

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208464Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10/21/2016
From	Russell Fleischer, PA-C, MPH
Subject	Cross-Discipline Team Leader Review
NDA#	208464
Applicant	Gilead Sciences Inc.
Date of Submission	1/11/2016
PDUFA Goal Date	11/11/2016
Proprietary Name / Non-Proprietary Name	Vemlidy (tenofovir alafenamide)
Dosage form(s) / Strength(s)	25 mg tablet
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with chronic hepatitis B virus infection
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	<i>Treatment of adults with chronic hepatitis B virus infection with compensated liver disease.</i>

1. Benefit-Risk Assessment

I am in agreement with the Risk-Benefit Assessment as provided in the Clinical Review by Dr. Tanvir Bell; therefore this section closely mirrors that found in the Clinical Review with the exception of relatively minor revisions that do not substantively impact the overall risk-benefit assessment.

Benefit-Risk Summary and Assessment

Tenofovir alafenamide (TAF) is a nucleoside analogue. It is metabolized to the same active compound as the approved drug Viread (tenofovir disoproxil fumarate): tenofovir diphosphate. However, since TAF is more stable in plasma and yields higher intracellular levels compared to TDF, it was theorized that TAF would provide an efficacy and safety benefit over Viread; neither of which was clearly apparent in the current application.

Chronic Hepatitis B virus infection (CHB) is a serious disease as the virus is oncogenic and integrates into host DNA. CHB affects between 240-300 million people worldwide, and over 750,000 die each year. Varying prevalence exists globally with the highest in Africa and Asia. In the US, it is estimated that 700,000 to 1.4 million persons have CHB. In the US, universal Hepatitis B vaccination of newborns has decreased the prevalence substantially.

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 ALT when compared to other genotypes, and genotypes C and D are associated with higher progression rates to liver fibrosis.

There are three main stages of disease: immune tolerant, immune active, and inactive carrier. The immune tolerant stage is characterized by extremely high levels of HBV DNA, HBeAg+, HBeAb-, normal ALT and no necroinflammation. In the immune active stage, HBV DNA is >20,000 IU/mL, HBeAg+, HBeAb-, ALT is increased and there is necroinflammation on biopsy. 2-5% of patients will progress to cirrhosis each year and there is an increased risk of HCC. Patients in the immune active stage may spontaneously seroconvert the HBeAg at a rate of 12-16% per year. In general, the higher the ALT level, the more likely seroconversion will occur; often the seroconversion is predated by a flare of hepatitis with a marked elevation in the ALT level. HBeAg conversion is a desirable effect as it marks the onset of the inactive carrier stage of disease. Inactive carriers are HBsAg+ with HBV DNA <20,000 IU/mL, HBeAg-, HBeAb+, and have normal ALT levels. These patients can have exacerbations of disease with or without HBeAg reversion. There is an 8-10% annual risk of progression to cirrhosis and the risk for HCC remains. Patients in the immune active stage and those with HBeAg- chronic hepatitis are considered candidates for therapy. **There are eight well-known genotypes of the HBV.** Clinical outcomes of chronic HBV infections are variable, and many factors, such as host factors, HBV genotype, specific viral mutations, viral load, and quantitative HBsAg levels are important in their prediction. (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017058> and 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)

Viread was approved in 2000. The goal of therapy is to suppress virus to induce immune system activation to further control the infection to prevent liver related morbidity and mortality by moving the patient out of the immune active stage of disease. Loss of

HBsAg with conversion to HBsAb occurs rarely under nucleoside therapy: approximately 1-2% per year. As such, nucleoside therapy of CHB is often considered “life-long.”

The safety and efficacy of TAF in patients with chronic HBV were assessed in two randomized, double blind, 96-week studies. Study 108 included 425 patients negative for hepatitis B e antigen (HBeAg), and Study 110 included 873 patients positive for HBeAg. In each study, subjects were randomized 2:1 to 25 mg TAF or 300 mg TDF administered once-daily. The primary efficacy endpoint at 48 weeks was the proportion of patients with plasma HBV DNA levels <29 IU/mL using an FDA approved assay.

The results demonstrated that TAF met non-inferior criteria compared to TDF using a 95% confidence interval (CI) approach, with a noninferiority margin of 10%. In Study 108, 94% of subjects receiving TAF and 93% of subjects receiving TDF achieved HBV DNA below 29 IU/mL (95% CI, -3.6% to 7.2%) after 48 weeks of treatment. In Study 110, 64% of subjects receiving TAF and 67% of subjects receiving TDF achieved HBV DNA below 29 IU/mL (95% CI, -9.8% to 2.6%).

Further, subgroup analyses demonstrated that in Study 110 there were numeric but non-significant trends in favor of treatment with Viread in subjects with high baseline viral load, those previously treated with nucleoside analogues and those with cirrhosis.

As a secondary endpoint, alanine aminotransferase (ALT) normalization was assessed using a central laboratory cut-off value. During the conduct of the trials, the American Association for the Study of Liver Diseases (AASLD) revised criteria for more stringent upper limit of normal ALT levels, and these values were also applied in the analysis. The analysis found that TAF provided an overall small and statistically significant increase in rates of ALT normalization compared with TDF when measured using the AASLD criteria, and no difference when evaluated using the central lab cut-off levels.

Important serologic outcomes included loss of HBeAg and HBeAb seroconversion in Study 110 and loss of HBsAg and HBsAb seroconversion in both studies. In Study 110, HBeAg loss and seroconversion to anti-HBeAb occurred in comparable proportion of subjects: 14%/10% and 12%/8%, respectively. This is in line with the known spontaneous seroconversion rate to HBeAb in 8-12% of patients. HBsAg loss was a rare occurrence; ~1% in both treatment groups of both trials, which is consistent with the one-year untreated rate of spontaneous HbsAg clearance.

The safety profile of TAF was comparable to TDF. Tenofovir-related risks include changes in bone mineral density (BMD) and renal laboratory abnormalities. In both studies, patients who received TAF yielded a smaller mean percentage decrease in hip and spine bone mineral density vs. subjects receiving TDF. Because the data are of short duration, it is not possible to determine if these differences are clinically relevant. However, data from long term follow-up studies have suggested that the BMD changes associated with tenofovir do not translate into excess risk of osteopenia or osteomalacia-related fractures. (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) As such, the WARNING related to changes in BMD will be removed. Since they were observed in both treatment groups, changes in BMD will be included in the Adverse Reactions section.

