dated January 7, 2016

Studies 104 and 111 (HIV)

Overview of Design

Studies 104 and 111 are identical in design. Both are ongoing, double-blind trials in which antiretroviral treatment-naïve HIV-1 positive adults with an eGFR by Cockcroft-Gault (eGFR_{CG}) of ≥ 50 mL/min were randomized 1:1 to Genvoya or Stribild. The primary efficacy objective is to evaluate non-inferiority of Genvoya versus Stribild as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48. One of the secondary objectives is to determine the safety of the two treatment regimens as determined by change from baseline in serum creatinine at Week 48. Double-blind treatment is planned through Week 144. With the current efficacy supplement, the applicant provided the results of an interim analysis after all randomized subjects completed the Week 96 visit or prematurely discontinued study drug.

Renal Monitoring

Serum chemistries and urinalysis are performed at baseline, Weeks 2, 4, 8, 12, 16, and 24 then every 12 weeks, and at the unblinding and 30-day follow-up visits. Urine biomarkers are assessed at baseline, Weeks 2, 4, 12, 24, 48, 96, 108, 120, 132, and 144 including proteinuria by urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR); tubular proteinuria by urine retinol binding protein (RBP) to creatinine ratio and urine beta-2-microglobulin (B2M) to creatinine ratio; and markers of proximal renal tubular function including renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate [TmP/GFR], fractional excretion of phosphate (FEPO₄), and fractional excretion

of uric acid (FEUA). Cystatin C was measured at baseline. No renal events are specified as adverse events of interest.

Renal Endpoints and Analysis Plan

There are no pre-specified renal efficacy or safety endpoints. Renal safety parameters are to be summarized descriptively using the safety analysis set including all randomized subjects who received at least one dose of study drug.

Results

Studies 104 and 111 are identical in design, so the results below are pooled.

Disposition

Overall, 866 subjects were randomized to Genvoya and 867 to Stribild. The median duration of exposure is 96 weeks in both groups with approximately one third of subjects having exposures of ≥ 108 weeks (Table 1).

Table 1: Duration of study drug exposure

	Genvoya (n=866)	Stribild (n=867)
Median weeks (Q1, Q3)	96 (95, 108)	96 (92, 108)
≥ 48 weeks	827 (96%)	809 (93%)
≥ 96 weeks	564 (65%)	556 (64%)
≥ 108 weeks	286 (33%)	274 (32%)

Source: Applicant, Summary of Clinical Safety, Table 2.

Baseline Subject Characteristics

The study population is predominantly male with a mean age of 36 years (Table 2). Renal-related baseline characteristics were similar between the treatment arms. Subjects generally have preserved renal function with a mean baseline eGFR_{CG} of 120 mL/min. One tenth of subjects had proteinuria on dipstick urinalysis at baseline.

Table 2: Baseline characteristics

	Genvoya (n=866)	Stribild (n=867)
Male	733 (85%)	740 (85%)
Age mean years (SD)	35 (10)	36 (11)
Serum creatinine mean mg/dL (SD)	0.93 (0.17)	0.94 (0.17)
eGFR _{CG} mean mL/min (SD)	121 (31)	119 (31)
Proteinuria by urinalysis	88 (10%)	86 (10%)

Source: Applicant, Summary of Clinical Safety, Tables 4 and 6.

Renal Adverse Events

No subject died of a renal-related adverse event. Three subjects had a renal-function related SAE, two in the Genvoya arm (ureteric calculus and nephrotic syndrome) and one in the Stribild arm (acute kidney injury). None resulted in discontinuation of study drug. The case of nephrotic syndrome (1936-4682) was in a 21 year-old man with HIV-1 but no other significant medical history or concomitant medications. On Study Day 109 he developed fever, sore throat, and cough and was treated with “roxithromycin for presumptive influenza. A rapid influenza test was negative.” On Study Day 112, he presented with lower extremity edema and frothy urine and was diagnosed with nephrotic syndrome. Approximately 1 month later, he underwent a renal biopsy that showed membranous nephropathy believed to be related to viral illness. Study drug was continued.

No Genvoya subjects discontinued study drug because of a renal adverse event; however, five Stribild subjects discontinued study drug because of worsening renal function and one discontinued because of Fanconi syndrome:

Study 0104

Case 1: Subject 0121-4052 (decreased glomerular filtration rate): 50 year-old man with no relevant medical history or concomitant medications with a baseline $eGFR_{CKD-EPI_{Cr}}$ of 67 mL/min/1.73m² and UPCR of 40 mg/g. By Day 255, his $eGFR_{CKD-EPI_{Cr}}$ had declined to 43 mL/min/1.73m² with a UPCR of 187 mg/g. On Day 425, study drug was discontinued. At that time (Day 426), his $eGFR_{CKD-EPI_{Cr}}$ was stable at 46 mL/min/1.73m² with a UPCR of 321 mg/g. He did not have glycosuria. On Day 464, his $eGFR_{CKD-EPI_{Cr}}$ was 61 mL/min/1.73m².

Case 2: Subject 0698-4029 (worsening renal insufficiency): 41 year-old man with no relevant medical history of concomitant medications with a baseline $eGFR_{CKD-EPI_{Cr}}$ of 83 mL/min/1.73m² and UPCR of 30 mg/g. By Day 6, his $eGFR_{CKD-EPI_{Cr}}$ was 69 mL/min/1.73m² declining further to 59 mL/min/1.73m² by Day 16 then stabilizing at this level. His UPCR increased to 135 mg/g by Day 168. Study drug was discontinued on Day 194. He did not have glycosuria. On Day 208, his $eGFR_{CKD-EPI_{Cr}}$ was 71 mL/min/1.73m².

