sNDA 208464/S.14: Tenofovir alafenamide (VEMLIDY®)
Clinical Review and Cross Discipline Team Leader Summary Review

Date	October 10, 2022
From	Jency Daniel, MD Medical Officer Division of Antivirals (DAV)
Through	Samer El-Kamary, MD, MPH Acting Team Leader
Subject	Clinical Review

Supplemental NDA #	208464 / Supplement 14
Applicant	Gilead Sciences, Inc.
Date of Submission	April 19, 2022
PDUFA Goal Date	October 19, 2022
Proprietary Name/ Established (USAN) names	VEMLIDY® / tenofovir alafenamide (TAF)
Approved dosage forms / Strength	VEMLIDY®: TAF 25 mg oral tablets approved in adults with compensated liver disease
Proposed dosage form / Strength	TAF 25 mg oral tablets for pediatric patients (b) (4)
Proposed indication(s)	Indicated for the treatment of chronic Hepatitis B virus (HBV) infection in (b) (4) adolescents
Recommendation on Regulatory Action	(b) (4) Supplement 14: 12 to < 18 years: Approval (b) (4)

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1. Benefit-Risk Integrated Assessment

Gilead Sciences, Inc. requests the approval of VEMLIDY® (tenofovir alafenamide, TAF) for the treatment of chronic Hepatitis B (CHB) (b) (4) TAF is a prodrug of tenofovir (TFV), a nucleotide analogue that interferes with viral replication. Tenofovir disoproxil fumarate (TDF), is an older product that is also a prodrug of TFV. Both have been approved for treatment of CHB in adults. VIREAD® is also approved for the treatment of CHB in children 2 years of age or older, and weighing at least 10kg. The major difference between TDF and TAF relates to the intracellular cellular uptake in target cells. TDF is not readily absorbed into target cells; it enters target cells after conversion to TFV in plasma/blood. TAF is more readily absorbed in target cells, leading to higher concentration of the active agent TFV-diphosphate. Both TAF and TDF, each in combination with other antiretroviral drugs, are also approved for the treatment of HIV infection in adults and children.

This Clinical Review summarizes the key Week 24 clinical safety and efficacy results from a pivotal pediatric trial evaluating the use of TAF for the treatment of CHB: Study GS-US-320-1092, '*A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B (CHB) Virus Infection',* which is an ongoing study conducted by Gilead Sciences, hereafter referred to as Trial 1092.

Efficacy

The Week 24 efficacy data from Cohort 1 (pediatric subjects 12 to <18 years of age) support the approval of VEMLIDY® for the treatment of CHB in children 12 to < 18 years of age (for the purpose of this review, this cohort will also be referred to as 'adolescents'). Specifically, at Week 24, the proportion of adolescents meeting the primary efficacy endpoint of viral suppression (defined as HBV DNA <20 IU/mL) was 21.3% for the VEMLIDY® treatment group, compared to 0% for the placebo treatment group (treatment difference and 95% CI: 21.3% (6.3%, 36.2; *p=0.0199*)). In contrast, for Cohort 2, Group 1 (participants aged 6 to <12 years old and weighing at least 25 kg), the proportion of subjects who achieved the primary efficacy endpoint in the VEMLIDY® and placebo treatment groups were 8.3% and 0%, respectively (treatment difference and 95% CI: 8.3% (-19.8, 36.5%)). (b) (4)

- Supplement 14: corresponding to the adolescent cohort (Cohort 1);

(b) (4)

Supplement 14 will be recommended for approval, (b) (4) The primary focus of this review is to discuss the results from the adolescent age group (Cohort 1) supporting the indication. Where appropriate, the results of Cohort 2, Group 1 (6 to < 12 years) will also be discussed.

There are several potential reasons for the apparent difference in response to treatment between Cohort 1 and 2. These include, but are not limited to, differences in baseline disease characteristics (HBV viral load, HBV genotype) and adherence to medication/pill tolerability. Because the baseline HBV viral load was higher in Cohort 2, a larger proportion of participants from this age group are expected to achieve viral suppression after a longer duration of therapy (e.g., 48 or 72 weeks of treatment). (b) (4)

(b) (4)

Safety
TAF has been previously studied in pediatric patients with HIV infection at the same (or similar) dose. Therefore, the safety profile of TAF has been previously well characterized in children weighing at least 25kg (~6 years of age). While the safety of TAF is being evaluated in this new patient population (pediatric subjects with CHB), no new drug-related safety signals were anticipated in this population, compared to adults or children with HIV, or adults with HBV. The most serious adverse reactions associated with VEMLIDY® (i.e., Warning language) include new or worsening renal impairment, lactic acidosis or severe hepatomegaly with steatosis, and severe exacerbation of hepatitis B after discontinuation of therapy.

At Week 24, no subject experienced lactic acidosis, hepatotoxicity, or severe exacerbation of hepatitis B after discontinuation of therapy. No renal toxicity was observed in this study, as no patient demonstrated a significant decline in glomerular function or renal tubule injury. Further, no remarkable changes in spine or whole-body bone mineral density (BMD) were observed for either cohort.

No deaths or AEs leading to premature study discontinuation occurred during the 24-week period. There were no drug interruptions due to AEs reported among adolescents during the 24-week period. There were no notable adverse treatment effects on Tanner stage, bone age, height, weight, BMI percentiles or vital signs. Review of the Week 24 safety data did not reveal any new or unexpected toxicities. The most commonly reported adverse reactions were headache, Vitamin D decreased, and upper respiratory tract infection. Three participants in Cohort 1 experienced an SAE during the double-blind treatment phase (1 in the TAF group and 2 in the placebo group). The TAF group participant had Grade 2 scarlet fever which was considered unrelated to the study drug.

Conclusion: benefit and risks assessment
In conclusion, based on the Week 24 data from this clinical trial, the benefit of TAF for the treatment of CHB in adolescents outweighs the risks, supporting the approval of VEMLIDY® for the treatment of CHB infection in children 12 to <18 years of age. (b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic hepatitis B (CHB) infection remains a significant global health cause of chronic liver disease, cirrhosis, hepatocellular carcinoma and death. • HBV is transmissible through perinatal, percutaneous, and sexual exposures, and most pediatric HBV infections in the US are the result of vertical transmission. • Up to 95% of perinatally infected children are expected to develop CHB. • Children with active CHB inflammation are at a high risk of liver fibrosis and cirrhosis, and given their early infection, the likelihood of developing these	Chronic HBV infection remains a major cause of morbidity and mortality worldwide. It is particularly serious when acquired in childhood, given the likelihood of developing serious or fatal complications by early adulthood. This can result in a debilitating disease at an individual's prime productive years, with significant limitations in professional and personal activities, disability,

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>complications by early adulthood is very high.
• While universal HBV vaccination as a preventive measure is safe, affordable, and highly effective, it is only useful if given prior to infection.</td><td>reduced healthy life expectancy, and potential years of life lost.</td></tr>
<tr><td>Current Treatment Options</td><td>There are several approved drugs for HBV infection; each of these treatments have advantages and limitations:
First line:
• Tenofovir disoproxil fumarate (TDF) is approved for children ≥ 2 years of age weighing ≥10 kg; it has high efficacy but causes a slower gain in bone mineral density over time and is associated with nephrotoxicity.

Secondary options:
<table>
<tr><th>Drug name</th><th>Approved ages</th><th>Advantages</th><th>Limitations</th></tr>
<tr><td>Interferon (IFN) alfa-2b</td><td>Children ≥ 1 year</td><td rowspan="2">Finite duration of therapy</td><td rowspan="2">• Poor tolerability and safety profile
• Only curative in a small fraction</td></tr>
<tr><td>Pegylated IFN alfa-2a</td><td>≥ 3 years</td></tr>
<tr><td>Lamivudine</td><td>≥ 2 years</td><td></td><td>• High rates of viral resistance</td></tr>
<tr><td>Entecavir</td><td>>2 years</td><td>Low rate of drug resistance</td><td>• Higher rate of resistance if used after lamivudine
• Efficacy only ~40-49% in all ages</td></tr>
<tr><td>Adefovir</td><td>≥ 12 years</td><td></td><td>• Weak antiviral activity
• Renal toxicity</td></tr>
<tr><td>Telbivudine</td><td>≥ 16 years of age</td><td></td><td>• Not approved for younger ages</td></tr>
</table></td><td>There are multiple treatment options for children infected with CHB. However, only two other drugs (entecavir and TDF) are available as oral medications. Entecavir has only moderate efficacy for children 2 to <12 years old. TDF has high efficacy for the same age group, but there are concerns about nephrotoxicity and bone-related toxicity (of particular concern in skeletally immature pediatric patients).

The availability of another efficacious oral therapy with a more favorable safety profile is highly desirable.</td></tr>
<tr><td>Benefit</td><td>• To support an efficacy claim for the use of TAF (VEMLIDY®) (b) (4) , the Applicant submitted Week 24 efficacy and safety results from a single, Phase 2, randomized, double-blind, placebo-controlled trial.
• In this study, 88 HbeAg positive (99%) and negative (1%) subjects aged 6 years to less than 18 years of age with chronic HBV infection were treated once daily</td><td>TAF was efficacious in suppressing HBV in children 6 to <18 years old compared to placebo by Week 24 of treatment. However, the efficacy was substantially lower in the younger age cohort (8%) compared to the older one (21%). The viral suppression in both cohorts led to a higher</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
for 24 weeks with either VEMLIDY® 25-mg adult strength oral tablets (N=59) or placebo (N=29):

Cohort 1: adolescents aged 12 to <18 years weighing >35 kg.
Cohort 2, Group 1: children aged 6 to <12 years weighing >25 kg.

The trial demonstrated that, for the overall population, a significantly greater proportion of subjects in the TAF group achieved the primary endpoint of HBV DNA <20 IU/mL at Week 24 compared with the placebo group. However, when efficacy was assessed based on age group, significant benefit was only demonstrated for the adolescent age group:

<table>
<tr><th rowspan="2">HBV DNA <20 IU/mL at Week 24</th><th colspan="2">Cohort 1</th><th colspan="2">Cohort 2 Group 1</th><th colspan="2">Total</th></tr>
<tr><td>TAF 25mg (N=47)</td><td>Placebo (N=23)</td><td>TAF 25mg (N=12)</td><td>Placebo (N=6)</td><td>TAF 25mg (N=59)</td><td>Placebo (N=29)</td></tr>
<tr><td>Response rate</td><td>10/47 (21.3%)</td><td>0/23 (0%)</td><td>1/12 (8.3%)</td><td>0/6 (0%)</td><td>11/59 (18.6%)</td><td>0/29 (0%)</td></tr>
<tr><td>95% CI for response rate</td><td>(10.7,35.7)</td><td>(0, 14.8)</td><td>(0.2, 38.5)</td><td>(0, 45.9)</td><td>(9.7, 30.9)</td><td>(0, 11.9)</td></tr>
<tr><td>Difference</td><td colspan="2">21.3%</td><td colspan="2">8.3%</td><td colspan="2">18.6%</td></tr>
<tr><td>95% CI for difference</td><td colspan="2">(6.3, 36.2)</td><td colspan="2">(-19.8, 36.5)</td><td colspan="2">(5.4, 31.6)</td></tr>
<tr><td>P-value</td><td colspan="2">0.0199</td><td colspan="2">.</td><td colspan="2">0.0137</td></tr>
</table>
HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
P values were based on a 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.
95% CIs were calculated using the Clopper-Pearson method.
</td><td>
proportion of subjects with ALT normalization, which is reflective of reduced hepatic inflammation.