The small median change in glomerular filtration rates also favored TAF over TDF. However, due to the small number of subjects enrolled, short duration of exposure, and that all subjects had normal renal function, the clinical relevance of these changes is also unknown.

Abnormalities of lipid metabolism were observed more often among TAF treated subjects. For example, the differences between the two products in the proportion of subjects with Grade 3 and 4 LDL cholesterol levels was notable with 4% in the TAF group compared to 0% in the TDF group. Information about the changes in cholesterol levels and the potential need for changes or additions to lipid-lowering therapies will be included in the label.

No deaths or SAEs were attributable to study drugs. Approximately 2% of subjects in both treatment arms discontinued therapy due to adverse events; no pattern to these events was observed. The most frequently reported treatment emergent adverse events reported in $\geq 5\%$ of TAF-treated subjects that were plausibly related to tenofovir were nausea, headache, abdominal pain, fatigue, back pain, nasopharyngitis and cough.

Of note, a potential signal for pancreatitis was identified as there were subjects treated with TAF who had increased amylase levels with associated symptoms (i.e., nausea, back pain, abdominal pain, biliary pancreatitis); one subject experienced a positive rechallenge of symptoms following restarting TAF.

In summary, Vemlidy provides for an alternative nucleoside therapy for treatment of CHB, with a manageable safety profile. The trials are ongoing and it is possible that differences in safety and efficacy may become more apparent once longer duration data becomes available.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Chronic Hepatitis B (CHB) is a liver infection caused by the Hepatitis B virus (HBV) and is transmitted through blood or body fluids via injection-drug use, sexual contact, and transmission from the mother to fetus. If left untreated, chronic Hepatitis B can lead to serious health issues, like cirrhosis or liver cancer. About a third of the world's population has been infected at one point in their lives, 	<p>CHB is a significant public health concern. Current treatment approaches are not effective at eradicating the virus. Virologic</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>including 240 million to 350 million who have chronic infection, and over 750,000 people die of HBV infection each year.</p> <ul style="list-style-type: none"> • The disease is more common in East Asia and sub-Saharan Africa. • There are eight well-known genotypes of the HBV. Genotype A is widespread in sub-Saharan Africa, Northern Europe, and Western Africa; genotypes B and C are common in Asia; genotype C is primarily observed in Southeast Asia; genotype D is dominant in Africa, Europe, Mediterranean countries, and India; genotype G is reported in France, Germany, and the United States; and genotype H is commonly encountered in Central and South America. • In the US, universal Hepatitis B vaccination of newborns has decreased the prevalence substantially. • Infection with Hepatitis B virus is life-long as the virus integrates into host DNA. • There are three main stages of disease: immune tolerant, immune active and inactive carrier. • The immune tolerant stage is characterized by extremely high levels of HBV DNA, HBeAg+, HBeAb-, normal ALT and no necroinflammation. • In the immune active stage, HBV DNA is >20,000 IU/mL, HBeAg+, HBeAb-, ALT is increased and there is necroinflammation on biopsy. 2-5% of patients will progress to cirrhosis each year and there is an increased risk of HCC. Patients in the immune active stage may spontaneously seroconvert to HBeAg at a rate of 12-16% per year. In general, the higher the ALT level, the more likely seroconversion will occur; often the seroconversion is predated by a flare of hepatitis with a marked elevation in the ALT level. HbeAg conversion is a desirable effect as it marks the onset of the inactive carrier stage of disease. • Inactive carriers are HBsAg+ with HBV DNA <20,000 IU/mL, HBeAg-, HBeAb+, and have normal ALT levels. These patients can have exacerbations of disease with or without HBeAg reversion. There is an 8-10% annual risk of progression to cirrhosis and the risk for HCC remains. • Patients in the immune active stage and inactive carriers are considered candidates for therapy. • The goal of therapy is to suppress virus to induce immune system activation to further control the infection to prevent liver related morbidity and mortality by moving the patient out of the immune active stage of disease. 	<p>control of HBV infection is defined as loss of hepatitis B surface antigen (HBsAG) with seroconversion conversion to anti-HBsAg. Virologic control is associated with a reduction in complications of end-stage liver disease both for infected individuals and the population as a whole (see Terrault, etal). In addition, widespread treatment may help to reduce the incidence of new HBV infections in a large proportion of patients who have not received vaccination.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Loss of HBsAg with conversion to HBsAb occurs rarely under nucleoside therapy: approximately 1-2% per year. As such, nucleoside therapy of CHB is often considered “life-long.” 	
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> • There are seven agents currently licensed for treatment of CHB in the United States. These include the nucleos(t)ide analogues lamivudine (Epivir), adefovir (Hepsera), tenofovir (Viread), telbivudine (Tyzeka) and entecavir (Baraclude), and two immune system modulators interferon alpha-2a (PEG-Intron) and PEGylated interferon alpha-2a (Pegasys). • Treatment of CHB typically results in suppression of HBV DNA and normalization of aminotransferase levels; however, virologic cure is rare (estimated ~2%/year). 	<p>The goal of treatment is to achieve HBV DNA suppression with HBsAg loss (with conversion to anti-HBsAB). This endpoint has been associated with long term reductions in liver related morbidity (primarily hepatocellular carcinoma) and mortality. Unfortunately, this outcome is rarely achieved during the first year of treatment (<2%), and reports demonstrate that multiple years of suppressive therapy is required.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> • Across two clinical trials, TAF demonstrated comparability to currently approved Viread with respect to HBV DNA suppression, normalization of ALT levels, and important serologic endpoints. Small numeric trends in favor of Viread in subjects with high viral load or those with cirrhosis were observed. 	<p>Two clinical trials provide substantial short-term evidence of effectiveness of TAF. The trials are ongoing and it is expected that 96 and 144-week blinded data will be submitted in the future.</p>