Case 3: Subject 4140-4374 (worsening renal disease): 37 year-old man with a history of acute renal failure and hypertension on concomitant medications including losartan and nifedipine. At baseline, his $eGFR_{CKD-EPI_{Cr}}$ was 55 mL/min/1.73m² with nephrotic range proteinuria and a UPCR of 11 g/g. On Day 65, he had an $eGFR_{CKD-EPI_{Cr}}$ of 42 mL/min/1.73m². Study drug was discontinued on Day 72. At that time, he had a UPCR of 16 g/g. He had normoglycemic glycosuria at baseline and throughout the study. Following study drug discontinuation, his renal function continued to decline with an $eGFR$ on Day 424 of 14 mL/min/1.73m².

Study 0111

Case 4: Subject 0986-5540 (renal insufficiency): 53 year-old woman with a history of sickle cell disease and type 2 diabetes on concomitant medications propranolol and ibuprofen. At baseline, her $eGFR_{CKD-EPI_{Cr}}$ was 63 mL/min/1.73m² with a UPCR of 283 mg/g. Her $eGFR_{CKD-EPI_{Cr}}$ declined to 48 by Day 14 then stabilized through Day 252. On Day 312, she was hospitalized with a hypertensive crisis and started on captopril. On Day 319, she was admitted with a hypertensive crisis and hemorrhagic stroke and was started on hydrochlorothiazide. On Day 324, she was found to have acute kidney injury with an $eGFR$ of 6 mL/min/1.73m² and UPCR of 1829 mg/g. Study drug was discontinued on Day 328.

Case 5: Subject 1534-5566 (elevated creatinine): 50 year-old man with a history of nephrolithiasis and a baseline $eGFR_{CKD-EPI_{Cr}}$ of 80 mL/min/1.73m² and UPCR of 157 mg/g. On Day 15, his $eGFR_{CKD-EPI_{Cr}}$ had declined to 39 mL/min/1.73m² but then stabilized between the 40s to 50s until study drug was discontinued on Day 591. On Day 592, his $eGFR_{CKD-EPI_{Cr}}$ was 47 mL/min/1.73m² and UPCR was 350 mg/g. By that time, he had also developed 2+ glycosuria without hyperglycemia. The subject was reported to have "tubulointerstitial nephritis" on Day 637. On Day 683, his $eGFR_{CKD-EPI_{Cr}}$ was 57 mL/min/1.73m² and UPCR was 242 mg/g.

Case 6: Subject 2493-5198 (Fanconi; glycosuria): 51 year-old man with no significant medical history. On Day 610, he was reported to have Fanconi syndrome and glycosuria. His baseline $eGFR_{CKD-EPI_{Cr}}$ was 84 mL/min/1.73m², declining to 57 mL/min/1.73m² by Day 169. On Day 600, his $eGFR_{CKD-EPI_{Cr}}$ was 55 mL/min/1.73m² with a UPCR of 301 mg/g and 2+ glycosuria (serum glucose 156 at that visit). Study drug was discontinued on Day 610. On Day 645, his $eGFR_{CKD-EPI_{Cr}}$ was 77 mL/min/1.73m², UPCR was 55 mg/g, and his glycosuria had resolved (serum glucose 99).

Reviewer’s comment: Cases 3 and 4 have alternative explanations for the renal events (baseline nephrotic range proteinuria likely from glomerular pathology, and acute kidney injury in the setting of a hypertensive crisis and initiation of RAAS blocker and diuretics). Although it is possible that study drug played a causative role in the remaining four, we cannot say with confidence based on the available information that the cases represent drug-related proximal tubular toxicity/Fanconi syndrome.

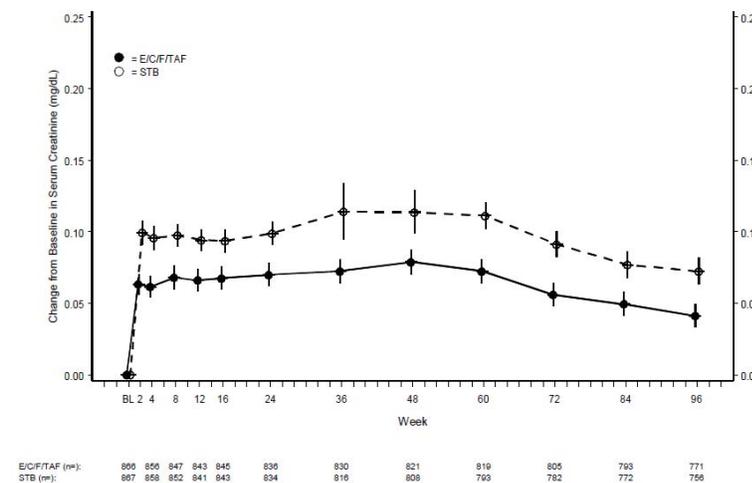
One additional Stribild subject reported “renal tubular disorder” that did not result in study drug discontinuation.

A total of 12 (1.4%) Genvoya and 31 (3.6%) Stribild subjects reported adverse events in the Renal and Urinary disorders SOC with the only event occurring in $\geq 1\%$ of subjects in either arm being proteinuria (8 [0.9%] Genvoya and 18 [2.1%] Stribild).

Changes in Laboratory Parameters

In both treatment arms, there was a small increase in serum creatinine in the first two weeks without significant change thereafter (Figure 1). The early increase was slightly greater in the Stribild as compared to the Genvoya arm. The time course suggests this is not an effect on the irreversible loss of renal function. It may be related to cobicistat, which is known to inhibit the tubular secretion of creatinine without affecting glomerular filtration. The mean change from baseline to Week 96 in serum creatinine was essentially unchanged in both arms (increase of <0.1 mg/dL). Data are not available at Week 96 for $\sim 12\%$ of subjects.

Figure 1: Change from baseline in serum creatinine by visit (observed data)



Source: Applicant, Summary of Clinical Safety, Figure 3.