The results support that TAF is superior to placebo in achieving viral suppression at Week 24 for the adolescent age group.

As seen in longitudinal findings from adult studies, sustained suppression of HBV virus reduces subsequent liver inflammation and leads to fewer long-term health issues such as fibrosis, cirrhosis, liver failure and hepatocellular complications. It is reasonable to infer that long-term viral suppression in children 12 to <18 years old would also lead to fewer complications later in life.

For the younger age group, superiority to placebo was not demonstrated. While this conclusion should be interpreted with caution (due to small sample size and lack of power), the review team's conclusion remains that additional, longer-term data is needed to evaluate the treatment benefit of TAF for this age group (or younger).
</td></tr>
<tr><td>Risk and Risk Management</td><td>

At Week 24, the overall mean spine and whole-body bone mineral density (BMD) had increased in both the TAF and placebo groups; no statistically significant differences were noted between treatments groups. However, long-term effects in younger children with CHB are still unknown; TAF, as part of

</td><td>The frequency of treatment-related adverse events observed in this study were similar to those noted in adults. Key adverse reaction such as a decrease in BMD or renal toxicity were not observed in this</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	combination ARV treatment for HIV is approved for use in children. • Renal toxicity is a well-described complication of TDF. The USPI for TAF also summarizes the risk of renal toxicity with TAF therapy. In this trial, no significant differences in renal-related adverse events were observed in the TAF-treatment group, compared to the placebo-treatment group. • No deaths occurred in the study; the one serious adverse event reported in the TAF-treatment group (scarlet fever) was unrelated to study drug. • No AEs led to study drug discontinuation or treatment interruption among adolescents.	study. TAF demonstrated an overall favorable safety profile in this pediatric population with CHB. Safety concerns identified with use of TAF are adequately described in labeling.

2. Background

2.1 Introduction

The Applicant, Gilead Sciences Inc., seeks approval of VEMLIDY® (TAF, tenofovir alafenamide) for the treatment of chronic hepatitis B infection (HBV) in pediatric patients (b) (4) This supplemental new drug application (sNDA, S-14), submitted to the VEMLIDY® NDA 208464, contains Week 24 safety and efficacy data from an ongoing Phase 2 study in pediatric subjects with CHB.

Study GS-US-320-1092 (Trial 1092), the pivotal pediatric trial, is a 2:1 randomized, placebo-controlled trial in subject 6 to18 years of age with chronic HBV. Safety and efficacy of VEMLIDY® in any pediatric patients with CHB have not previously been established, as this is the first pediatric supplement for this NDA (sNDA). However, it should be noted that, TAF, in combination with other antiretroviral drugs, has been evaluated in HIV-infected children weighing at least 25kg.

(b) (4)

2.2 Analysis of Condition

Although universal hepatitis B virus (HBV) vaccination is recommended in the United States and other parts of the world to prevent hepatitis B infection, chronic HBV (CHB) infection remains a significant global health problem resulting in chronic liver disease, cirrhosis, hepatocellular carcinoma, and death {World Health Organization (WHO) 2015, Wright 2006}. An estimated 25,000 infants are born to mothers diagnosed with HBV each year in the United States, and approximately 1,000 mothers transmit HBV to their infants, with vertical transmission accounting for the majority of pediatric HBV infections in the U.S. Of those, up to 95% of patients with perinatal HBV infection are expected to develop chronic HBV infection {Health and Human Services (HHS) 2022}. Among pediatric patients in the United States with CHB, an estimated 5-10% spontaneously clear hepatitis B early antigen (HBeAg) each year. Upon HBeAg clearance, the infection usually becomes inactive, although a few will later reactivate. Because the spontaneous clearance rate is significant but somewhat variable, there is no consensus regarding optimal timing of treatment in younger pediatric patients {Terrault NA, 2018}. Although the proportion of children (6 to <18 years or older) in the United States with chronic HBV is relatively few, additional treatment options are still needed.

In general, as outlined in FDA Guidance for Industry, considering the dynamic relationship between viral replication and the host immune response, the natural history of CHB infection in adults and children may be different. Therefore, extrapolation of efficacy may not be possible, although it could be considered under certain conditions depending on the mechanism of action of the investigational drug(s) and the pediatric age group being evaluated. A placebo-controlled study was therefore requested to evaluate the efficacy of TAF for CHB treatment in pediatric subjects.

2.3 Available Pediatric Treatment Options

Approved products for the treatment of CHB in pediatric patients are summarized in Table 1. Most of the products have some significant limitations, including rapid development of resistance (lamivudine), weak antiviral activity and renal toxicity that limits dosing (adefovir), poor tolerability and safety profile (interferon alfa-2b; and pegylated interferon alfa-2a); telbivudine is not approved for use in children < 16

years old (telbivudine). TDF, while highly efficacious, is associated with renal and bone toxicities. Therefore, better treatment options are needed for this population.

Table 1. Drugs Approved for Chronic Hepatitis B Infection

Generic Name	Trade Name	Dose	Approved Ages
Interferon-alfa-2b	Intron A® (for injection)	3 million IU/m^2 three times a week, followed by 6 million IU/m^2 three times a week. Max dose 10 million IU three times a week	≥ 1 year of age
Pegylated interferon alfa-2a	Pegasys® (for injection)	180 micrograms/1.73 m^2 SQ once weekly	≥ 3 years of age
Lamivudine	Epivir® (tablet)	3 mg/kg once daily, maximum dose 100mg daily	≥ 2 years of age
Adefovir	Hepsera® (tablet)	10 mg once daily	≥ 12 years of age
Entecavir	Baraclude® (tablet)	0.5 mg once daily	≥ 2 years of age
Telbivudine	Tyzeka® (tablet)	600 mg once daily	≥ 16 years of age
Tenofovir disoproxil fumarate (TDF)	Viread® (tablet)	If ≥35 kg: 300 mg once daily If <35 kg: 8 mg/kg (150, 200, 250, or 300 mg tablet) once daily	≥ 2 years of age

2.4 Important Safety Issues With Consideration to Related Drugs

Currently approved NRTIs for CHB, including telbivudine, entecavir, lamivudine, and adefovir, have a boxed warning cautioning about the risk of lactic acidosis, severe hepatomegaly with steatosis, and severe acute exacerbations of HBV infection. Similarly, the product labeling for TAF also includes the boxed warning language. Additionally, TDF carries a boxed warning for nephrotoxicity (namely, acute renal failure and Fanconi syndrome) and bone toxicity (i.e., decreased in bone mineral density); the product labeling for TAF also contains similar language accordingly.

2.5 Product Information

VEMLIDY® is the brand name for tenofovir alafenamide (TAF), a prodrug that is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. It functions as a hepatitis B virus nucleoside analog reverse transcriptase inhibitor. TAF was originally developed as a nucleotide reverse transcriptase inhibitor for treatment of HIV-1 infection. It 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.

TAF is an oral prodrug of tenofovir (TFV). After absorption, TAF is slowly converted to TFV, which is metabolized intracellularly to the active metabolite, TFV diphosphate, a potent and selective inhibitor of both hepatitis B virus (HBV) polymerase and human immunodeficiency virus type-1 (HIV-1) reverse transcriptase. Tenofovir disoproxil fumarate (TDF) is another oral prodrug of tenofovir which is currently approved for the treatment of CHB in pediatric patients aged ≥2 years old weighing ≥10 kg. It is highly effective but associated with nephrotoxicity and bone-related toxicity, the latter of which is of particular concern in skeletally immature pediatric patients. In adult studies comparing TAF to TDF, TAF has

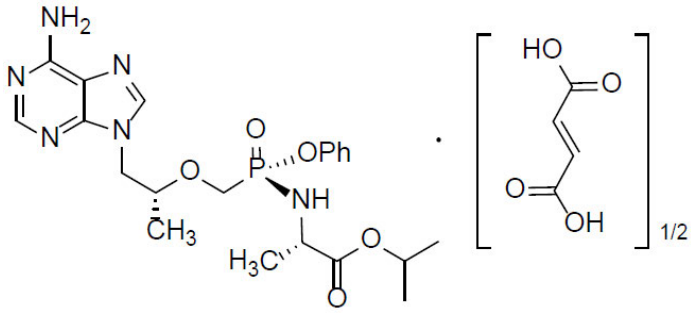
notable benefits: a longer plasma half-life and thus greater stability in plasma; higher intracellular levels of active phosphorylated metabolite in target infected cells; 90% lower circulating levels of tenofovir; and hence, a better safety profile (i.e., significantly higher rates of ALT normalization, smaller decreases in bone mineral density, and smaller changes in eGFR in participants).

Chemical name: L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1)

Molecular formula: $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$

Molecular weight: 534.50

Structural formula:



Each VEMLIDY ® 25-mg adult tablet contains 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

2.6 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant submitted IND 115561 for TAF for treatment of CHB on July 30, 2012. The IND opening study, GS-9883-US-120-0104 (Study 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.

On January 11, 2016, Gilead Sciences, Inc. submitted NDA 208464 for the use of TAF in the treatment of CHB infection in adults with compensated liver disease. The application was approved on October 7, 2016. In accordance with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), PREA PMRs were issued at the time of the original approval. Studies in children younger than 2 years of age were waived because a study would be impossible to conduct, considering the epidemiology and natural history of the disease in infants and young children. A Pediatric Written Request (PWR) was also issued to the Applicant. The PREA PMRs requesting study(ies) in children 2 years of age and older are:

> PMR 3130-1: Conduct the deferred pediatric study to assess the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide in HBV infected subjects 12 to less than 18 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity

PMR 3130-2: Conduct the deferred pediatric study to access the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide in HBV infected subjects 2 to less than 12 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity.

The protocol for Study GS-US-320-1092 (Trial 1092) "*A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection*" was submitted in March 2016 with an amendment in April 2016.

The current sNDA (208464, S-14), received on April 19, 2022, was submitted in response to fulfill PREA PMR 3130-1, and to partially address PMR 3130-2 and the PWR.

The original study protocol (submitted 29 March 2016) outlined a prospective, randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of tenofovir alafenamide (TAF) in adolescents with CHB virus infection. The original study protocol was amended 5 times.