Dimension	Evidence and Uncertainties				Conclusions and Reasons	
	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)			
		TAF (N=285)	tenofovir disoproxil fumarate (N=140)	TAF (N=581)		tenofovir disoproxil fumarate (N=292)
	HBV DNA <29 IU/mL	94%	93%	64%		67%
	Treatment Difference	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%
	Baseline HBV DNA <7 log ₁₀ IU/mL ≥7 log ₁₀ IU/mL	96% (221/230) 85% (47/55)	92% (107/116) 96% (23/24)	NA		NA
	Baseline HBV DNA <8 log ₁₀ IU/mL ≥8 log ₁₀ IU/mL	NA	NA	88% (132/150) 55% (239/431)		78% (60/77) 63% (135/215)
	Nucleoside naïve Nucleoside experienced	94% (212/225) 93% (56/60)	93% (102/110) 93% (28/30)	68% (302/444) 50% (69/137)		70% (156/223) 57% (39/69)
	Subjects with Cirrhosis	92% (22/24)	93% (13/14)	63% (26/41)		67% (16/24)
	No Virologic Data at Week 48	4%	4%	5%		3%
	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)			
		TAF (N=285)	tenofovir disoproxil fumarate (N=140)	TAF (N=581)		tenofovir disoproxil fumarate (N=292)
	ALT Normalized ALT (Central Lab)	83%	75%	72%		67%
	Normalized ALT (AASLD)	50%	32%	45%		36%
	Serology HBeAg Loss / Seroconversion	N/A	N/A	14% / 10%		12% / 8%
	HBsAg Loss / Seroconversion	0 / 0	0 / 0	1% / 1%		<1% / 0

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk</u></p>	<ul style="list-style-type: none"> • The safety of TAF and TDF was generally comparable with numerically less bone loss and renal events associated with TAF use; however, the clinical relevance of these small observed differences is unknown. • A potential new signal for TAF-related pancreatitis was observed with one subject with symptomatic elevation in amylase levels experiencing a positive rechallenge when TAF was restarted. • The most frequently reported treatment emergent adverse events reported in >5% of TAF-treated subjects that were plausibly related to tenofovir were nausea, headache, abdominal pain, fatigue, back pain, nasopharyngitis and cough. • Significant and early elevations in aminotransferase levels have been observed primarily in HBeAg positive patients as a response to treatment initiation. These flares of ALT occurred infrequently in the trials, and in nearly all cases resolved with continued treatment; there was no evidence of acute hepatotoxicity. • Preclinical and other clinical trial data suggest that TAF may be associated with posterior uveitis; however, ocular events were comparable between treatments in the two studies and there were no cases of uveitis. 	<p>The adverse event profile of TAF is manageable through labeling recommendations. Ocular-related adverse events bear further evaluation in the post-marketing setting. It is also reasonable to include information about the potential risk of pancreatitis associated with TAF into labeling, and to engage in post-marketing pharmacovigilance for this event.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • Tenofovir-related decreases in bone mineral density and/or renal toxicity have been reported in clinical trials, and may occur many months to years after exposure. (b) (4) (b) (4) the trials were generally small and of short duration and conducted in subjects with normal renal function: (b) (4) (b) (4) . • The bone WARNING was removed because long-term data from HIV clinical trials and observational cohorts have not demonstrated that the changes in BMD have not been demonstrated to be clinically significant enough to warrant continuation of the WARNING (Wong et al;Hepatology, Vol 62, No. 3, 2015). Clinical data from the trials will be included in the label. 	<p>The safety concerns associated with TAF are adequately addressed in product labeling.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Increased amylase and a new signal for risk of pancreatitis are recommended for inclusion in labeling. • A description of lipid abnormalities is recommended for inclusion in the labeling. 	

2. Background

HBV is a DNA virus classified in the virus family Hepadnaviridae. Humans are the only known natural host. (<http://epirev.oxfordjournals.org/content/28/1/112.full>) An estimated 2 billion persons worldwide have been infected with HBV, and more than 350 million persons have chronic, lifelong infections. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 50% of hepatocellular carcinomas (HCC). The World Health Organization estimated that more than 600,000 persons died worldwide in 2002 of hepatitis B-associated acute and chronic liver disease. (<http://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html>)

While most acute HBV infections in adults result in complete recovery, fulminant hepatitis occurs in about 1% to 2% of acutely infected persons. About 200 to 300 Americans die of fulminant disease each year (case-fatality rate 63% to 93%). Although the consequences of acute HBV infection can be severe, most of the serious complications associated with HBV infection are due to chronic infection.

Safe and effective vaccines against HBV infection have been available since 1982. The implementation of mass immunization programs, which have been recommended by the World Health Organization since 1991, have dramatically decreased the incidence of HBV infection among infants, children, and adolescents in many countries.[2] However, not all countries have adopted these recommendations and there remains a large number of persons that were infected with HBV prior to the implementation of immunization programs.

Conventional interferon alfa, pegylated interferon, and nucleoside analogues such as lamivudine, adefovir, entecavir, and tenofovir disoproxil fumarate have been the primary treatments to date. The interferons produce a durable response in a moderate proportion of patients but have undesirable side-effects and must be administered subcutaneously. Nucleoside analogues also produce a response in a modest proportion of patients and cause few side-effects. However, prolonged treatment is often necessary to prevent relapse on cessation of therapy. (<http://www.medscape.com/viewarticle/471470>)

Tenofovir alafenamide (TAF) is a prodrug of the N(t)RTI tenofovir (TFV) and is more stable in plasma than TDF. Like TDF, TAF has potent antiviral activity against both HIV-1 and hepatitis B virus (HBV). Tenofovir alafenamide has pharmacokinetic properties that distinguish it from TDF. For example, Tenofovir alafenamide 25 mg achieves > 4 fold higher intracellular levels of the pharmacologically active phosphorylated metabolite tenofovir diphosphate (TFV DP) in peripheral blood mononuclear cells (PBMCs) and ~90% lower circulating levels of TFV relative to TDF (300 mg). The Applicant purports that this marked reduction in circulating TFV is associated with smaller changes in clinical markers of renal function (eg, proteinuria) and in Bone Mineral Density (BMD).

On July 30, 2012, Gilead submitted IND 115561 for the treatment of hepatitis B virus (HBV) infection. The original IND was opened with Phase 1 study to assess the safety, viral kinetics, and anti-HBV activity of GS-7340 in treatment-naive adults with CHB infection. An EOP-2 meeting was held in June 2013 during which the design of the Phase 3 trials were discussed and agreed upon. In December 2015 a Type-C pre-NDA meeting was held to discuss the topline results of the two registration clinical trials. On January 11, 2016, the NDA was submitted and designated for a standard review. This IND was not granted fast track or breakthrough therapy designation.