During the trial, 38 subjects (4.4%) in the TAF arm had compared with 55 (6.4%) subjects in the TDF arm had “graded laboratory abnormalities for serum creatinine” (Grade 1: >1.50 to 2.00 mg/dL; Grade 2: >2.00 to 3.00 mg/dL; Grade 3: >3.00 to 6.00 mg/dL; Grade 4: >6.00 mg/dL).

According to the applicant, exploratory analyses of treatment-emergent proteinuria by dipstick urinalysis, UPCR, UACR, RBP, B2M, and FEUA all favored TAF at Week 96 while changes in TmP/GFR were similar between the two treatment arms and FEPO₄ increased in both arms (Table 3). The significance of these findings, as relates to the risk of clinically significant tenofovir-induced renal toxicity, is unclear.

Table 3: Mean (SD) change in selected biomarkers from baseline to Week 96¹ by treatment group

	Genvoya (n=866)	Stribild (n=867)
UPCR (mg/g)	-14.2 (169)	2.2 (229)
UACR (mg/g)	-4.6 (103)	-6.3 (150)
Urine RBP (µg/g)	-1.9 (244)	366 (1881)
Urine B2M (µg/g)	-224 (1836)	-563 (5095)
FEUA (%)	-0.5 (2.3)	0.5 (2.7)
TmP/GFR (mg/dL)	-0.3 (0.8)	-0.3 (0.8)
FEPO ₄ (%)	1.1 (5.2)	1.9 (5.9)

Source: Applicant, Integrated Summary of Safety Tables, Figures, and Listings, Tables 29.2, 29.3, 29.4, 29.5, 31.2, 32.2, and 33.2.

¹Approximately 15% of subjects do not have data for each parameter at Week 96.

Study 112 (HIV)

Overview of Study Design

The design of Study 112 was described in detail in our consult response dated May 29, 2015. In brief, Study 112 is an ongoing, open-label, single arm study in 252 adults with HIV-1 and stable mild to moderate renal impairment (eGFR_{CG} 30 to 69 mL/min) who are on ART (Cohort 1) or are ART-naïve (Cohort 2). All subjects are treated with open-label Genvoya once daily. Subjects were not eligible if they had previously discontinued a TDF-based regimen for worsening renal function. The primary objective is to evaluate the effect of Genvoya on renal parameters at Week 24. A secondary objective is to evaluate the effect on renal parameters at 96. With the May 4, 2016 major amendment to the efficacy supplement, the applicant provided the results of an interim analysis after all randomized subjects completed the Week 96 visit or prematurely discontinued study drug.

Renal Monitoring

Serum chemistries (including serum creatinine and cystatin C), urinalysis, and other urine parameters (UPCR, UACR, phosphate, and uric acid) are assessed at Weeks 1, 2, 4, 8, 12, 16, and 24 and then every 12 weeks through Week 96. Urine RBP and B2M are assessed at Weeks 1, 2, 4, 12, 24, 48, and 96. No renal events are specified as adverse events of interest.

Renal Endpoints and Analysis Plan

There were no pre-specified renal efficacy or safety endpoints for the Week 96 interim analysis. Renal safety parameters are to be summarized descriptively using the safety analysis set including all randomized subjects who received at least one dose of study drug.

Results

The applicant has reported the safety results separately for Cohorts 1 (subjects on ART at baseline) and 2 (ART-naïve subjects). The results below are limited to Cohort 1, which includes 242 of 248 (97.6%) subjects in the safety set.

Disposition

Overall, 51 (64%) subjects with a baseline eGFR <50 mL/min and 144 (89%) with a baseline eGFR ≥ 50 mL/min have reached 96 weeks exposure (Table 4). At the time of the Week 96 interim analysis, 69 (86%) of subjects with a baseline eGFR <50 mL/min and 146 (90%) with a baseline eGFR ≥50 mL/min were still on treatment. The most common reason for study drug discontinuation was an adverse event, with premature study drug discontinuation occurring in 8 (10%) of subjects with an eGFR <50 mL/min and 4 (2%) of subjects with an eGFR ≥50 mL/min (Table 5).

Table 4: Duration of study drug exposure

	Baseline eGFR_{CG} <50 mL/min (n=80)	Baseline eGFR_{CG} ≥ 50 mL/min (n=162)
Median weeks (Q1, Q3)	108 (92, 109)	108 (108, 120)
≥ 48 weeks	74 (93%)	152 (94%)
≥ 72 weeks	72 (90%)	149 (92%)
≥ 96 weeks	51 (64%)	144 (89%)

Source: Applicant, Study GS-US-292-0112 Interim Week 96 Clinical Study Report, Table 11-1.

Table 5: Subject disposition

	Baseline eGFR_{CG} <50 mL/min (n=80)	Baseline eGFR_{CG} ≥ 50 mL/min (n=162)
Still on treatment	69 (86%)	146 (90%)
Completed treatment	1 (1%)	0
Premature treatment discontinuation	10 (13%)	16 (10%)
Adverse event	8 (10%)	4 (2%)
Lost to follow-up	1 (1%)	2 (1%)
Withdrew consent	0	4 (2%)
Investigator's Discretion	0	2 (1%)
Lack of Efficacy	1 (1%)	1 (0.6%)
Death	0	1 (0.6%)
Noncompliance	0	1 (0.6%)
Protocol violation	0	1 (0.6%)
Completed treatment	1 (1%)	0

Baseline Subject Characteristics

The baseline subject characteristics for study 112 were described in detail in our consult response dated May 29, 2015. In brief, the population was predominantly male (80%) with a mean age of 58 years. The mean baseline serum creatinine was 1.46 mg/dL and mean baseline eGFR was 55 mL/min with approximately one third having an eGFR of 30 to <50 mL/min. Approximately two thirds were taking TDF at baseline.