Protocol Amendments
Key changes to the protocol for each amendment were as follows:

- **Amendment 1 (30 May 2016)**: The duration of the double-blind, placebo-controlled phase was shortened from 48 to 24 weeks, and the open-label extension phase was extended accordingly from 192 to 216 weeks to maintain the total 240-week duration of the study
- **Amendment 2 (13 October 2017)**: Key changes included the addition of a ClinicalTrials.gov Identifier (#NCT02932150); expansion of the number of study centers from 40 to 60; updates to the design and conduct of the intensive PK substudy to be optional for enrolled subjects; and clarification of the "evidence of hepatocellular carcinoma" Exclusion Criteria regarding the use of alpha-fetoprotein (AFP) to determine need for imaging studies.
- **Amendment 3 (30 October 2017)**: A minor revision was made to Eligibility Criteria regarding ability of participants to swallow oral tablets *whole.*
- **Amendment 4 (6 February 2018)**: The study was expanded to double the number of anticipated subjects (150, up from 75) and expanded eligibility to younger participants (ages 2 to <18 years old) divided into 2 age cohorts: adolescents aged 12 to <18 years old weighing at least 35 kg (Cohort 1, 75 participants), and children aged 2 to <12 years old (Cohort 2, 75 participants). For Cohort 1, the primary objective remained to evaluate safety, tolerability, and antiviral activity of TAF 25 mg once daily in adolescents, with an **option** to participate in an intensive PK substudy. Cohort 2 was divided into **Part A** (**required** intensive PK substudy plus dose confirmation study) and **Part B** (to evaluate safety, tolerability, and antiviral activity of TAF once daily versus placebo). Dose formulations were adjusted to account for the younger age group (e.g., TAF 15 mg tablets for 6 to <12-year-old participants who weigh <25 kg). The first 24 weeks are designed to be double-blind **and placebo-controlled** followed by an open-label extension phase of 216 weeks. An additional Exclusion Criterion was added to preclude participants with chronic liver disease of non-HBV etiology (e.g., hemochromatosis, alpha-1 antitrypsin deficiency, cholangitis). Testing for HIV, Hepatitis D, and Hepatitis C were added to the screening assessments. Treatment-free follow-up assessments were also added, and an additional safety endpoint was included for closer monitoring of nephrotoxicity (e.g., evaluation beta-2-microglobulin in both cohorts). Finally, PK statistical analyses were amended to determine whether the exposure of TAF in the younger age cohort achieved comparable TAF systemic exposures to that in adults based on integrated historical control Elvitegravir (E)/Cobicistat (C)/Emtricitabine (F)/TAF HIV studies (Phase 3 population PK data.

- **Amendment 5 (3 September 2021)**: Number of participants revised (at least 144 total: at least 69 adolescents in Cohort 1, and at least 75 children in Cohort 2). Study schema amended to divide Cohort 2 into 3 dose groups by age and weight (Table 2), with each dose group being subdivided into Part A (mandatory intensive PK sub-study to confirm dose) and Part B (into which remaining Cohort 2 subjects will be enrolled following dose confirmation). A 7.5-mg TAF dose was also included for the youngest age group (Cohort 2, Part A, Group 3) as outlined below.

Table 2. Protocol Amendment 5, to divide Cohort 2, Part A[a] into 3 Dose Groups by Age and Weight

Group	Age Range	Weight Range	TAF Dose	Number of Subjects
Group 1	6 to < 12 years	≥ 25 kg (≥ 55 lbs)	25 mg tablet	n = 6
Group 2	6 to < 12 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)	15 mg oral granules (2 × TAF 7.5 mg oral granules)	n = 9
Group 3	2 to < 6 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)	15 mg oral granules (2 × TAF 7.5 mg oral granules)	n = 12 at least 6 subjects weighing ≥ 10 to < 14 kg
		≥ 10 kg to < 14 kg (≥ 22 lbs to < 30 lbs)	7.5 mg oral granules	

[a] All subjects in Cohort 2, Part A will undergo a mandatory intensive PK evaluation at either the Week 4 visit (± 7 days), the Week 8 visit (± 7 days), or the Week 12 visit (± 7 days) to confirm the dose of TAF.

Source: Modified from Study Protocol GS-US-320-1092, Amendment 5, "Study Design" (p807)

2.7 Review Approach for Current Submission

This efficacy supplement was reviewed by a multidisciplinary team, including clinical, clinical pharmacology, virology and statistical team. As there were no new product quality information to review, no additional CMC-related reviews were conducted. Similarly, no new non-clinical data were submitted for review.

For additional details, please refer to the detailed reviews by Drs. Yifan Wang, Yang Zhao, and Jonathan Rawson for the statistical, clinical pharmacology and virology considerations, respectively. This clinical review considered all the conclusions from the relevant disciplines to determine benefit and risks of VEMLIDY® for the treatment of chronic HBV in pediatric patients.

(b) (4) , this review primarily focuses on the safety and efficacy outcome at Week 24 for adolescents which supports labeling. (b) (4)

3. Product Quality

There were no CMC or Manufacturing-related issues in this submission. The 25 mg oral tablets studied in this trial are approved for use in adults who have CHB with compensated liver disease and are commercially available.

4. Nonclinical Pharmacology/Toxicology

TAF is an FDA-approved drug. No additional nonclinical data were submitted.

5. Clinical Pharmacology

A brief description of the Clinical Pharmacology review is included here. Please refer to Dr. Yang Zhao's Clinical Pharmacology Review for full details.

The clinical pharmacology review of this sNDA supplement focused on the following aspects:

1. TAF and TFV exposures in children with CHB receiving the proposed Vemlidy® regimen was compared to the following adult patient groups:
    a. Adult patients with CHB receiving the same Vemlidy® (TAF) dose (as supportive evidence for efficacy)
    b. Adult patients with HIV-1 who received a fixed-dose combination of elvitegravir/cobicistat/emtricitabine/TAF (Genvoya®) (as supportive evidence for safety, and additional PK analysis)
2. Exposure-response analyses for safety and efficacy findings in CHB pediatric patients

1. <u>TAF and TFV exposure comparisons between pediatric patients with CHB pediatric patients, adults with CHB, and adults with HIV-1</u> receiving the proposed TAF dose were performed using both intensive and sparce PK data. Specifically, a noncompartmental analysis (NCA) approach was used with intensive PK data to compare TAF and TFV exposure between pediatric patients with CHB (receiving the proposed Vemlidy® dosing regimen, n=18) and adult patients with CHB (receiving the currently approved Vemlidy dosing regimen, n=8). A population PK (popPK) based approach was utilized to compare the posterior-predicted TAF and TFV exposure between pediatric patients with CHB (receiving the proposed Vemlidy® dosing regimen, n=59) and HIV-1 patients (receiving a fixed-dose combination of elvitegravir/cobicistat/emtricitabine/TAF (Genvoya®).

   TAF AUCtau estimates from intensive PK data in pediatric subjects with CHB were comparable (approximately 16% lower) to the historical data in adults with CHB. Compared to the historical adult data, TAF Cmax estimates were approximately 30% lower in Cohort 1 (12 to < 18 years), and approximately 44% higher in Cohort 2 Group 1 (6 to < 12 years. When comparing the popPK model-derived exposure metrics for the 59 pediatric subjects to the historical data from adults with HIV-1, the TAF exposures in Cohort 1 were comparable to the TAF exposures observed in adults; the TAF exposures in Cohort 2 Group 1 were numerically lower (~15% in terms of AUCtau) compared to the TAF exposures of the reference adult population.

   For TFV exposures discussion, please refer to the detailed clinical pharmacology review. Previous considerations on the utility of TFV exposure-efficacy analysis suggest that such analysis may be less relevant (compared to TAF-based analysis) because TFV concentration from administration of TAF are approximately 10%.

   Overall, the review team concluded that TAF exposures (AUCtau and Cmax) with the proposed dose of 25 mg QD in CHB pediatric patients 12 to 18 years of age are similar to exposures observed in adults with CHB receiving 25 mg QD.

2. <u>Exposure-response analyses for safety and efficacy findings in CHB pediatric patients</u>
   Based on the Week 24 data, no correlations were identified between TAF exposures, and efficacy or safety outcomes in the 59 pediatric subjects with CHB.

   The Applicant conducted exposure-response (E-R) analyses for efficacy endpoints (including categorical HBV DNA outcome (<20 IU/mL) and normalized ALT at Week 24) and safety

endpoints (including percent change from baseline in spine bone mineral density (BMD), percent change from baseline in whole-body BMD, and maximum increase from baseline in serum creatinine).

Based on the PopPK derived exposure quartiles, there is a lack of E-R efficacy or safety relationship. The Clinical Pharmacology review team also conducted exploratory E-R analysis (in terms of HBV DNA reduction from baseline against exposure metrics from intensive PK subjects). There were no correlations identified between TAF exposures (AUCtau and Cmax) and HBV DNA reduction from baseline to Week 24.

(b) (4)

6. Clinical Virology

There was no evidence that tenofovir resistance had emerged during the study period. No treatment-emergent substitutions (TES) known to be associated with TAF, TDF, or tenofovir resistance were identified in sequenced samples from study GS-US-320-1092 at Week 24. Samples from 4 subjects with virologic breakthrough or blips did not contain TES in rt. Although 8 TES were identified in Week 24 samples from other subjects, they are considered unlikely to be associated with TAF resistance. Please refer to Dr. Jonathan Rawson's Clinical Virology Review for full details.

7. Clinical/Statistical- Efficacy

7.1 Study design and protocol summary

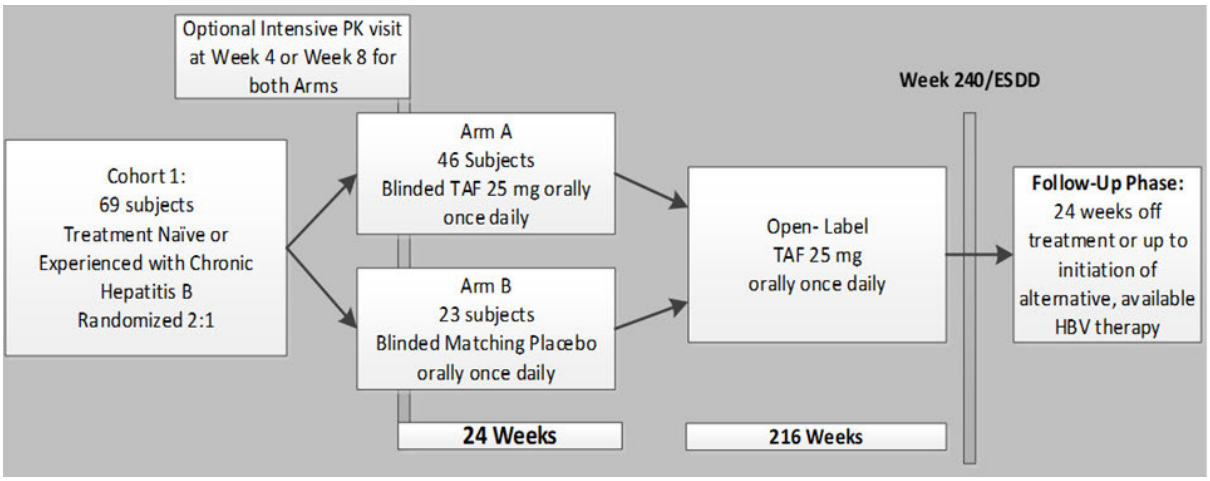
Study GS-US-320-1092 "*A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection*", is a randomized (2:1), placebo-controlled trial to evaluate TAF vs placebo for the treatment of CHB.