This application also represents the first approval of TAF as a stand-alone product. TAF is currently approved as a component of three fixed-dose combinations indicated for treatment of HIV-1 infection: Genvoya, Descovy and Odefsey.

3. Product Quality

The NDA submission included adequate information to allow the OPQ review team to evaluate the characteristics and quality of the drug substance for the single entity TAF and the final drug product, Vemlidy tablets. For a complete discussion of the OPQ issues, please refer to Dr. Steve Miller's Quality Assessment as well as individual reviews provided by the OPQ review team: Drs. Yong Wang (drug product), Jin Li (biopharmaceutics), Ying Wang (process), Frank Wackes (facilities), and Florence Aisida (RBPM). The following descriptions of key CMC issues are summarized from the Product Quality reviews. The Product Quality team recommends approval of Vemlidy

General product quality considerations

The Drug Substance Quality review focused on review of TAF (tenofovir alafenamide fumarate). TAF is not considered a New Molecular Entity because it is currently approved as a component of multiple fixed-dose combinations indicated for treatment of HIV-1 infection.

TAF is a prodrug of tenofovir that differs from the currently approved prodrug TDF (Viread®) by features such as the (b) (4). The drug substance is produced in a (b) (4) (b) (4) (b) (4). Starting materials for TAF synthesis and their specifications were reviewed and agreed upon after some discussion with the Applicant. Drug substance specifications for all key tests were reviewed and agreed upon, including: identity, clarity of solution, water content, impurity content (for specified and unspecified impurities), residual solvents, melting point, and particle size.

As noted in the Product Quality Review, the applicant provided sufficient data to demonstrate the consistency of the proposed Vemlidy commercial manufacturing process at the proposed commercial scale. Tablets are manufactured using a (b) (4) (b) (4) procedure. The Vemlidy drug product contains 28 mg of TAF fumarate in a

round, yellow, film-coated tablet debossed with “GSI” on one side and “25” on the other. Tablets are packaged as a 1-month supply in 30-count HDPE bottles with child-resistant closure; each bottle contains a silica gel desiccant and a polyester coil. There are no novel excipients, and all components are compendial. All analytical methods are described in reasonable detail and have been validated. The 24-month expiration dating period with labeling of “Store below 30 ° C (86 ° F)” is adequately justified by the stability at 30°C/75%RH ((b) (4)) plus accelerated, open-dish, and photostability studies.

Facilities review/inspection

At the time of this CDTL Review, all facilities inspections and reviews have been completed for all drug substances and the final drug product. The Offices of Compliance and New Drug Quality Assessment have determined these facilities to be acceptable.

Other notable issues (resolved or outstanding)

There are no outstanding product quality issues related to either TAF drug substance or the Vemlidy tablet drug product.

4. Nonclinical Pharmacology/Toxicology

TAF is a component of Genvoya®, which is a fixed-dose combination containing elvitegravir, cobicistat, TAF and emtricitabine (E/C/F/TAF). The Pharmacology/Toxicology of TAF was fully evaluated in support of approval of Genvoya® (NDA 207561), and no new Pharmacology/ Toxicology data were submitted as part of this application.

Important preclinical findings included:

- Chronic administration of TAF led to dose-dependent, slight to moderate renal cortical tubular degeneration/regeneration and karyomegaly in the dog as well as renal karyomegaly in the rat. In the dog, partial recovery was observed after three months. These findings were qualitatively similar to the renal findings in the TDF nonclinical program.
- Dose dependent reductions in bone mineral density and mineral content, as well as changes in markers of bone turnover and in related hormones, were observed in rats and dogs. Partial recovery was observed after three months in dogs. The bone findings were also qualitatively similar to those identified in the TDF nonclinical program.
- In dogs, a minimal to slight infiltration of mononuclear cells of the posterior uvea was seen in animals receiving the high dose with similar severity after three and nine month administration of TAF. Reversibility was seen after a three months recovery period but a mechanism for this finding was not identified.
- The TAF chronic dosing study in dogs showed a PR prolongation at the mid and high doses, and a reversible reduction in heart rate associated with mild QT

prolongation in the high dose animals at week 39. These changes were associated with decreases in serum T3. Recovery was observed after 13-weeks. The systemic TAF exposure at the no-effect level, was lower in dogs than expected in humans; therefore, no safety margins for this toxicity were established.

- TAF is not mutagenic or teratogenic and has not been evaluated in women during pregnancy.

Clinical findings supported the preclinical bone and renal observations and resulted in Warnings being included in the Viread and Genvoya labels. Based on the data contained in this application, as well as long term data from other clinical trials and observational cohorts, it was decided that the Warning related to changes in bone mineral density could be removed with the clinical data included in Section 6. The renal Warning was retained without revision. The potential for ocular toxicity was examined in the Genvoya safety database and was not observed in sufficient quantity to merit special mention in the label; it was evaluated in the current NDA with a similar conclusion being reached. A thorough QT/QTc study demonstrated that TAF did not affect the QT/QTc interval and did not prolong the PR interval.

PLLR information was included in the application and deemed consistent with the information contained in the labels of other TAF-containing products.

5. Clinical Pharmacology

Drs. Mario Sampson and Islam Younis were the primary clinical pharmacology reviewer and team leader and concur with the approval of this application. TAF is a component of Genvoya, which is a fixed-dose combination of elvitegravir, cobicistat, emtricitabine and TAF. The Clinical Pharmacology of TAF was fully evaluated in support of approval of Genvoya (NDA 207561).

Briefly, after cellular entry, TAF is metabolized to its active metabolite, tenofovir-diphosphate which 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.

Four issues were identified in which there were differences between assessments conducted by the Applicant and the FDA Clinical Pharmacology reviewers.

Food Effect

In the HBV trials, TAF was administered without regard to food intake. Efficacy data were generated in subjects recommended to administer TAF with food. In addition, at lower TAF exposures expected when TAF is administered fasted, exposure-response

relationships are unclear. Based on these findings, it is recommended that TAF be administered with food.

Renal Impairment

(b) (4)

(b) (4) Based on the available data, TAF use should be limited to patients with CrCl >15 mL/min.