Renal Adverse Events

Two subjects have had renal SAEs. Subject 8225-8085 was reviewed in our previous consult response (subject with a history of polycystic kidney disease who developed acute kidney injury after diuretics were adjusted). Subject 1609-8007 developed urinary retention on Day 747 after outpatient cholecystectomy that resolved the following day. Study drug was continued in both cases.

Five subjects have had renal AEs leading to study drug discontinuation. Subjects 5122-8191 and 2475-8012 were reviewed in our previous consult response (subject with an unexplained change in serum creatinine from 1.4 to 2.1 to 1.7 mg/dL resulting in study drug discontinuation on Day 83; subject with unexplained gradual increase in serum creatinine from 3.2 to 5.6 mg/dL resulting in study drug discontinuation on Day 347). The three new cases are as follows:

Case 1: Subject 1790-8152 was a 41 year-old man with a history of hypertension with a baseline eGFR_{CKD-EPI Cr} of 35 mL/min on concomitant lisinopril, hydrochlorothiazide, and valacyclovir. The subject was noted to have stable renal function but worsening proteinuria (UPCR 38 to 1435 mg/g

from baseline to Day 435) attributed to “poorly controlled hypertension.” Study drug was discontinued on Day 476. On Day 482, his UPCR was 5300 mg/g. There was no glycosuria.

Case 2: Subject 1790-8153 was a 54 year-old man with a history of hypertension and type 2 diabetes with a baseline $eGFR_{CKD-EPI Cr}$ of 42 mL/min on concomitant losartan, glibenclamide, nebivolol, doxazosin, pravastatin, fluconazole, tenoretic, and glipizide. On Day 295, $eGFR_{CKD-EPI Cr}$ was 27 mL/min attributed to diabetes and hypertension. Study drug was discontinued on Day 480. UACR was 2.9 g/g at baseline and 1.4 g/g on Day 295. There was no normoglycemic glycosuria.

Case 3: Subject 4140-8229 was a 68 year-old man with a history of type 2 diabetes with a baseline $eGFR_{CKD-EPI Cr}$ of 55 mL/min on concomitant diazepam, ibuprofen, and alendronate. On Day 338, his $eGFR$ was 40 mL/min. Around Day 365, losartan was started. On Day 421, his $eGFR$ was 29 mL/min. Study drug and losartan were both discontinued around Day 435 for worsening renal function. On Day 457, his $eGFR$ was 37 mL/min. UACR remained stable and, according to the applicant, the patient had persistent hyperglycemia and glycosuria.

Reviewer’s comment: There were no obvious or clear cut cases of proximal tubular injury and it is hard to determine whether the drug (vs. other factors) played a causative role in these renal events or whether the events represented progression of underlying disease.

The applicant reports that there were no AEs of proximal renal tubulopathy including Fanconi syndrome.

Reviewer’s comment: In the Week 24 Clinical Study Report for study 0112, the applicant evaluated for cases of “subclinical renal tubulopathy defined as confirmed abnormalities in any two out of the following four renal parameters:

- *Increase in serum creatinine ≥ 0.40 mg/dL from baseline.*
- *Confirmed ≥ 2 grade level increase from baseline in proteinuria*
- *Confirmed ≥ 1 grade level increase from baseline in hypophosphatemia*
- *Confirmed ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)*

The applicant has not updated these analyses with the Week 96 data, so we have recommend that the primary review team request these analyses for study 112 and also for studies 104 and 111. Although the serum glucose level at which glycosuria occurs in the absence of proximal tubular dysfunction can vary, it is generally ~160 to 200 mg/dL. This is higher than the applicant’s cutoff in the fourth bullet above, so we have requested that the applicant also run the analyses with a cutoff of 160 mg/dL.

Laboratory Assessments

According to the applicant, there were no differences in mean serum creatinine, $eGFR$, cystatin C, serum phosphorus, UPCR, or UACR and decreases in urine RBP and B2M from baseline through Week 96, although approximately 10% of subjects were missing data at Week 96 (Table 6). The significance of these findings, as relates to the risk of clinically significant tenofovir-induced renal toxicity, is unclear. There were no changes from baseline to Week 96 in in other markers of tubular function including FEUA, TmP/GFR, or FEPO₄ (not shown).

Table 6: Mean (SD) or median (IQR) laboratory values at baseline and Week 96

	Baseline	Week 96¹
Creatinine (mg/dL)	1.46 (0.4)	1.41 (0.35)
eGFR _{CG} (mL/min)	55 (12)	57 (14)
Cystatin C (mg/dL)	1.15 (0.3)	1.09 (0.34)
Serum phosphorus (mg/dL)	3.2 (0.6)	3.1 (0.6)
Median UPCr (mg/g)	161 (73, 337)	87 (52, 153)
Median UACr (mg/g)	29 (8, 84)	11 (5, 35)
Median urine RBP (µg/g)	801 (130, 5100)	191 (88, 566)
Median urine B2M (µg/g)	1563 (218, 10922)	201.6 (68, 839)

Source: Applicant, Study GS-US-292-0112 Interim Week 96 Clinical Study Report, Tables 11-5, 11-9, 10.1.1, 10.1.4, 10.1.5, and 10.1.6.

¹Approximately 10% of subjects do not have data for each parameter at Week 96.

Studies 108 and 110 (CHB)

Overview of Study Design

Studies GS-US-320-0108 and -0110 are ongoing phase 3, randomized, double-blind, non-inferiority studies in which adults with HBeAg-negative (Study 108) or HBeAg-positive (Study 110) CHB were randomized 2:1 to TAF 25 mg daily or TDF 300 mg daily for up to 96 weeks followed by an optional 48-week open-label extension period. Subjects who lose HBsAg with confirmed seroconversion to anti-HBs discontinue study drug within 3 to 6 months of confirmation or after the Week 48 visit for subjects who seroconvert before Week 48.