The current submission of the supplemental NDA (Supplement 14 focused on the results of an interim analysis for participants aged 12 to < 18 years weighing ≥ 35 kg (Cohort 1), and participants aged 6 to < 12 years weighing ≥ 25 kg (Cohort 2 Group 1), who are receiving the adult dose of TAF 25 mg or the placebo once daily. The interim analysis was performed when all participants in Cohort 1 and Cohort 2 Group 1 had completed their Week 24 visit or prematurely discontinued from the study. Following double-blind treatment for 24 weeks, all participants are eligible to roll over to receive open-label TAF for a total duration of study treatment of 240 weeks.

Cohort 1:

At least 69 male and female adolescent participants (12 to < 18 years of age) were planned to be enrolled and randomized to receive either the blinded TAF 25 mg tablet or placebo tablet once daily through Week 24. Randomization was stratified by age (12 to < 15 and 15 to < 18 years of age). Adolescent participants who were enrolled were eligible to take part in an optional intensive PK substudy that was performed at either the Week 4 visit (± 7 days) or the Week 8 visit (± 7 days). For participants who consented to participate in the optional intensive PK substudy, blood samples were collected at 0 (predose, ≤ 30 minutes prior to dosing), 15, and 30 minutes, and 1, 1.5, 2, 3, 4, 5, and 8 hours postdose.

Figure 1: Study Schema (Cohort 1: 12 to < 18 years of age, ≥ 35 kg body weight) – Study GS-US-320-1092

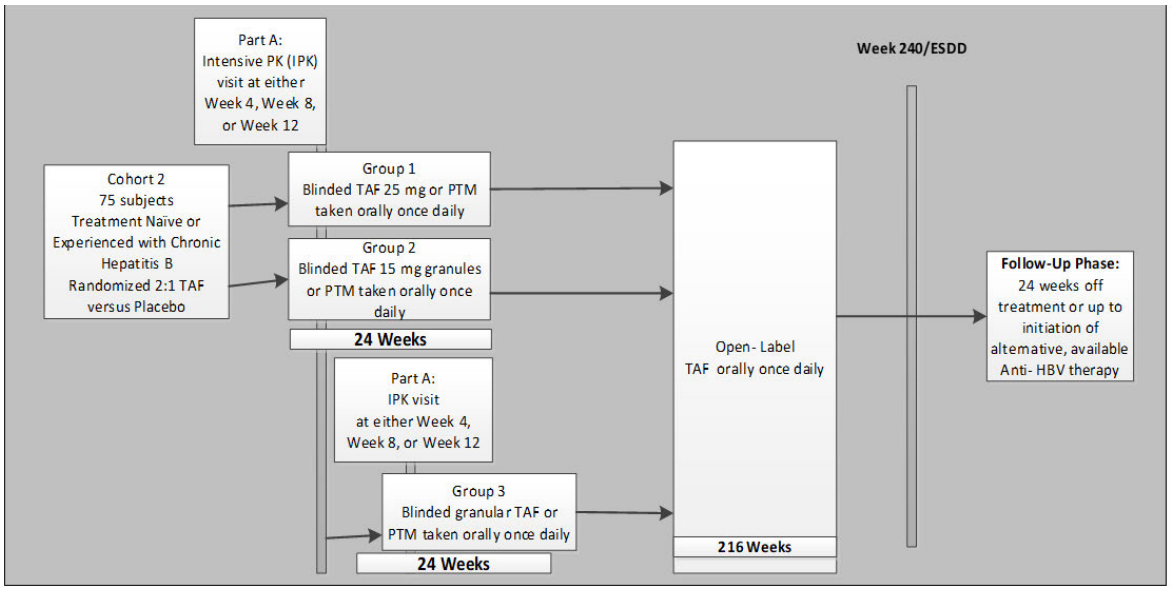


Source: Applicant's Clinical Study Report Figure 1, Page 34/642

Cohort 2:

At least 75 children were planned to be enrolled in Cohort 2 of the study. Cohort 2 is divided into three dose groups (Groups 1, 2, and 3) by age and weight, with enrollment into each dose group divided into two parts without overlapping: Part A (mandatory intensive PK to confirm the dose) and Part B. Intensive PK data are to be collected from participants in Part A to confirm the dose of TAF in each dose group and the remaining participants are planned to be enrolled into Part B once dose confirmation was achieved. Part A is planned with a minimum of 27 enrolled participants (a minimum of 6, 9, and 12 participants in Groups 1, 2, and 3, respectively) and Part B is planned to have at least 48 enrolled participants across all 3 groups.

Figure 2: Study Schema (Cohort 2: 2 to < 12 years of age) – Study GS-US-320-1092



Source: Applicant's Clinical Study Report Figure 2, Page 35/642

- **Cohort 2 Part A**: Enrollment and dosing for Cohort 2 Part A was planned as follows.

Table 3. Enrollment and Dosing for Cohort 2 Part A (Intensive PK Evaluation for Confirming the Dose) – Study GS-US-320-1092

Group	Age Range	Weight Range	TAF Dose	Number of Participants
Group 1	6 to < 12 years	≥ 25 kg (≥ 55 lbs)	25 mg tablet	n = 6
Group 2[b]	6 to < 12 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)	15 mg oral granules (2 × TAF 7.5 mg oral granules)	n = 9
Group 3[b]	2 to < 6 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)	15 mg oral granules (2 × TAF 7.5 mg oral granules)	n = 12 at least 6 participants weighing ≥ 10 to < 14 kg
		≥ 10 kg to < 14 kg (≥ 22 lbs to < 30 lbs)	7.5 mg oral granules	

TAF = tenofovir alafenamide; PK = pharmacokinetic(s)
a All participants in Cohort 2 Part A were to undergo a mandatory intensive PK evaluation at either Week 4 visit (± 7 days), Week 8 visit (± 7 days), or Week 12 visit (± 7 days) to confirm the dose of TAF. Cohort 2 Part B is identical to Cohort 2 Part A in design, without an intensive PK requirement.
b Results from Cohort 2 Groups 2 and 3 will be reported separately.

Source: Applicant's Clinical Study Report Table 2, Page 35/642

- **Cohort 2, Part B**: Cohort 2, Part B is identical to Cohort 2, Part A in design, without the inclusion of an intensive PK requirement. Screening was planned to be initiated for Cohort 2, Part B (Groups 1 and 2) following confirmation of the TAF dose in Part A for each group, respectively. Screening will be initiated for Cohort 2, Part B (Group 3) following confirmation of the clinical safety and PK results of the TAF dose from Cohort 2, Part A (Groups 1, 2, and 3). Participants who participated in Cohort 2 Part A were not planned to be rolled over into Cohort 2, Part B. Approximately 48 additional participants were planned for enrollment in Part B across all 3 groups to evaluate the safety, tolerability, and antiviral activity of TAF in a total of 75 participants in Parts A and B combined.

A brief outline of Study GS-US-320-1092 is presented in Table 4.

Table 4. Summary of Trials Assessed in the Statistical Review – Study GS-US-320-1092

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
GS-US-320-1092	Randomized (2:1), double-blind, placebo-controlled, multicenter	TAF 25mg / FAS: Cohort 1 N=47 Cohort 2 Group 1 N=12 Total N=59 Placebo / FAS: Cohort 1 N=23 Cohort 2 Group 1 N=6 Total N=29	Primary endpoint: Proportion of subjects with HBV DNA <20 IU/mL at Week 24 Analysis: The superiority of TAF over placebo for the proportion of HBV DNA < 20 IU/mL was tested using stratified Cochran-Mantel-Haenszel (CMH) test adjusted for age at baseline.	Overall, the proportion of participants with HBV DNA <20 IU/mL was 18.6% (11 of 59 participants) with TAF versus 0.0% (0 of 29 participants) with placebo (*p*-value = 0.0137) at Week 24. Gilead concluded that the antiviral response with TAF treatment is superior to placebo.

	Total N=88

FAS: Full Analysis Set, which included all participants who were randomized into the study and received at least one dose of study drug.
Source: Reviewer's Table using results from the Clinical Study Report

Primary Objectives:
Primary objectives for this study by subject cohort are as follows:

Cohort 1 (adolescents 12 to < 18 years, ≥ 35 kg):

- To evaluate the safety, tolerability and antiviral activity (HBV DNA < 20 IU/mL) of TAF 25 mg once daily versus placebo at Week 24 in adolescent subjects with CHB

Cohort 2 (children 2 to < 12 years of age):

Part A:

- To evaluate the steady-state PK of TAF and TFV, and confirm the dose of TAF given once daily in children with CHB

Part B:

- To evaluate the safety, efficacy, and tolerability of TAF given once daily at Week 24 in children with CHB
- To evaluate the antiviral activity (HBV DNA < 20 IU/mL) of TAF given once daily versus placebo at Week 24 in children with CHB

Secondary objectives:

- To evaluate the open-label safety and tolerability of TAF given once daily at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the antiviral activity (HBV DNA < 20 IU/mL) of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the serologic response (loss of HBeAg and seroconversion to anti-HBe, and loss of HBsAg and seroconversion to anti-HBs) of TAF versus placebo at Week 24, and of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the biochemical response (ALT normalization) of TAF versus placebo at Week 24, and of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the change in fibrosis as assessed by FibroTest of TAF versus placebo at Week 24, and of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the palatability and acceptability of TAF at baseline and at Weeks 4, 24, and 36 in adolescents and children with CHB
- To evaluate the incidence of drug resistance mutations associated with TAF at Weeks 24, 48, 96, and 240 in adolescents and children with CHB
- To evaluate the steady-state PK of TAF and TFV following administration of TAF 25 mg once daily in adolescents with CHB

Primary Endpoint
The primary safety endpoint for all cohorts is:

- Incidence of treatment-emergent SAEs and all treatment-emergent AEs in subjects treated with TAF or placebo at Week 24

The primary efficacy endpoint for all cohorts is:

- The percentage of subjects with plasma HBV DNA < 20 IU/mL at Week 24

Secondary Endpoints
The secondary safety endpoints are:

- Graded laboratory abnormalities, Tanner Stage assessments, selected bone and renal safety parameters, including percentage change from baseline in BMD of whole body (minus head) and lumbar spine performed by DXA scan, and change in sCr, and eGFR by the Schwartz formula to evaluate the safety and tolerability of the treatment regimen at Weeks 24, 48, 96, and 240
- Incidence of treatment-emergent SAEs and all treatment-emergent AEs in subjects treated with TAF or placebo for 24 weeks followed by open-label TAF at Weeks 48, 96, and 240
- Evaluation of sCr, glucose, phosphate, urine RBP to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio at Weeks 4, 8, 12, 24, and 48

The secondary efficacy endpoints are:

- The percentage of subjects with plasma HBV DNA < 20 IU/mL at Weeks 48, 96, and 240
- The proportion of subjects with plasma HBV DNA < 20 IU/mL (target not detected) at Weeks 24, 48, 96, and 240
- The percentage of subjects with ALT normalization at Weeks 24, 48, 96, and 240
- The percentage of subjects achieving the composite endpoint of both ALT normalization and HBV DNA < 20 IU/mL at Weeks 24, 48, 96 and 240
- The change from baseline in fibrosis as assessed by FibroTest at Weeks 24, 48, 96, and 240
- The percentage of subjects with HBeAg loss and seroconversion to anti-HBe at Weeks 24, 48, 96, and 240 (HBeAg-positive subjects only)
- The percentage of subjects achieving the composite endpoint of both HBeAg seroconversion and HBV DNA < 20 IU/mL at Weeks 24, 48, 96, and 240 (HBeAg-positive subjects only)
- The percentage of subjects achieving the composite endpoints of ALT normalization, HBeAg seroconversion, and HBV DNA < 20 IU/mL at Weeks 24, 48, 96, and 240 (HBeAg-positive subjects only)
- The percentage of subjects with HBsAg loss and seroconversion to anti-HBs at Weeks 24, 48, 96, and 240
- The change from baseline in qHBsAg log10 IU/mL at Weeks 24, 48, 96, and 240
- Incidence of resistance mutations at Weeks 24, 48, 96, and 240
- Assessment of acceptability/palatability of study drug at baseline, and Weeks 4, 24, and 36 The primary PK endpoint for Cohort 2 is:
- The PK parameter AUCtau for TAF

The secondary PK endpoints for Cohorts 1 and 2 are:

- PK parameters of AUClast, Cmax, Clast, Tmax, Tlast, λz, CL/F, Vz/F, and t1/2 for TAF and TFV, and AUC_{tau}, and C_{tau} for TFV

Enrollment eligibility:
Inclusion Criteria
Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Males and non-pregnant, non-lactating females
2. Age at screening: 2 to < 18 years old
3. Weight at screening as follows

Cohort (Group)	Age Range	Weight

Cohort 1	12 years to < 18 years	≥ 35 kg (≥ 77 lbs)
Cohort 2 (Group 1)	6 years to < 12 years	≥ 25 kg (≥ 55 lbs)
Cohort 2 (Group 2)	6 years to < 12 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)
Cohort 2 (Group 3)	2 years to < 6 years	≥ 10 kg to < 14 kg (≥ 22 lbs to < 30 lbs) or ≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)

4. Willing and able to provide written informed consent/assent (child and parent/legal guardian)
5. Documented evidence of CHB (eg, HBsAg-positive for ≥ 6 months)
6. HBeAg-positive, or HBeAg-negative, chronic HBV infection with all of the following:
   a. Screening HBV DNA ≥ 2 × 104 IU/mL
   b. Screening serum ALT > 45 U/L (> 1.5 × ULN: 30 U/L) and ≤ 10 × ULN (by central laboratory range)
7. Treatment-naive (defined as < 12 weeks of OAV treatment with any oral nucleos(t)ide analogue) **OR** treatment-experienced subjects (defined as subjects meeting all entry criteria [including HBV DNA and serum ALT criteria] and ≥ 12 weeks of OAV treatment with any oral nucleos(t)ide analogue) will be eligible for enrollment. All subjects taking OAV treatment must have discontinued oral nucleos(t)ide therapy ≥ 16 weeks prior to screening to avoid ALT flare if randomized to the placebo arm.
8. Any previous treatment with IFN (pegylated or non-pegylated) must have ended at least 24 weeks prior to the baseline visit.
9. Estimated CL_{cr} ≥ 80 mL/min/1.73m2 (using the Schwartz formula; = k × L/sCr)
   (k is a proportionality constant; L is height in centimeters; and sCr is serum creatinine [mg/dL])
10. Normal electrocardiogram (ECG) (or if abnormal, determined by the investigator not to be clinically significant)
11. Must be willing and able to comply with all study requirements

Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Pregnant females, females who are breastfeeding or who believe they may wish to become pregnant during the course of the study
2) Males and females of reproductive potential who are unwilling to use an "effective", protocol-specified method(s) of contraception during the study.
3) Coinfection with HCV, HIV, or hepatitis D virus (HDV)
4) Evidence of HCC (Note: if screening alpha fetoprotein [AFP] is ≤ 50 ng/mL no imaging study is needed; however, if the screening AFP is > 50 ng/mL an imaging study is required)
5) Any history of, or current evidence of, clinical hepatic decompensation (eg, ascites, encephalopathy or variceal hemorrhage)
6) Abnormal hematological and biochemical parameters, including:
   a) Hemoglobin < 10 g/dL
   b) Absolute neutrophil count < 1500/mm3
   c) Platelets ≤ 100,000/mm^3
   d) AST or ALT > 10 × ULN (by central laboratory range)
   e) Total bilirubin > 2.5 × ULN
   f) Albumin < 3.0 g/dL
   g) International normalized ratio (INR) > 1.5 × ULN (unless on stable anticoagulant regimen)
7) Chronic liver disease of non-HBV etiology (eg, hemochromatosis, alpha-1 antitrypsin deficiency, cholangitis)

8) Received solid organ or bone marrow transplant
9) Currently receiving therapy with immunomodulators (eg, corticosteroids), or immunosuppressants
10) Significant renal, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator
11) Malignancy within the 5 years prior to screening. Subjects under evaluation for possible malignancy are not eligible.
12) Known hypersensitivity to study drugs, metabolites, or formulation excipients
13) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
14) Subjects on prohibited concomitant medications (see Table 5-1). Subjects on prohibited medications, otherwise eligible, will need a washout period of at least 28 days prior to the baseline visit.
15) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.

An external multidisciplinary Data Monitoring Committee (DMC) reviewed the progress and safety of this study with interim reviews of safety data at approximately 24 weeks during the blinded phase of the study (i.e., until the last subject completes Week 24) and approximately annually thereafter until the last subject completes the open-label study drug, and provide recommendations to the Applicant regarding design, modification, or early termination of the study based on the nature, frequency, and severity of AEs associated with the study drug.

7.2 Results

A brief summary of the statistical review and assessment of efficacy is provided here. Please refer to Dr. Yifan Wang's statistical review for full details.

Demographics

Demographic and baseline characteristics were generally similar between the two treatment groups. The majority of participants were male (58%) and Asian (65.9%).

Table 5. Demographic Characteristics (Safety Analysis Set) – Study GS-US-320-1092

	Cohort 1		Cohort 2 Group 1		Total	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
Age (years)						
N	47	23	12	6	59	29
Mean (SD)	15 (1.9)	15 (1.5)	10 (1.3)	8 (0.8)	14 (2.7)	13 (3.0)
Median (min, max)	15 (12, 17)	15 (12, 17)	10 (7, 11)	8 (7, 9)	14 (7, 17)	14 (7, 17)
Sex						
Female	20 (42.6%)	7 (30.4%)	5 (41.7%)	5 (83.3%)	25 (42.4%)	12 (41.4%)
Male	27 (57.4%)	16 (69.6%)	7 (58.3%)	1 (16.7%)	34 (57.6%)	17 (58.6%)
Race						
Asian	33 (70.2%)	18 (78.3%)	4 (33.3%)	3 (50.0%)	37 (62.7%)	21 (72.4%)
Black or African American	2 (4.3%)	2 (8.7%)	1 (8.3%)	0	3 (5.1%)	2 (6.9%)
Native Hawaiian or Other Pacific Islander	1 (2.1%)	0	0	0	1 (1.7%)	0
Other	2 (4.3%)	0	0	0	2 (3.4%)	0
White	9 (19.1%)	3 (13.0%)	7 (58.3%)	3 (50.0%)	16 (27.1%)	6 (20.7%)
Ethnicity						
Hispanic or Latino	2 (4.3%)	0	0	0	2 (3.4%)	0
Not Hispanic or Latino	44 (93.6%)	22 (95.7%)	12 (100.0%)	6 (100.0%)	56 (94.9%)	28 (96.6%)
Not permitted	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)
Weight (kg)						
N	47	23	12	6	59	29
Mean (SD)	54.0 (10.74)	56.5 (10.96)	37.9 (7.96)	30.8 (4.97)	50.7 (12.09)	51.2 (14.53)
Median (min, max)	54.6 (36.3, 87.5)	55.8 (35.0, 78.5)	37.1 (29.0, 54.1)	32.2 (24.0, 36.5)	52.2 (29.0, 87.5)	52.0 (24.0, 78.5)
Height (cm)						
N	47	23	12	6	59	29
Mean (SD)	161.8 (9.74)	164.6 (9.95)	141.4 (9.14)	136.8 (5.11)	157.6 (12.63)	158.8 (14.62)
Median (min, max)	160.5 (143.0, 183.0)	166.5 (144.8, 179.5)	140.2 (125.0, 155.0)	136.4 (130.0, 144.0)	156.4 (125.0, 183.0)	161.3 (130.0, 179.5)
Body Mass Index (kg/m^2)						
N	47	23	12	6	59	29
Mean (SD)	20.5 (2.89)	20.7 (2.57)	18.8 (2.70)	16.4 (2.16)	20.2 (2.91)	19.8 (3.02)
Median (min, max)	20.4 (15.5, 29.4)	20.3 (16.0, 27.3)	18.2 (15.8, 24.3)	16.4 (13.6, 19.7)	20.1 (15.5, 29.4)	19.7 (13.6, 27.3)

Body Mass Index (kg/m^2) = [Weight (kg)/Height $(cm)^2$] * 10,000
Source: Table 5, Dr. Yifan Wang's Statistical Review.