Hepatic Impairment

No dose adjustments are required for patients with mild hepatic impairment. However, subjects with moderate or severe hepatic impairment were not enrolled in the phase 3 studies. Data on unchanged total or unbound plasma exposures are not sufficient to recommend use of TAF in this population. The reason to not use PK to extrapolate efficacy is because the target of the drug is the liver and exposure-response relationships may be altered in patients with hepatic impairment.

Co-administration with Carbamazepine

A lower TAF exposure is expected when TAF is administered with carbamazepine, exposure-response relationships are unclear. For this reason the TAF dose should be doubled (50 mg) so as to match typical exposures.

6. Clinical Microbiology

Please refer to the virology review by Dr. Sung Rhee for a detailed assessment of the clinical and non-clinical virology data. Dr. Rhee concurs with approval of TAF for the treatment of chronic HBV as recommended in the prescribing information.

Viread (TDF) has been in use for many years and to date no resistance associated substitutions that convey reduced activity have been identified. Likewise, in the current trials, very few subjects experienced virologic failure and no resistance associated substitutions were identified.

Like Viread, TAF is also a prodrug of the N(t)RTI tenofovir (TFV). The antiviral activity of TAF was assessed in a transient transfection assay using HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC₅₀ values for TAF ranged from 34.7 to 134.4 nM, with an overall mean EC₅₀ value of 86.6 nM. The CC₅₀ 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. Further, no cross resistance with lamivudine or entecavir was observed in an in vitro study.

The 25 mg/day TAF dose was taken forward into clinical development based on the results of a phase 1 study that demonstrated anti-HBV activity at all doses evaluated with a plateau effect noted at doses ≥ 25 mg.

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 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.

7. Clinical/Statistical- Efficacy

To support the efficacy of TAF for treatment of chronic HBV infection, the Applicant conducted two similarly designed adequate and well controlled trials. Study 0108 was conducted in HBeAg negative subjects and Study 0110 was conducted in HBeAg positive subjects. In both trials, a TAF dose of 25 mg/day was compared to the approved 300 mg/day dose of TDF (Viread®). Because TAF and TDF are both metabolized to the same active compound, tenofovir, it was reasonable for the studies to compare the two treatments in a head-to-head manner.

Based on feedback from the Division, the trials were amended to extend blinded treatment to 144 weeks and to utilize a HBV DNA cut off of <29 IU/mL as the basis for assessing efficacy.

Subjects were randomized 2:1 to TAF or TDF and stratified by baseline HBV viral load ($\leq > 7 \log_{10}$ in Study 0108 and $\leq > 8 \log_{10}$ in Study 0110). The rationale for the difference was that subjects with HBeAg positive disease typically have higher viral load levels.

Enrolled subjects 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. Higher, and comparable, baseline viral load ($\geq 8 \log_{10}$ U/mL) and ALT levels were observed in Study 0110, which is consistent with the known characteristics of HBeAg positive disease. 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. Among those with data, ~11% had evidence of compensated (no evidence of hepatic encephalopathy, variceal bleeding,

ascites, INR $<1.5 \times \text{ULN}$, total bilirubin $<2.5 \times \text{ULN}$, and albumin $>3.0 \text{ mg/dL}$) cirrhosis (Metavir or Knodell fibrosis score ≥ 4 or Ishak fibrosis score ≥ 5 on liver biopsy, or Fibroscan $\geq 12.5 \text{ KpA}$) The proportions of subjects in the trials with diabetes, hypertension, cardiovascular disease or hyperlipidemia were low ($<10\%$) and comparable.

1298 subjects were treated in the two studies, and overall 93% completed 48 weeks of treatment. Reasons for premature study discontinuation (adverse event, investigator discretion, withdrew consent, lost to follow-up, non-compliance, pregnancy, protocol specified criteria, death, and lack of efficacy) were balanced across arms (1-3% in each category). Of note, there were 25 subjects in total who were discontinued due to consent withdrawal or investigator discretion, and of these, 10 (8 TAF and 2 TDF) were reclassified by the clinical reviewer as discontinuations due to adverse events. Thus, the proportion of subjects who discontinued study drug did not change; only their classification changed.

The selected efficacy endpoints, assessment of HBV DNA suppression, normalization of ALT levels, and HBe and HBs serologies were reflective of endpoints that have been demonstrated to be clinically relevant to the treatment of chronic HBV infection, as outlined in internal and external guidance.

The primary endpoint for both trials was the proportion of subjects with HBV DNA $<29 \text{ IU/mL}$ at Week 48 of blinded treatment. The Applicant measured viral load using the FDA approved Roche COBAS ®Taqman®HBV Test for Use with the High Pure System assay with a LLOQ of 29 IU/mL . As noted above, achievement of undetectable HBV DNA is a valid surrogate for improved long-term reductions in liver related morbidity and mortality.

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. According to the Statistical review, the 10% NI margin would be acceptable, given the TDF was approved on the basis of trials showing TDF to be superior to adefovir by considerably more than 10% in both HBeAg negative and HBeAg positive subjects.

Subjects were stratified by baseline HBV DNA level ($< 7 \log_{10} \text{ IU/mL}$, ≥ 7 to $< 8 \log_{10} \text{ IU/mL}$, $\geq 8 \log_{10} \text{ IU/mL}$ in Study 0108, and $<8 \log_{10} \text{ IU/mL}$, $\geq 8 \log_{10} \text{ IU/mL}$ in Study 0110) and oral antiviral treatment status (treatment-naive vs treatment-experienced). If non-inferiority was established, a test for superiority was to be conducted.

Both studies demonstrated non-inferiority of TAF to TDF. In Study 110 it is notable that the lower bound of the 95% CI was -9.8, which was very close to the non-inferiority margin of -10%. Given the pharmacologic properties of TAF compared to TDF, the reasons for this finding are unknown at the present time. Superiority of TAF over TDF was not established in either trial.

The outcome of the primary efficacy analysis for the entire study population and for the two stratification factors for Study 108 and 110 are shown in the following tables.