The primary objective for both studies is to compare the efficacy of TAF versus TDF for the treatment of CHB at Week 48. According to the protocol, key secondary safety objectives are to compare the safety of TAF versus TDF as determined by change from baseline in hip and spine bone mineral density (BMD) at Week 48 and change from baseline in serum creatinine at Week 48 (changed from creatinine clearance per Protocol Amendment 1). The SAPs specified an additional key secondary objective to compare the safety of TAF versus TDF as determined by treatment-emergent proteinuria through Week 48.

The NDA submission contains the results of interim analyses for both studies conducted after all randomized subjects completed the Week 48 visit or prematurely discontinued study drug before the Week 48 visit.

Renal-related Eligibility Criteria

Eligible subjects could be hepatitis B treatment-naïve or treatment-experienced (including prior treatment with TAF and/or TDF per Protocol Amendment 1). Subjects were to have a creatinine clearance (CrCl) by Cockcroft-Gault of ≥ 50 mL/min (reduced from ≥ 60 mL/min per Protocol Amendment 2), have no “significant renal...disease in the opinion of the investigator,” and not be taking immunomodulators, nephrotoxic agents, or “agents capable of modifying renal excretion.”

Overview of Renal Monitoring

Serum chemistries including creatinine and phosphorus and dipstick urinalysis are performed at screening, baseline, every 4 weeks through Week 48, every 8 weeks through Week 96, and every 12 weeks through Week 144/Early Discontinuation. Cystatin C measurement was added at baseline per Protocol Amendment 2. Urine samples for renal biomarkers including retinol binding protein (RBP) and beta-2-microglobulin (B2M) are collected at baseline and Weeks 4, 12, 24, 48, 72, 96, and 144. The protocol did not specify the timing of quantitative measures of proteinuria.

Subjects who permanently discontinue study drug because of confirmed seroconversion to anti-HBs on or after the week 48 visit will be followed off treatment every 4 weeks for 12 weeks then per the study visit schedule through Week 144. All others will be followed every 4 weeks for 24 weeks off treatment or

until initiation of an alternative, commercially available, standard of care HBV therapy, whichever occurs first. Follow-up visits will include testing according to the schedule above.

Subjects who develop a CrCl < 50 mL/min during the study are to have a serum creatinine measured again within 3 days of receipt of the results along with measurement of cystatin C. Any subject with a confirmed CrCl < 50 mL/min and a > 20% reduction from baseline in eGFR using the CKD-EPI Cystatin C equation (CKD-EPI_{cys C}) is to be managed as follows:

- For a confirmed CrCl ≥ 30 and < 50 mL/min, change to every other day dosing. If the CrCl subsequently rises to ≥ 50 mL/min, can increase study drug to daily dosing after discussion with the medical monitor.
- For a confirmed CrCl < 30 mL/min, permanently discontinue study drug.

Subjects with a change from baseline in serum creatinine of ≥ 0.4 mg/dL should have serum creatinine repeated with concurrent urinalysis and urine chemistries within two weeks of receipt of results.

Management will be based on CrCl as follows:

- For a confirmed CrCl < 50 ml/min or other clinical and/or laboratory evidence of acute renal failure, manage according to the guidance above.
- For a confirmed CrCl ≥ 50 ml/min with repeat testing confirming a Grade 1 (>1.5 to 2.0 mg/dL) or Grade 2 (>2.0 to 3.0 mg/dL) serum creatinine elevation, monitor weekly until the serum creatinine level returns to normal.

Subjects with negative or trace proteinuria at baseline that develop $\geq 1+$ proteinuria on urinalysis must have a repeat urinalysis and urine chemistries within two weeks of receipt of results, and subjects with confirmed new proteinuria are asked to return to the clinic for further evaluation.

Endpoints

The primary endpoint for both studies is a non-inferiority comparison of the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48. The secondary safety endpoints for both studies were 1) percent change from baseline at Week 48 in hip BMD, 2) percent change from baseline at Week 48 in spine BMD, and 3) change from baseline at Week 48 in serum creatinine. The statistical analysis plans specified a fourth secondary safety endpoint, treatment-emergent proteinuria by urinalysis (dipstick) through Week 48. For study 110, an additional secondary efficacy endpoint related to loss of HBeAg and seroconversion to anti-HBe.

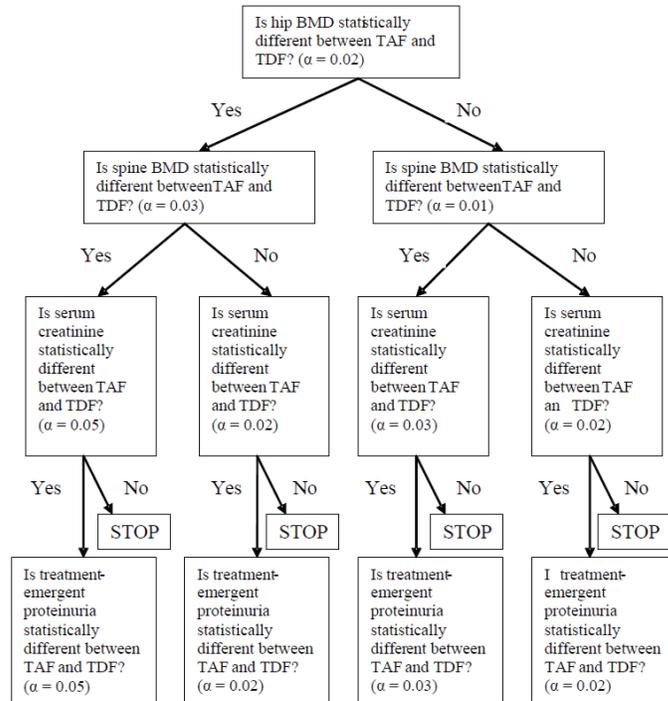
Statistical Analysis Plan

Power Calculations

The studies were each powered based on the primary endpoint. For Study 108, the sample size was also expected to provide 52% power to detect a 0.03 mg/dL difference in the change from baseline in serum creatinine at Week 48 (assuming a 0.04 mg/dL change from baseline in TDF 300 mg arm and 0.01 mg/dL change from baseline in TAF 25 mg arm, with a standard deviation of 0.12). For Study 110, the sample size was expected to provide at least 85% power using the same assumptions.