Baseline Disease Characteristics

Table 6. Baseline Disease Characteristics (Safety Analysis Set) – Study GS-US-320-1092

	Cohort 1		Cohort 2 Group 1		Total	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
HBV DNA (log10 IU/mL)						
N	47	23	12	6	59	29
Mean (SD)	7.9 (1.13)	8.1 (0.80)	8.0 (1.09)	8.3 (0.28)	7.9 (1.12)	8.1 (0.72)
Median (min, max)	8.1 (2.5, 9.2)	8.3 (5.4, 9.2)	8.1 (5.0, 9.2)	8.3 (7.8, 8.6)	8.1 (2.5, 9.2)	8.3 (5.4, 9.2)
HBsAg (log10 IU/mL)						
N	47	23	12	6	59	29
Mean (SD)	4.4 (0.50)	4.5 (0.57)	4.4 (0.84)	4.7 (0.49)	4.4 (0.58)	4.6 (0.55)
Median (min, max)	4.5 (3.3, 5.1)	4.6 (2.9, 5.1)	4.5 (2.0, 5.1)	4.7 (3.8, 5.1)	4.5 (2.0, 5.1)	4.7 (2.9, 5.1)
HBsAg status						
Positive	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)
HBeAg status						
Negative	1 (2.1%)	0	0	0	1 (1.7%)	0
Positive	46 (97.9%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	58 (98.3%)	29 (100.0%)
ALT (U/L)						
N	47	23	12	6	59	29
Mean (SD)	112 (134.4)	110 (110.5)	85 (69.0)	96 (94.0)	106 (123.9)	107 (105.9)
Median (min, max)	68 (19, 793)	76 (20, 502)	59 (22, 274)	60 (43, 286)	65 (19, 793)	66 (20, 502)
Baseline fibrosis score category						
0.00-0.48	43 (95.6%)	21 (95.5%)	11 (91.7%)	6 (100.0%)	54 (94.7%)	27 (96.4%)
0.49-0.74	2 (4.4%)	1 (4.5%)	1 (8.3%)	0	3 (5.3%)	1 (3.6%)

TAF = tenofovir alafenamide; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; ALT = alanine aminotransferase
Source: Table 6, Dr. Yifan Wang's Statistical Review.

Efficacy outcomes

For the primary efficacy endpoint at Week 24, the total proportion of participants (6 to < 18 years) with HBV DNA <20 IU/mL was 18.6% (11 of 59 participants) in the TAF-treatment group, compared to 0.0% (0 of 29 participants) in the placebo-treatment group (*p-value = 0.0137*) (Table 7).

In addition, HBV DNA levels progressively declined from baseline to Week 24 in TAF-treated participants and mean (SD) $\log_{10}$ IU/mL decreases were significantly greater (p-value < 0.0001) in participants treated with TAF versus placebo at each time point from Week 4 through Week 24. A significantly greater proportion of participants treated with TAF versus placebo achieved ALT normalization at Week 24 when evaluated by both central laboratory and AASLD criteria.
Rates of HBeAg loss/seroconversion were similar between the TAF and placebo groups, and no participant in either group had HBsAg loss through Week 24.

Table 7. Overall Efficacy Outcome at Week 24

	Total TAF 25 mg vs Total Placebo			
	TAF 25 mg (N = 59)	**Placebo (N = 29)**	***P* Value**	**Prop Diff (95% CI)**
HBV DNA <20 IU/mL at Week 24	11/59 (18.6%)	0/29	0.0137	18.5% (5.4% to 31.6%)

Key Review Issue

While the efficacy outcome for TAF was superior to placebo for the overall population, the review team had concerns about the benefit observed for Cohort 2, as summarized in the table below (Table 8).

In Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg), the proportion of participants with HBV DNA <20 IU/mL was 21.3% (10/47) in the TAF treatment group, compared to 0.0% (0/ 23) in the placebo-treatment group. In Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg), the proportion of participants with HBV DNA <20 IU/mL was 8.3% (1 of 12 participants) in the TAF-treatment group compared to 0.0% (0 of 6 participants) in the placebo treatment group.

The team acknowledges that the interpretation of the primary efficacy outcome by age-group should be made with caution (particularly for Cohort 2) due to the small sample size and lack of power.

Table 8. Efficacy Outcome at Week 24 in Cohort 1 and Cohort 2, Group 1

HBV DNA <20 IU/mL at Week 24	**Cohort 1**		**Cohort 2 Group 1**		**Total**	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
Response rate	10/47 (21.3%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	11/59 (18.6%)	0/29 (0%)
95% CI	(10.7%, 35.7%)	(0%, 14.8%)	(0.2%, 38.5%)	(0%, 45.9%)	(9.7%, 30.9%)	(0%, 11.9%)
Difference	21.3%		8.3%		18.6%	
95% CI for difference	(6.3%, 36.2%)		(-19.8%, 36.5%)		(5.4%, 31.6%)	
P-value	0.0199		-		0.0137	

HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
P values were based on a 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.
95% CIs were calculated using the Clopper-Pearson method.

Assessment:

To elucidate the possible causes of the lower efficacy outcome in the younger cohort, the multidisciplinary review team evaluated baseline disease characteristics and exposure-response relationships.

1. Known baseline factors that impact treatment response include:
    - Higher baseline viral load (i.e., HBV DNA >8 $\log_{10}$ IU/mL)
    - Lower baseline ALT level (>1.5 x ULN)
    - Infection with the HBV genotype D.

    The Applicant provided additional baseline disease characteristics information. As summarized below, these factors may have contributed the lower response rate observed in Cohort 2, Group 1 (Table 9).

The Applicant also noted that based on historical evidence, (e.g., TDF data), the response rates improve with longer treatment duration.

Table 9. Features Associated with Delayed Viral Suppression in Response to Tenofovir Therapy

	Cohort 1	Cohort 2, Group 1
Baseline HBV DNA $\geq$8 $\log_{10}$ IU/mL	30/47 (63.8%)	9/12 (**75%**)
Baseline ALT $\geq$1.5xULN by Central Laboratory Criteria	29/47 (61.7%)	6/12 (**50%**)
HBV genotype D	17/47 (39.5%)	7/12 (**58.3%**)

Source: Summarized from Applicant 's response to the FDA Information Request (SN0139, dated September 14, 2022).

2. The review team also considered if the relatively lower medication adherence rate in the younger age group could explain the lower efficacy rate. Among subjects randomized to the active (TAF) treatment group, 74.5% and 66.7% of subjects in Cohort 1 and Cohort 2 were $\geq$ 95% adherent to the study drug, respectively. The Clinical Pharmacology and Pharmacometrics review team evaluated whether this lower adherence contributed to lower drug exposures, hence contributing to a lower efficacy outcome.

   The exposure-response analysis –for safety and efficacy, was based on PK sampling, which included all 59 CHB subjects (n=47 in Cohort 1; n=12 in Cohort 2 Group 1). Based on the pop-PK analysis, no meaningful exposure-response relationships were identified for either safety or efficacy. Therefore, the differential in treatment response between Cohort 1 and 2 is unlikely to be driven by PK/PD dynamics.

   For a detailed review of the PK and exposure-response evaluation, please see the detailed review by Dr. Yang Zhao's Clinical Pharmacology Review.

Conclusions

The Week 24 results for the overall population enrolled in Study 1092 show that TAF is superior to the placebo for the treatment of chronic HBV infection. When the efficacy outcome was assessed by age-group, a significant treatment difference (between TAF and placebo) was observed only in the adolescent age group. (b) (4)

[redacted]

8. Safety

Trial 1092 demonstrated that TAF is a well-tolerated treatment for CHB in children. The adverse events reported in this study are similar to those previously described in adult and adolescent studies of patients with HBV and HIV.

No deaths or treatment-related serious adverse events were reported. There were no AEs leading to premature study discontinuation among adolescents and no deaths. There were no remarkable changes in spine and whole-body bone mineral density (BMD), and no significant differences were observed between the active and placebo treatment groups. Renal toxicity was also not observed in this study as no patients demonstrated a significant decline in glomerular function or renal tubule injury.

The most commonly reported adverse reactions were headache, 'Vitamin D decreased', and upper respiratory tract infection. Three participants in Cohort 1 experienced a serious adverse event (SAE) during the double-blind treatment phase (1 in the TAF group and 2 in the placebo group). The TAF group participant had Grade 2 scarlet fever which was considered unrelated to the study drug, and the placebo group subjects had Grade 3 ankle fracture (Day 7, trauma-related); and grade 3 ALT increased (Day 27, considered related to study drug). There were no notable effects of treatment on vital signs, development, or growth including Tanner stage, bone age, height, weight, and BMI percentiles.

A 90-day Safety Update Report (SUR) was submitted and no new safety concerns for TAF were identified based on the data presented in the SUR. The SUR included data from the open-label phase for all participants in Cohort 1 and Cohort 2 Group 1 who received the 25-mg adult strength tablets. The TAF safety data with the longer duration of exposure in pediatric (children and adolescents) participants remained unchanged relative to the initial sNDA submission.

Overall, the safety review did not reveal new signals to monitor. Further details regarding adverse events and safety monitoring are described in Sections 8.2.

8.1 Approach to Safety Review

8.11 Studies/Clinical Trials Used to Evaluate Safety

The results of Trial 1092, a single Phase 2, randomized, double-blind placebo controlled clinical trial of TAF-naïve children and adolescents infected with HBV 6 to <18 years old, were reviewed to evaluate the safety of TAF. The Safety Analysis Set was used to perform the analyses in this review and included 70 randomized subjects in the adolescent group who received at least one dose of study drug (47 subjects were randomized to the TAF arm and 23 subjects to the placebo arm); and 18 randomized subjects in the younger age group (6 to < 12 years) who received at least one dose of study drug (12 subjects were randomized to TAF, and 6 subjects to placebo). All 88 participants completed the 24-week double-blind treatment phase.

The source of data for the safety review is from Trial 1092. Using the Applicant's STDM and ADAM datasets, the primary clinical reviewer conducted all safety analyses presented in this section using JMP Clinical 7.1.2, unless otherwise specified.

8.12 Categorization of Adverse Events

Investigator-reported verbatim terms were translated into preferred terms using the MedDRA dictionary Version 24.0 used by the Applicant. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms.

8.13 Pooling of Data Across Studies to Estimate and Compare Incidence

Not applicable.

8.2 Safety Findings

8.2.1 Treatment Emergent Adverse Events and Adverse Drug Reactions

Table 9 presents an overall summary of AEs by treatment group during the double-blind treatment phase. Overall, the incidence of AEs was similar between TAF and placebo treatment groups. In total, in both cohorts, 59.3% (35 participants) in the TAF group and 55.2% (16 participants) in the placebo group experienced at least 1 AE during double-blind treatment. The overall incidence of AEs was similar between TAF and placebo.

Cohort 1

A total of 29 (62%) subjects in the TAF treatment group and 12 (52%) in the placebo treatment group were assessed as having Treatment-Emergent AEs (TEAEs). Of those, 8/47 (17%) subjects in the TAF group and 3/23 (13%) of subjects in the placebo group had TEAEs assessed as related to the study drug by the investigator (Table 7). In the TAF treatment group, of the TEAEs considered related to the study drug, one was Grade 2 and the remaining seven were Grade 1. The AEs with the highest incidence in the TAF treatment group were headache, decreased Vitamin D, and upper respiratory tract infection (each occurring in 5/47, or 10.6% of participants).

Cohort 2, Group 1
A total of 6 (50%) subjects in the TAF-treatment group and 4 (66.7%) in the placebo group were assessed as having TEAEs. Of those, 2/12 (16.7%) subjects in the TAF group and 0/6 (0%) of subjects in the placebo group had TEAEs assessed as related to the study drug by the investigator (Table 10). Of the TEAEs in the TAF-treatment group considered related to the study drug, both were Grade 1. The AEs with the highest incidence in this group were upper abdominal pain (16.7%), nausea (16.7%) and headache (8.3%).