Table 1 Virologic outcomes, Study 108

	Vemlidy N=285	TDF N=140	Difference (95% CI)
HBV DNA <29 IU/mL	94%	93%	1.8 (-3.6% to 7.2%)
Baseline HBV DNA <7 log ₁₀ IU/mL	96% (221/230)	92% (107/116)	+3.8 (-1.9% to 9.6%)
≥7 log ₁₀ IU/mL	85.5% (47/55)	96% (23/24)	-10.4 (-25.2 to 4.5%)
Treatment naïve	94% (212/225)	93% (102/110)	-1.6% (-4.3% to 7.6%)
Treatment experienced	93% (56/60)	93% (28/30)	-0.2% (-12.4% to 12.7%)

Table 2 Virologic outcomes, Study 110

	Vemlidy N=581	TDF N=292	Difference (95% CI)
HBV DNA <29 IU/mL	64%	67%	-3.6 (-9.8% to 2.6%)
Baseline HBV DNA <8 log ₁₀ IU/mL	82% (254/309)	82% (123/150)	0.1% (-7.4% to 7.5%)
≥8 log ₁₀ IU/mL	43% (117/242)	51% (72/142)	-7.6% (-17.8% to 2.5%)
Treatment naïve	68% (302/444)	70% (156/223)	-2.8% (-9.7% to 4.1%)
Treatment experienced	50% (69/137)	56.5% (39/69)	-6.2% (-20.4% to 7.9%)

In Study 110, subjects were stratified using a baseline viral load cut-off of 8 log₁₀ IU/mL, and the difference between TAF and TDF did not reach statistical significance. When the statistics reviewer used the same baseline HBV DNA strata that were used for Study 108 (7 log₁₀ IU/mL) the Zelen exact test for treatment by baseline interaction was statistically significant (p=0.017 at the 0.05 level) due to the lack of homogeneity of treatment effect in the baseline HBV DNA strata.

Initiation of anti-HBV therapy that leads to successful DNA suppression can be followed by elevated aminotransferase levels moving toward normal levels, suggesting reductions in hepatic inflammation.

ALT normalization was a pre-specified secondary efficacy endpoint. In the current studies, normalization of ALT levels were assessed using the upper limit of normal (ULN) from both a central lab (>43 U/L for males aged 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), and more simplified and lower American Association for the Study of Liver Disease (>30 U/L males and >19 U/L females) cut-offs. The lower AASLD levels likely provide a more sensitive assessment of aminotransferase levels, which indicate ongoing inflammation. The data demonstrate that, based on the AASLD cut-offs, the frequency of ALT normalization was relatively low in both treatment arms; however, the difference between TAF and TDF did reach statistical significance.

Table 3 ALT normalization rates

ALT	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N=285)	tenofovir disoproxil fumarate (N=140)	VEMLIDY (N=581)	tenofovir disoproxil fumarate (N=292)
Normalized ALT (Central Lab) ^b	83%	75%	72%	67%
Normalized ALT (AASLD) ^c	50%	32%	45%	36%

Other secondary and clinically relevant endpoints were: loss of HBeAg with seroconversion to HBeAb in Study 0110 and loss of HBsAg (with conversion to anti-HBsAb) in both trials; no difference between TAF and TDF in either of these parameters was observed. Specifically, comparable proportions of subjects experienced HBeAg loss and seroconversion in Study 0110: 14% and 10% for TAF and 12% and 8% for TDF, respectively. Only 1% of subjects experienced HBsAg loss after 48 weeks of treatment in either treatment group. These outcomes are typical following short duration treatment and may increase over time with more prolonged treatment.

Approximately 11% of study subjects had cirrhosis at baseline. In Study 108, both treatments resulted in 92% of subjects achieving the primary endpoint. Again in Study 110, there was a small numeric trend in favor of treatment with TDF in this population: 67% compared to 63%. The Applicant attempted to assess shifts in fibrosis stage by FibroTest. At Week 48; the overall mean change from baseline in FibroTest scores was small and not indicative of an appreciable improvement in hepatic architecture.

1% of subjects in Study 108 and 3% in Study 110 experienced virologic failure. Resistance to tenofovir was assessed in 41 subjects with detectable HBV DNA at Week 48, and no resistance associated mutations were identified.

There were no clinically relevant differences in response rates based on HBV genotype, gender, age, race or ethnicity.

Conclusions on the Substantial Evidence of Effectiveness:

In summary, the Applicant has submitted substantial evidence from two adequate and well controlled efficacy studies demonstrating statistical non-inferiority of Vemlidy to currently approved Viread based on reductions in HBV DNA levels. It is notable that for HBeAg+ subjects TAF barely met the non-inferiority test, and for those with high viral load, prior exposure to nucleoside analogues, and cirrhosis, there are numeric trends in favor of TDF. This is an interesting finding given that more subjects treated with TAF experienced ALT normalization. As in other trials of CHB therapies, the outcome of most interest, loss of HBsAg, occurred rarely after 48 weeks of treatment, and likely reflects the short duration of the data. The trials are ongoing and higher rates may be observed following longer duration of blinded treatment.

8. Safety

The Vemlidy safety database contains data on 866 subjects treated with a 25 mg dose of TAF for at least 48 weeks, which is adequate to determine the overall safety profile of the drug. Further, TAF is currently approved as a component of Genvoya®, and the safety profile was fully evaluated across at least six studies contained in the Genvoya NDA in which TAF was administered to over 2000 subjects for ≥ 48 weeks. In general the safety profile observed in the HBV trials was comparable to that observed in the HIV trials, with the exception of a new signal for TAF-related pancreatitis.

In the current NDA, no deaths were attributable to study drugs. A single related SAE of ocular toxicity was reported in both treatment arms. Approximately 2% of study subjects discontinued due to adverse events; the frequency was similar between treatments and no specific patterns of adverse events were identified.

In general, TAF was well tolerated with most adverse events being mild or moderate in severity. In previous TDF trials in subjects with CHB and compensated liver disease, the most frequently reported TEAEs ($>5\%$) included: abdominal pain, diarrhea, headache, fatigue, nasopharyngitis, back pain and skin rash. It was therefore reasonable to assess the frequency of these events as these have been associated with the active ingredient tenofovir, to which both TAF and TDF are metabolized. As in the earlier TDF studies, with the exception of dizziness, skin rash, arthralgia and diarrhea, the other listed events were observed in $>5\%$ of subjects treated with both TAF and TDF always with the frequency being similar or slightly higher in the TAF group. TEAEs reported in $\geq 5\%$ of subjects in studies 108 and 110 are shown in the following table.