Control of Type 1 Error

If non-inferiority was established for the primary efficacy endpoint, the secondary endpoints, including the renal safety endpoint, were to be tested sequentially according to the following flowchart for Study 108 (flowchart for Study 110 added additional level for HBeAg seroconversion):



Analysis of Renal Endpoints

The creatinine-based renal safety endpoint was analyzed using an ANOVA model with baseline serum creatinine as a covariate and treatment group as fixed effects. Baseline was defined as the last non-missing value on or prior to Study Day 1

The proteinuria-based renal safety endpoint was analyzed by comparing the distribution of the highest treatment-emergent post baseline graded value for dipstick proteinuria using a rank ANCOVA adjusted for baseline proteinuria.

Missing data was handled by the Last Observation Carried Forward method.

Exploratory Renal Safety Analyses

The SAP specified exploratory analyses of urine RBP, urine B2M, quantitative proteinuria using urine protein creatinine ratio (UPCR) and albumin creatinine ratio (UACR) (percent change from baseline, UPCR ≤ 200 mg/g vs. >200 mg/g, UACR <30 mg/g vs. ≥ 30 mg/g), and urine phosphate (TmP/GFR, and FEPO₄) and uric acid (FEUA) excretion.

The SAP specified analyses of “treatment-emergent confirmed renal abnormalities” defined as:

- Confirmed increase from baseline in creatinine of at least 0.5 mg/dL,
- Confirmed CrCl <50 mL/min, or
- Confirmed phosphorus <2 mg/dL

The Clinical Study Reports specified analyses of “subclinical renal tubulopathy” defined as confirmed (observed at two consecutive post baseline measurements or one measurement following study drug discontinuation) abnormalities in any two out of the following four renal parameters:

- Confirmed increase in serum creatinine ≥ 0.40 mg/dL from baseline
- Confirmed ≥ 2 grade level increase from baseline in proteinuria
- Confirmed ≥ 1 grade level increase from baseline in hypophosphatemia

- Confirmed ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)

Datasets

Safety analyses were conducted using the safety analysis set including all randomized subjects who received at least one dose of study drug according to the treatment they actually received.

Results

Disposition

In Studies 108 and 110, a total of 866 subjects received TAF and 432 received TDF (Applicant, Summary of Clinical Safety, Table 1). As of the cutoff dates for the Week 48 interim analyses, 93% of subjects in both treatment arms remained on double-blind study drug. Of the remaining subjects, approximately 5% in each treatment arm had prematurely discontinued double-blind study drug and 2% had transitioned to the open-label extension phase. The median duration of exposure is 56 weeks in both arms with approximately 20% of subjects having exposures of ≥ 72 weeks (Table 7).

Table 7: Duration of study drug exposure

	TAF (n=866)	TDF (n=432)
Median weeks (Q1, Q3)	56 (48, 64)	56 (48, 65)
≥ 48 weeks	669 (77%)	346 (80%)
≥ 72 weeks	190 (22%)	92 (21%)

Source: Applicant, Summary of Clinical Safety, Table 4.

Baseline Subject Characteristics

The study population is 63% male with a mean age of 41 years (Table 8). Subjects generally have preserved renal function with a mean baseline creatinine of 0.82 mg/dL and CrCl of 110 mL/min. Fewer than 10% of subjects had baseline proteinuria on dipstick urinalysis.

Table 8: Baseline characteristics

	TAF (n=866)	TDF (n=432)
Male	544 (63%)	275 (64%)
Age years mean (SD)	40 (12)	41 (12)
Creatinine mg/dL mean (SD)	0.81 (0.17)	0.83 (0.16)
CrCl mL/min mean (SD)	111 (28)	109 (28)
Proteinuria by urinalysis	58 (7%)	38 (9%)
Diabetes	56 (7%)	29 (7%)

Source: Applicant, Summary of Clinical Safety, Tables 2 and 3.

Renal Safety Endpoints

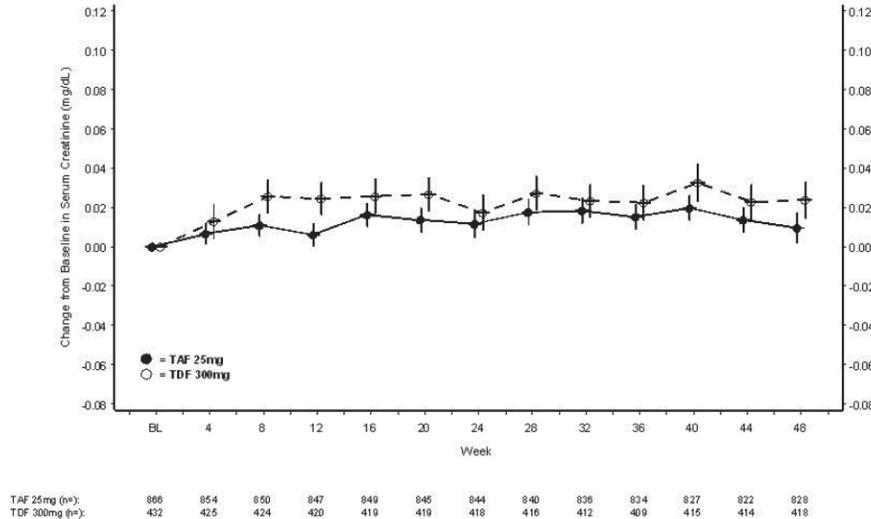
The third secondary safety endpoint in both studies was change from baseline to Week 48 in serum creatinine. In both treatment arms, serum creatinine remained essentially unchanged through Week 48 (Table 9, Table 10). Although the p-value for this endpoint in Study 110 reached statistical significance, the magnitude of the difference between treatment arms is small and of unclear clinical significance. Based on the time course shown below, this small difference between treatment arms appeared early in the course of therapy, suggesting that even if this finding is real, it probably does not reflect an effect on the irreversible loss of renal function.