The majority of reported AEs were considered mild or moderate in severity and did not lead to treatment discontinuation.

Table 10. Overall Summary of Adverse Events During the Double-Blind Treatment Phase (Safety Analysis Set, Double-Blind Phase)

	Cohort 1		Cohort 2 Group 1		Total	
	TAF (N=47)	**Placebo (N=23)**	**TAF (N=12)**	**Placebo (N=6)**	**TAF (N=59)**	**Placebo (N=29)**
Number of Subjects with any TEAE	29 (61.7%)	12 (52.1%)	6 (50.0%)	4 (66.7%)	35 (59.3%)	16 (55.1%)
Maximum Toxicity Grade						
Grade 1 (mild)	26 (89.6%)	10 (43.5%)	6 (50.0%)	3 (50.0%)	32 (54.2%)	13 (44.8%)
Grade 2 (moderate)	7 (14.9%)	3 (13.0%)	1 (8.3%)	2 (33.3%)	8 (13.5%)	5 (17.2%)
Grade 3 (severe)	-	2 (8.7%)	-	-	-	2 (6.9%)
Grade 4 (life-threatening)	-	-	-	-	-	-
Deaths	-	-	-	-	-	-
Any Subject TE SAE	1 (2.1%)	2 (8.7%)	-	-	1 (1.7%)	2 (6.9%)
Drug-related TE SAE	-	-	-	-	-	-
Drug-related AEs	8 (17.0%)	3 (13%)	2 (16.7%)	-	10 (16.9%)	3 (10.3%)
Drug-related Grade 1 AE	8 (17.0%)	2 (8.7%)	2 (16.7%)	-	10 (16.9%)	2 (6.9%)
Drug-related Grade 2 AE	1 (2.1%)	1 (4.3%)	-	-	1 (1.7%)	1 (3.4%)
Drug-related Grade 3 AE	-	1 (4.3%)	-		-	1 (3.4%)
AE Leading to Premature Discontinuation	-	-	-	-	-	-
AE Leading to Dose Modification or Temporary Interruption	-	1 (4.3%)	1 (8.3%)	-	1 (1.7%)	1 (3.4%)

Source: Reviewer analysis of the adae.xpt dataset, and Table 24 in Applicant CSR (page 124)

Table 11 presents an overall summary of AEs reported in ≥ 5% of participants in either treatment group, in descending overall incidence. The AE with the highest incidence in both treatment groups was

headache (10.2% of participants in the TAF group and 13.8% participants in the placebo group). Other AEs reported in ≥ 5% of participants in the TAF group were abdominal pain upper, vitamin D decreased, and upper respiratory tract infection (8.5% each), nasopharyngitis and nausea (6.8% each), and cough, rhinitis allergic, and Vitamin D deficiency (5.1% each).

Table 11. Adverse Events Reported in ≥ 5% of Participants in Either Treatment Group (Safety Analysis Set, Double-Blind Phase)

	Cohort 1		Cohort 2 Group 1		Total	
Preferred Term	TAF (N=47)	Placebo (N=23)	TAF (N=12)	Placebo (N=6)	TAF (N=59)	Placebo (N=29)
Headache	5 (10.6%)	2 (8.7%)	1 (8.3%)	2 (33.3%)	6 (10.2%)	4 (13.8%)
Abdominal pain upper	3 (6.4%)	1 (4.3%)	2 (16.7%)	1 (16.7%)	5 (8.5%)	2 (6.9%)
Vitamin D decreased	5 (10.6%)	2 (8.7%)	-	-	5 (8.5%)	2 (6.9%)
Nasopharyngitis	4 (8.5%)	1 (4.3%)	-	1 (16.7%)	4 (6.8%)	2 (6.9%)
Upper respiratory tract infection	5 (10.6%)	1 (4.3%)	-	-	5 (8.5%)	1 (3.4%)
Nausea	2 (4.3%)	1 (4.3%)	2 (16.7%)	-	4 (6.8%)	1 (3.4%)
Cough	3 (6.4%)	-	-	-	3 (5.1%)	-
Rhinitis allergic	2 (4.3%)	-	1 (8.3%)	-	3 (5.1%)	-
Vitamin D deficiency	2 (4.3%)	-	1 (8.3%)	-	3 (5.1%)	-
Rhinitis	-	-	-	2 (33.3%)	-	2 (6.9%)
Ankle fracture	-	2 (8.7%)	-	-	-	2 (6.9%)
AST increased	-	1 (4.3%)	-	1 (16.7%)	-	2 (6.9%)
ALT increased	-	1 (4.3%)	-	1 (16.7%)	-	2 (6.9%)

Source: Independent analysis of adae.xpt dataset by reviewer, and from Table 25 in Clinical Study Report, page 125.

The most common treatment-related AEs which occurred in >1 subject in the Cohort 1 TAF group were headache (4/47, or 8.5%), nausea, upper abdominal pain, and fatigue, each reported in 2/47 subjects (4.3%). In Cohort 2, Group 1, none of the treatment-related AEs occurred in > 1 subject.

8.2.2 Deaths

No deaths occurred through the 24 weeks of treatment, or during the 90 day Safety Update Report.

8.2.3 Serious Adverse Events

Overall, 3 participants, all in Cohort 1, experienced an SAE during the double-blind treatment phase—1 participant in the TAF group and 2 participants in the placebo group:

a. One participant (TAF) experienced an SAE of Grade 2 scarlet fever from Day 106 to Day 110; considered not related to the study drug; no action was taken with study drug
b. Two participants (both placebo group) experienced an SAE:
    i. Grade 3 ankle fracture (Day 7, trauma-related)
    Grade 3 ALT increased (Day 27, considered related to underlying HBV infection).

8.2.4 Dropouts and/or Discontinuations Due to Adverse Events (AEs)

One participant in the TAF group (Cohort 2) experienced several Grade 1 AEs that led to temporary interruption of study drug, which resolved and were considered unrelated to the study drug. One

participant in the placebo group (Cohort 1) had study drug interrupted due to the SAE of ALT increased. There were no AEs leading to premature study discontinuation and no deaths.

8.2.5 Adverse Events of Special Interest

Exacerbation of Hepatitis and ALT Flairs

During the first 24 weeks of double-blind treatment, one participant in the Cohort 1 TAF group (1.7%) met criteria for ALT elevation (>2x baseline and >10x ULN, with or without associated symptoms) with 2 participants in the Cohort 1 placebo group also meeting criteria for ALT flare (ALT elevations at 2 consecutive postbaseline visits), one of which was considered serious. Both participants with ALT flare had graded elevations in ALT at baseline and their total bilirubin values remained normal. Additionally, both subjects remained HBsAg positive; neither had a corresponding increase in HBV DNA. None of the subjects in Cohort 2, group 1, had an ALT flare or exacerbation of hepatitis.

For general analysis of laboratory toxicities related to serum biochemistry abnormalities, refer to Section 8.2.8.

Bone-related Safety Analysis

Change in Spine and Whole-Body Bone Mineral Density (BMD)

A decline in BMD in adults and slower gain in adolescents are well-known AEs associated with TFV exposure, and thus changes in BMD were monitored as an AE of special interest. For both treatment groups, observed mean spine and whole-body BMD Z-score values were within the normal range for the participant population from baseline through 24 weeks of double-blind treatment (Z-scores > -1 at baseline and at Week 24). At Week 24 of this study, there were no statistically significant differences noted between the TAF and placebo groups in either spine BMD or whole-body BMD percentage change or Z-scores compared to baseline in either age group:

Spine

BMD percent change *at Week 24 (p-value= 0.767*):
Cohort 1: TAF mean (SD): +2.4% (3.31), Placebo: +1.9% (3.08),
Cohort 2, Group 1: TAF mean (SD): -1.2% (8.6), Placebo: +1.9 (1.7)

Z-scores change at Week 24:
Cohort 1: TAF: -0.03 (0.21), Placebo: -0.09 (0.31)
Cohort 2, Group 1: +0.12 (0.39), Placebo: -0.01 (0.14)

Whole body

BMD percent change at Week 24 (p-value = 0.827)
Cohort 1: TAF mean (SD): +1.5% (2.26), Placebo +1.9% (2.56),
Cohort 2, Group 1: TAF mean (SD): +3.2 (3.49), Placebo: +2.7 (2.68)

Z-scores:
Cohort 1: TAF: -0.05 (0.22), Placebo: -0.01 (0.24)
Cohort 2, Group 1: TAF: 0.0 (0.31), Placebo: -01.7 (0.27)

Overall, 4 participants (all in the TAF group, Cohort 2 Group 1) had a ≥ 4% decrease in spine BMD (3 participants) or whole-body BMD (1 participant). Of note, Z-scores for these participants remained within normal range for their age and gender. Also of note, 3 participants who received TAF and had a spine or whole-body BMD Z-score ≤ −2 at Week 24 also had a BMD Z-score ≤ −2 at baseline.

Fracture events during double-blind treatment occurred in 3 participants, all trauma-related and within the placebo group. No other bone events occurred in any groups.

Independent analyses by the FDA Medical Officer were conducted to evaluate the bone-related safety in Trial 1092, including the baseline and percent change in spine and whole-body BMD from baseline to 24 weeks of treatment, and the analyses confirmed the findings of the Applicant. Table 12 below summarizes the mean percent change (standard deviation, SD) from baseline in lumbar spine and whole-body BMD at Week 24 (spine and whole-body DEXA analysis).

Table 12. Percent change from baseline in in Spine and Whole-Body Bone Mineral Density at Week 24

	Cohort 1				Cohort 2, Group 1				
	N	**TAF Mean (SD)**	**N**	**Placebo Mean (SD)**	**N**	**TAF Mean (SD)**	**N**	**Placebo Mean (SD)**	**P-Value**
Spine BMD									
Baseline (g/cm^2)	42	0.979 (0.1789)	21	0.979 (0.1727)	12	0.732 (0.1268)	6	0.713 (0.1041)	0.9363
% Change by Week 24	37	2.409 (3.3099)	18	1.925 (3.0776)	11	−1.216 (8.5533)	5	1.896 (1.6566)	0.7672
Whole-body BMD									
Baseline (g/cm^2)	44	0.910 (0.1002)	21	0.933 (01208)	12	0.723 (0.0661)	6	0.680 (0.0690)	0.8307
% Change by Week 24	39	1.517 (2.2603)	18	1.855 (2.5644)	11	3.207 (3.4900)	5	2.670 (2.6816)	0.8274

Source Adapted from Table 27 in Clinical Study Report (page 128) after verification by independent analysis using the ADBMD (Bone Mineral Density) dataset

Assessment:
There was no evidence of slower BMD gains in the TAF treatment groups compared to the placebo groups up to Week 24, but the Agency will continue to assess for this known AE of special interest with TFV therapy. Product labeling includes information about risk of bone toxicity with TAF therapy because risks remain unknown, particularly for younger age cohorts who may have long term exposure to the study drug during periods of active bone growth (see Section 13. Labeling in this Review).