Table 4 Integrated TEAEs associated with TAF

	VEMLIDY (N=866)	VIREAD (N=432)
Headache	9%	8%
Abdominal pain	7%	6%
Fatigue	6%	5%
Cough	6%	6%
Nausea	5%	5%
Back pain	5%	4%

Application-Specific Adverse Reactions

The target organ toxicity identified in nonclinical and clinical studies of TDF and tenofovir include proximal renal tubule dysfunction and bone mineral density loss. In addition, posterior uveitis was identified in nonclinical studies of TAF. The Applicant provided multiple analyses intended to address these safety concerns and demonstrate a favorable safety profile for TAF, particularly as compared to TDF. Clinical and laboratory monitoring schedules and data analyses related to bone and renal toxicity are described in detail in the Clinical Review. In addition, the Review Team sought input from FDA colleagues in the Division of Bone, Reproductive, and Urologic Products (DBRUP), the Division of Cardiovascular and Renal Products (DCRP), and the Division of Ophthalmologic and Transplant Products (DTOP), who provided secondary data review and recommendations on labeling.

Other events evaluated in the application that have a bearing on the safe administration of TAF include a new signal for elevations in amylase levels associated with pancreatitis, elevations in lipid parameters, and elevations in aminotransferase levels.

- **Changes in Renal Function**

Preclinical data suggest that the renal tubules are a target for tenofovir-related toxicity. However, in clinical practice, significant renal toxicity is rare and can take months to years of exposure to manifest. The Applicant designed the clinical trials to assess the difference between TAF and TDF as potential causes of renal toxicity. Renal monitoring included a comprehensive battery of tests.

Across the two trials, there were small and insignificant changes in serum creatinine levels between treatment groups. Through Week 48, median serum creatinine increased 0.01 mg/dL for TAF versus 0.03 mg/dL for TDF. One percent of subjects in both treatment groups had proteinuria. There were no differences in change from baseline in serum phosphorus levels between treatment groups.

Subjects treated with TDF had larger increases in UPCR, a quantitative assessment of urinary protein, compared to subjects receiving TAF. Additional investigational renal biomarkers such as urine retinol binding protein (RBP) to creatinine ratio and beta-2-

microglobulin to creatinine ratio also appeared to be less affected by treatment with TAF compared to TDF. These parameters are not routinely followed in clinical practice; therefore, the clinical relevance of these changes is currently unknown. No subject in these trials experienced proximal renal tubulopathy. Further, there were no clinically relevant differences in renal adverse events and no subject had a renal-related SAE or discontinued study medication due to a renal event.

(b) (4)

The Clinical Pharmacology reviewer disagreed with this conclusion as noted in Section 5 above. Based on his review, the final dosing recommendation will be to administer Vemlidy to patients with a creatinine clearance >15 ml/min.

(b) (4)

- **Changes in Bone Mineral Density**

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. osteoporosis, osteomalacia and/or pathological fractures. To assess bone toxicity, the Applicant provided serial DXA scans to evaluate BMD, measurements of biomarkers of bone turnover, and assessment of fractures in all the submitted trials.

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%). 25-OH-vitamin D was measured at baseline only; there was no correlation between levels and spine BMD response at week 48. The incidence of $\geq 5\%$ decline in spine BMD was 6.3% among TAF recipients, and 20.4% among TDF recipients ($p < 0.001$).

Total hip BMD, also a key secondary endpoint of studies 108 and 110, demonstrated a similar pattern of decline at weeks 24 and 48 with TDF, and much smaller declines with TAF. The incidence of $\geq 7\%$ decline in total hip BMD was 0.4% among TAF recipients, and 2.0% among TDF recipients ($p = 0.005$).

Femoral neck BMD changes in studies 108/110 were generally similar to total hip BMD incidence of $\geq 7\%$ decline in total hip BMD was 3.2% among TAF recipients, and 5.7% among TDF recipients.

Fracture events were reported for 6/866 subjects (0.7%) in the TAF group and 1/432 subjects (0.2%) in the TDF group. All of the fractures were determined not to be related to changes in BMD.

The Applicant proposed to not include a WARNING for bone loss and mineralization defects as currently included in the Viread and Genvoya labels. Nearly all reported cases of TDF-related osteomalacia in HIV patients have been associated with renal tubule toxicity, and according to the DBRUP consultant, 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). Data from HIV clinical trials and observational cohorts have generally failed to demonstrate that the changes in BMD are of such sufficient magnitude to justify the continued inclusion of a WARNING in labeling; changes in BMD will be described in section 6.

- **Amylase Elevations/Pancreatitis**

It was noted during the review that approximately 2% of subjects in both treatment groups reported >Grade 3 elevations in amylase levels. Most elevations were isolated or infrequent, were not associated with increases in lipase levels, were asymptomatic, and did not result in changes in study drug administration. However, one TAF subject did experience recurrence of amylase and lipase increases with diarrhea upon re-administration of TAF (positive rechallenge). A FAERS search of TAF-containing products identified a single case of pancreatitis that occurred shortly after a switch from a TDF-containing regimen to Genvoya. The labeling, therefore, will contain the frequency of >Grade 3 amylase levels, describe the rechallenge case, and the Division will recommend post-marketing follow-up for additional events.

- **Lipid Abnormalities**

Treatment with TAF has been shown to be associated with statistically significant increases in serum lipid parameters, including HDL, LDL and Triglyceride levels; this finding was initially observed in the Genvoya studies. The changes in lipid parameters in the current trials were again greater among subjects treated with TAF, but did not appear to be associated with an increase in risk of cardiovascular morbidity or mortality.

Table 5 Lipid Values, Mean Change from Baseline

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)
Triglycerides (N)	773	394
Mean	11	-10
Median	6	-7
Q1, Q3	(-13,26)	(-27,10)

The trials are ongoing and this risk will need to be reassessed once longer duration data becomes available. Throughout the first 48 weeks of treatment, 2% of subjects in both treatment groups initiated a new lipid-modifying agent (fish-oil, statin or fibrate). In summary, the overall clinical relevance of the findings of increases in lipid parameters associated with TAF is not fully established; however, it is reasonable to include the above data in labeling.