Table 9: Change from baseline in serum creatinine (SCr) at Week 48 by study

	TAF		TDF		p-value
	n/N	SCr Change	n/N	SCr Change	
Study 108	275/285	0.01 (0.09)	135/140	0.02 (0.10)	0.32
Study 110	553/581	0.01 (0.12)	283/292	0.03 (0.09)	0.02

Source: Applicant, Clinical Study Reports for Studies 108 and 110, Table 55 2.

Table 10: Mean (95% CI) Change from Baseline in Serum Creatinine by Visit



Source: Applicant, Summary of Clinical Safety, Figure 5.2.

The fourth secondary safety endpoint in both studies, according to the SAP, was treatment-emergent proteinuria by urinalysis (dipstick) through Week 48. A similar percentage of subjects in each treatment group had at least one episode of graded proteinuria by dipstick while on study drug.

Renal Adverse Events

There were two deaths in the TAF arm, one of which was associated with acute kidney injury with a decrease in CrCl from 61 to 50 mL/min in the setting of H1N1 influenza, pneumonia, sepsis, and respiratory failure.

One subject in the TAF arm with a history of hypertension and diabetes had a confirmed CrCl <50 mL/min (from 63 to 44 mL/min) and increase in serum creatinine ≥ 0.5 mg/dL (from 1.28 to 1.82 mg/dL) that resulted in a change in study drug to every other day dosing at Week 44. Renal function returned to baseline by Week 72.

There were no additional renal-function related adverse events in either treatment arm including no SAEs, no discontinuations of therapy for an AE, and no reports of renal tubulopathy, renal failure, or acute kidney injury.

Five subjects in the TAF group (0.6%) and three subjects in the TDF group (0.7%) reported AEs of proteinuria of Grade 1 severity.

Changes in Laboratory Parameters

During the trial, six subjects (0.7%) in the TAF arm had “graded serum creatinine abnormalities” compared with no subjects in the TDF arm. The sponsor provided brief narratives for each subject. Five

had transient elevations in serum creatinine that returned to baseline with retesting. One subject had a persistent decline in renal function that required adjustment of study drug dosing (see above).

Five TAF (0.6%) and seven TDF (1.6%) subjects had a “treatment-emergent confirmed renal abnormality” as defined by the applicant (see above). According to the applicant, most were isolated, transient, and resolved without intervention.

No subject in either treatment arm met the criteria for “subclinical renal tubulopathy.”

Exploratory Renal Safety Analyses

According to the applicant, changes in UPCR, UACR, urine RBP, urine B2M, and FEUA favored TAF at Week 48 (Table 11). Changes in TmP/GFR were similar between the two treatment arms, and FEPO₄ increased in both arms. The significance of these findings, as relates to the risk of clinically significant tenofovir-induced renal toxicity, is unclear.

Table 11: Mean (SD) change in selected biomarkers from baseline to Week 48¹ by treatment group

	TAF (n=866)	TDF (n=432)
UPCR (mg/g)	-12 (353)	1 (149)
UACR (mg/g)	-6 (257)	-4 (60)
Urine RBP (µg/g)	13 (168)	50 (207)
Urine B2M (µg/g)	-3 (198)	191 (827)
FEUA (%)	-0.1 (3.2)	0.5 (3.2)
TmP/GFR (mg/dL)	-0.2 (0.7)	-0.2 (0.8)
FEPO ₄ (%)	1.5 (5.3)	1.2 (5.2)

Source: Applicant, Integrated Summary of Safety Tables, Figures, and Listings, Tables 34.1, 34.2, 34.3, 34.4, 36, 37, and 38.

¹According to the applicant, approximately 5% of subjects do not have data for each parameter at Week 48.

Glycosuria

In Section 6 of the proposed label, the applicant has included a table of selected Grade 3-4 laboratory abnormalities reported in ≥2% of subjects receiving TAF in Studies 108 and 110. This includes glycosuria ≥3+ reported in 5% of TAF and 1% of TDF subjects. No imbalance is noted in 1 or 2+ glycosuria events. In a follow-up to the original consult request, the primary review team has asked for DCRP input on this finding.

As noted in Table 2, above, 7% of subjects in each treatment arm had diabetes mellitus at baseline; however, during the trial, subjects in the TAF arm were more likely to have ≥ Grade 2 hyperglycemia than subjects in the TDF arm (Table 12). To explore whether glycosuria occurred in the setting of hyperglycemia, we identified 34 subjects (29 TAF, 5 TDF) not on an SGLT2 inhibitor with at least one episode of treatment-emergent 3+ or 4+ glycosuria who had a serum glucose recorded at the same visit (not necessarily simultaneous). The majority of glycosuria episodes occurred in the setting of a serum glucose ≥160 mg/dL (TAF 81/99 [82%], TDF 14/18 [78%]). All of the remaining events occurred in subjects with hyperglycemia (sometimes with concomitant glycosuria) at other trial visits (Source: *adlb01*, *alb03*, *adcm*). As a result, it is not clear that any of the glycosuria events reflect tubular dysfunction/drug-induced renal toxicity.

Table 12: Abnormalities in serum and urine glucose parameters

Parameter	Max Toxicity Grade	TAF	TDF
Serum glucose	1	229 (26%)	129 (30%)
	2	87 (10%)	19 (4%)
	3	24 (3%)	6 (1%)
	4	1 (0%)	0
Urine glucose (dipstick)	1+	12 (1%)	3 (1%)
	2+	28 (3%)	16 (4%)
	3+	39 (5%)	4 (1%)

Source: Analysis by Dr. Tanvir Bell using the integrated safety database.

Consult Questions for NDA 207561

Please review the data from Studies GS-US-292-0104, GS-US-292-0111 and GS-US-292-0112 in regards to renal safety of TAF. Please address the following questions:

1. Do you concur with Gilead's analysis of the three studies' renal data [REDACTED] (b) (4) associated with Genvoya use?

DCRP Response: *Studies 104 and 111 randomized relatively young subjects with preserved renal function to Genvoya or Stribild. During the study, no Genvoya subjects and six (0.7%) Stribild subjects discontinued study drug for a renal AE: five for worsening renal function and one for Fanconi syndrome. Of these six cases, two had alternative explanations for the events. Although it is possible that study drug played a causative role in the remaining four, we cannot say with confidence based on the available information that the cases represent drug-related proximal tubular toxicity/Fanconi syndrome. There was one additional report of "renal tubular disorder" in a Stribild subject that did not result in study drug discontinuation. The applicant believes their exploratory analyses of various biomarkers including UPCR, UACR, RBP, B2M, and FEUA favored the Genvoya arm, although the clinical significance of these findings is unclear.*

In study 112, subjects with mild to moderate renal impairment (eGFR_{CG} 30 to 69 mL/min) were treated with open-label Genvoya. Five subjects experienced renal AEs leading to study drug discontinuation. There were no obvious or clear cut cases of proximal tubular injury, but it is hard to determine whether the drug (vs. other factors) played a causative role in these renal events. Analyses of various biomarkers did not suggest significant changes from baseline through Week 96.

Although the results of studies 104 and 111 are encouraging, based on the available data, we cannot be confident that there is no risk of renal toxicity associated with Genvoya use. Given that the studies enrolled a low risk population, tenofovir nephrotoxicity is relatively rare, and toxicity may occur after years of therapy, it is possible that toxicity will manifest with broader use in the post-marketing setting. It is our understanding that this was the case following the initial approval of TDF. Similarly, although no obvious safety signal was observed in study 112, as we have noted previously, the study size, lack of a control arm, and nature of the population (e.g., 64% of patients had previously tolerated TDF) limits our ability to draw firm conclusions regarding the risk of renal toxicity in a population with renal impairment. [REDACTED] (b) (4)

(b) (4)

A second issue, however, is whether the risk of renal toxicity with TAF is less than with TDF. Across TAF development programs for various indications, it appears that there may be some cases of proximal tubular injury/Fanconi Syndrome in TDF but not TAF subjects. If this finding is real, it may be reasonable to include information in the label related to the relative risk of proximal tubular injury/Fanconi Syndrome with TAF vs. TDF and, in essence, provide a comparative safety claim. We do not know how many potential cases of proximal tubular injury/Fanconi Syndrome have been reported in subjects treated with TDF across TAF development programs. Another critical issue is whether these potential cases do in fact reflect drug-induced proximal tubular injury/Fanconi Syndrome. One possible path forward is for the applicant to institute an independent, blinded process whereby potential cases of proximal tubular dysfunction/Fanconi Syndrome are adjudicated as “confirmed,” “probable,” etc. Diagnostic criteria could be retrospectively applied to data from completed or ongoing trials and prospectively applied to future data. If a sufficient number of confirmed/probable cases are seen in TDF subjects without cases in TAF subjects, this information indicating a safety advantage of TAF over TDF could be added to labeling.

2. Since other than TAF there were no non-TDF containing regimens studied can Gilead’s contention of similarity of renal impact between Genvoya and all non-TDF regimens be supported?

DCRP Response: *Studies 104 and 111 compared a TAF-based regimen to a TDF-based regimen. In study 112, all subjects received TAF. None of the three studies compared TAF with a non-TDF-based regimen. As such, it is not obvious to us that one can draw conclusions about the relative renal safety of TAF-based vs. non-TDF-based regimens based on these studies.*

3.

(b) (4)

4. Please assist with renal labeling recommendations.

DCRP Response: *See our response to Question 3. We agree that the label should be updated to reflect the cumulative safety experience.*

Consult Questions for NDA 208464

1. Please assess the renal effects when comparing TAF to TDF in light of creatinine function and phosphate handling.
2. Please assess the renal effects when comparing TAF to TDF in light of urinalysis differences measured in the study.
3. Assist in the evaluation of proteinuria, markers of proteinuria, and markers of proximal tubular dysfunction that Gilead evaluated in this study. (b) (4)

DCRP Response to Questions 1, 2, and 3: *Although estimates vary, the incidence of nephrotoxicity severe enough to warrant discontinuation of TDF therapy is approximately 1% with <0.2% of patients experiencing severe renal failure. Nephrotoxicity often develops over a period of months but can also develop after years of therapy. In Studies 108 and 110, no obvious renal safety signal was*

DCRP Response: *Glycosuria can be an early indicator of proximal tubular dysfunction, particularly when it occurs in the setting of normal serum glucose; however, glycosuria is most commonly observed when the filtered glucose load exceeds the amount of glucose the proximal renal tubule can re-absorb. The serum glucose level at which glycosuria occurs varies but is generally ~160 to 200 mg/dL, although this threshold may be lower in some individuals such as those taking SGLT2 inhibitors.*

In Studies 108 and 110, 3+ glycosuria on urine dipstick was observed in 5% of TAF as compared with 1% of TDF subjects. Although the baseline prevalence of diabetes was similar between the treatment arms, subjects in the TAF arm were more likely to have hyperglycemic events during the trial. All glycosuria events we identified occurred in the setting of hyperglycemia or in subjects with hyperglycemia at other trial visits. As such, we do not believe this finding represents injury to the proximal tubule or an early indicator of Fanconi syndrome.

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/s/

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07/29/2016

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