- **Aminotransferase Elevations**

Aminotransferase elevations may occur post treatment initiation and may indicate immune mediated hepatitis associated with HBeAg loss or drug-induced liver injury (DILI).

Approximately 8% of study subjects in both treatment groups experienced at least one Grade 3/4 ALT elevation during the treatment period; most were isolated events. Of these, ~1% met Hy's law criteria for hepatotoxicity; however, based on a review of cases, none were considered overt DILI.

Overall <1% of TAF and TDF treated subjects experienced a hepatic flare, which was defined as a post baseline ALT >2 x baseline and 10 x ULN. Hepatic flares were not associated with a rise in bilirubin levels and resolved within a few weeks of continued treatment. Of note, two subjects treated with TAF were likely prematurely discontinued due to a hepatic flare; neither manifested evidence of hepatotoxicity. Also, flares did not occur more frequently in cirrhotic compared to non-cirrhotic subjects, and no subject with a flare in Study 0110 lost HBeAg.

- **Ocular Adverse Reactions**

Posterior uveitis was observed in a dog study. The Applicant instituted increased screening for eye disorders and a fundoscopic sub study. Overall, eye-related adverse events were infrequently reported and only slightly more often in subjects treated with TAF, 2% and 1%, respectively. There was one SAE of retinal detachment in a TAF recipient and one of uveitis in a TDF subject; neither were determined to be related to study drug and both subjects remained on their assigned treatment. The fundoscopic sub study enrolled a small number of participants and failed to identify any clinically-relevant drug-related ocular toxicities. A consult from the Division of Transplant and Ophthalmologic Products concurred that there were no drug-related events suggestive of uveitis. Overall, the numbers of events were too small to support a definitive conclusion; however, continued vigilance is recommended.

Laboratory abnormalities

Routine clinical laboratory monitoring was conducted in all the clinical trials. In the combined studies, comparable proportions of subjects had at least one Grade 3 or 4 laboratory abnormality: 30% treated with TAF and 27% treated with TDF. Overall there were no clinically relevant differences between treatments.

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.

Elevated creatine kinase was reported in 3% of subjects in both treatment groups, and was not associated with clinical symptoms of rhabdomyolysis. Elevated hepatic transaminases and amylase elevations are discussed above as are changes in lipid parameters.

9. Advisory Committee Meeting

This application was not presented before an advisory committee because TAF is not a first-in-class drug, efficacy was robust and comparable to currently approved treatment across multiple trials, and safety/tolerability issues are readily monitored for and manageable.

10. Pediatrics

There are no clinical data available to support a recommendation for administration of TAF to patients <18 years of age. (b) (4)

The Applicant submitted the required initial Pediatric Study Plan (iPSP) prior to the NDA submission. DAVP and the Pediatric Review Committee found the

iPSP to be satisfactory with DAVPs recommendations. The Applicant will be issued a PMR to evaluate TAF in pediatric subjects (b) (4) years and above.

11. Other Relevant Regulatory Issues

Four clinical sites were selected for inspection by the Office of Scientific Investigations (OSI). The sites (2 in Hong Kong, 1 in Taiwan and 1 in Canada) were selected because each had relatively high enrollment in the two trials. OSI determined that all sites complied with GMP processes and found no serious deviations that would affect the reliability or validity of the data.

12. Labeling

The proposed labeling underwent extensive revisions with input from the Labeling Development Team (LDT).

- INDICATIONS AND USAGE section:
 - The Applicant's proposed indication reads: Vemlidy is indicated for treatment of chronic hepatitis B virus infection in adults. The studies reviewed in this NDA enrolled only subjects with "compensated" hepatic function, defined as. As such there are no data on the safety or efficacy of TAF in subjects with decompensated liver disease. Thus the term "compensated" will be added to the Indication statement.
- DOSAGE AND ADMINISTRATION section:
 - The data contained in this NDA submission support the proposed 25 mg dose of TAF for treatment of CHB. During the clinical trials, the Applicant recommended that TAF be administered (b) (4) with (b) (4) food. The Clinical Pharmacology review concluded (b) (4); that TAF should be administered with food in order to maintain exposures expected to control the virus.
 - Dosing in patients with a creatinine clearance <15 mL/min will not be recommended (b) (4) (b) (4)
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
 - Retention of the BOXED WARNING related to the potential for lactic acidosis and risk of exacerbation of CHB upon discontinuation of TAF are warranted as these are risks associated with all nucleoside analogues approved for CHB.
 - Retention of the WARNINGS related to the potential for renal toxicity will be retained as the studies were too small, of too short a duration, and conducted in subjects with normal renal function to assess potential risk.
 - The WARNING for changes in BMD will be deleted and the relevant information moved to Section 6 as there are no sufficient long-term data from trials of other TAF-containing regimens or observational cohort studies demonstrating

that the changes in BMD observed in clinical trials are not associated with serious orthopedic-related negative outcomes.

- CLINICAL STUDIES section:
 - Both studies are adequate and well controlled. The results will be displayed in a manner that characterizes the outcomes in the overall population and various subgroups, such as those with high baseline viral load, cirrhosis, and prior nucleoside treatment experience. In addition, response by important non-virologic endpoints, such as ALT and hepatitis B serologies, will be included. Presentation of the efficacy results in this manner should preclude any misleading promotion that TAF represents a significant improvement in outcomes over Viread.

Other Labeling

- The proposed proprietary name, VEMLIDY, was reviewed by DAVP, OPDP, and DMEPA, and found to be non-promotional.
- Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use) are under review by OPDP and DRISK.
- The Container Label was reviewed by OPQ and determined to be adequate. The Applicant did not provide a carton label for review.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS are required for this application.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PREA

- Conduct a pediatric study in HBV infected (b) (4) 12 to less than 18 years to assess the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide (b) (4) of age (b) (4) (b) (4) followed by a rollover to a long-term, open-label, extension.
- Conduct a pediatric study in HBV infected (b) (4) 2 to less than 12 years to assess the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide (b) (4) of age (b) (4) (b) (4) followed by a rollover to a long-term, open-label, extension.

Clinical Virology

- 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.

Clinical

- Provide longer duration data from Studies 108 and 110.

14. Recommended Comments to the Applicant

There are no comments to be conveyed to the Applicant.

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/s/

RUSSELL D FLEISCHER
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