Change in Lumbar Spine and Whole-Body BMD Z-scores

Change in spine and whole-body BMD Z-scores was also analyzed to evaluate growth of children receiving TAF in comparison to healthy children with the same demographic variables. Table 13 below summarizes the percent changes from baseline in BMD Z-scores at Week 24 for subjects with available DEXA data. Lumbar spine and whole-body BMD Z-scores were similar at baseline. By Week 24, slight decreases from baseline were observed in both the TAF and placebo groups in both the mean spine and whole-body BMD z-scores. However, in both groups, the observed mean and median BMD Z-scores values were within the normal range for the population from baseline through 24 weeks of treatment.

Table 13. Change from Baseline in Spine and Whole-Body Bone Mineral Density Z-Scores at Baseline and Week 24 (Spine and Whole-Body DXA Analysis Sets, Double-Blind Phase)

	Cohort 1		Cohort 2, Group 1	
	TAF	**Placebo**	**TAF**	**Placebo**
Spine BMD Z-score				

Baseline				
N	42	21	12	6
Mean (SD)	−0.14 (1.034)	−0.02 (1.178)	0.19 (1.076)	0.66 (0.928)
Change from Baseline at Week 24				
N	37	18	11	5
Mean (SD)	−0.03 (0.213)	−0.09 (0.307)	0.12 (0.385)	−0.01 (0.140)
Whole-body BMD				
Baseline				
N	44	21	11	5
Mean (SD)	−0.36 (0.816)	−0.31 (1.039)	−0.17 (1.030)	0.44 (1.410)
Change from Baseline at Week 24				
N	39	18	10	4
Mean (SD)	−0.05 (0.222)	−0.01 (0.244)	0.00 (0.305)	−0.17 (0.265)

Source: Adapted from Table 30 in Clinical Study Report after verification by independent analysis using the ADBMD (Bone Mineral Density) dataset.

A BMD Z-score ≤ −2.0 is below the expected range for age and would reflect a clinically relevant degree of low BMD, while a Z-score > −2.0 is within the expected range for age. Most subjects in the Cohort 1 TAF and placebo groups had spine BMD Z-scores > −1 at baseline and at Week 24.

Overall, 2 participants in the Cohort 1 TAF group had a spine or whole-body BMD Z-score ≤ −2 at Week 24. Of note, these participants also had a BMD Z-score ≤ −2 at baseline.

- Participant (b) (6) had a spine and whole-body BMD Z-score ≤ −2 at baseline (spine −2.63, whole-body −2.43) and at Week 24 (spine −2.13, whole-body −2.93)
- Participant (b) (6) had a whole-body BMD Z-score ≤ −2 at baseline (−2.04) and at Week 24 (−2.31) and spine BMD Z-score of −1.90 at baseline and −2.15 at Week 24

Notably, no subjects had an appreciable *decrease* in spine or whole-body BMD Z-score < −2 at Week 24.

Bone Laboratory Parameters

Biochemical bone markers in serum and urine were evaluated at baseline and during double-blind treatment. Bone marker values were similar for the TAF and placebo groups at baseline and remained stable throughout the double-blind treatment period with no between-group differences noted at Week 24.

Fracture Events

Fracture events occurred in 3 participants during the double-blind treatment phase, all in the Cohort 1 placebo group. All were trauma-related, considered unrelated to the study drug, and did not result in discontinuation of the study drug. All 3 of these participants had spine and whole-body BMD Z-scores within the expected range for age.

Renal Toxicity

Renal toxicity is a well-described complication of TFV-containing therapies. During the 24-week study period, or the 90-day Safety Update Report, neither renal failure nor Fanconi's syndrome were reported. Further details regarding serum creatinine and estimated glomerular filtration rate (eGFR) are provided below.

Renal Clinical Adverse Events
One participant in the TAF Cohort 2 Group 1 arm experienced a non-serious, Grade 1 proteinuria on Day 2 of double-blind treatment. The AE was considered not related to study drug and no action was taken in response to the event. The AE resolved on Day 203. No subjects in Cohort 1 TAF or placebo groups experienced any renal adverse events.

Serum creatinine
At baseline, mean serum creatinine levels were similar for participants in the TAF (0.65 mg/dL) and placebo groups (0.65 mg/dL). Serum creatinine remained similar to baseline during the double-blind treatment phase for both the TAF and placebo groups, with mean increases from baseline of +0.05 mg/dL and +0.01 mg/dL, respectively, at Week 24. When evaluated by cohort, at Week 24, a greater increase in mean serum creatinine was noted in the TAF groups compared with placebo:

- Cohort 1 mean increase from baseline of 0.04 mg/dL and 0.02 mg/dL for TAF and placebo, respectively
- Cohort 2 Group 1 mean increase from baseline of 0.05 mg/dL and a mean decrease 0.01 mg/dL for TAF and placebo, respectively

Estimated Glomerular Filtration Rate (eGFR)
At baseline, the median (Q1, Q3) overall estimated glomerular filtration rate (eGFR, creatinine clearance [CL_{cr}] using the Schwartz formula) was similar for the TAF and placebo groups (TAF 154 [137, 169] mL/min, placebo 149 [143, 180] mL/min).

- Cohort 1 Baseline: TAF and placebo groups (TAF 154 [137, 169] mL/min/1.72 m^2, placebo 145 [142, 175] mL/min/1.72 m^2).
- Cohort 2, Group 1, Baseline: TAF and placebo groups (TAF 154 [142, 169] mL/min/1.72 m^2, placebo 173 [152, 189] mL/min/1.72 m^2).

For both the TAF and placebo groups, a significant overall median decrease from baseline in eGFR (CL_{cr}) were observed at Week 24 of the double-blind treatment period (TAF -9 (−19, 2) mL/min; placebo −1 (−7, 7) mL/min; P = 0.0303).

- Cohort 1, Week 24: TAF group (-6 [−19, 2] mL/min/1.72 m2) compared to the placebo group (0 [-7, 6] mL/min/1.72 m2)
- Cohort 2, Group 1, Week 24: TAF group (-14 [−21, 4] mL/min/1.72 m2) compared to the placebo group (-1 [-5, 24] mL/min/1.72 m^2)

Despite the significantly greater median decrease in eGFR from baseline, the median eGFR remained within normal range in all subjects, and no participant had an eGFR < 70 mL/min at 2 consecutive postbaseline visits.

'Confirmed' Renal Abnormalities
Confirmed renal abnormalities were defined as an increase from baseline in creatinine ≥ 0.3 mg/dL, an increase from baseline in creatinine ≥ 0.5 mg/dL, occurrence of serum phosphorous below 2.0 mg/dL, eGFRSchwartz < 50 mL/min, or eGFRSchwartz < 70 mL/min at 2 consecutive postbaseline visits. No participant had a confirmed renal abnormality through Week 24, after receiving double-blind treatment.

8.2.6 Growth

Body Weight, Height, and Body Mass Index
Body weight, height, and BMI Z-scores were calculated using the lambda mu and sigma (LMS) method based on Centers for Disease Control and Prevention (CDC) growth charts and reference methods. These Z-scores are established to compare an individual's weight and height in relation to other individuals of

the same age, sex, weight, and ethnic or racial origin. The score itself is the number of standard deviations above or below the mean (which is scored as 0). A score of -2 or lower is concerning for a height or weight that is significantly lower than the norm.

Body weight Z-scores, Height Z-scores and BMI Z-scores, were similar for the Cohort 1 and Cohort 2, Group 1, TAF and placebo groups at baseline. During the 24 weeks of double-blind treatment, mean changes in body weight Z-scores were not statistically significant, with no clinically significant changes in weight in the TAF group during the 24 weeks of treatment in both Cohorts.

8.2.7 Tanner Staging

As expected for the Cohort 1 study population of adolescents aged 12 to <18 years old, the majority of males and females in the TAF and placebo groups were categorized at Tanner Stage 3 through 5 through Week 24, and for the study population of Cohort 2 Group 1 (children aged 6 to < 12 years weighing ≥ 25 kg), the majority of males and females were categorized at Tanner Stage 1 to 2 (prepubertal) through Week 24.

8.2.8 Graded Laboratory Abnormalities

The majority of participants had a postbaseline graded laboratory abnormality during the double-blind phase (74.6% of participants who received TAF and 96.6% of participants who received placebo). The graded abnormalities in both treatment groups were mainly Grade 1 or 2. A similar percentage of participants in each group had Grade 3 or 4 laboratory abnormalities (TAF 11.9%, 7 participants total; placebo 13.8%, 4 participants).

Overall, no clinically relevant changes from baseline hematology or chemistry parameters were noted within the Cohort 1 TAF group, and median values were within normal ranges.

- Overall, 36/47 (76.6%) of subjects in the Cohort 1 TAF group and 22/23 (95.7%) in the placebo group had a graded lab abnormality, most of which were Grade 1 (mild) or 2 (moderate) in severity.
- In Cohort 2, Group 1, TAF group, 8 subjects (66.7%) and all 6/6 (100%) in the placebo group had a graded lab abnormality. Other than one subject in the TAF group (Grade 3), all the laboratory abnormalities were Grade 1 or 2.

Grade 3 (severe) or 4 (life-threatening) laboratory abnormalities
A similar percentage of participants in the Cohort 1 TAF group had Grade 3 (severe) or 4 (life-threatening) laboratory abnormalities: TAF 6/47 (12.8%) as compared to 4/23 (17.4%) in the placebo group. One participant in the TAF group had Grade 3 decreased platelets at one time point (Week 12) during double-blind treatment which were also low at baseline. Grade 3 or 4 chemistry and urinalysis abnormalities that occurred in >1 participant in Cohort 1 included increased ALT (TAF 4/47, 8.5%; placebo 2/23, 8.7%) and hematuria (TAF 2/47, 8.0% versus 1/23, 7.7% in the placebo group). The hematuria occurred at one time point with all other urinalyses negative for occult blood at all other time points during double-blind treatment.

In Cohort 2, Group 1, only 1 subject (8.3%) in the TAF group had a Grade 3 laboratory abnormality (hematuria); no other TAF or placebo subjects had a grade 3 or 4 laboratory abnormality in this Cohort.

8.2.8.1 Hepatic Laboratory Abnormalities

Graded liver-related laboratory abnormalities presented as elevations in ALT, AST and total bilirubin and were noted at similar rates in:

- Cohort 1:
  - ALT increased: TAF: 13/47 (27.7%), placebo: 9/23 (39.1%)

  - AST increased: TAF: 13/47 (27.7%), placebo: 10/23 (43.5%)
  - Total bilirubin increased: TAF: 6/47 (12.8%), placebo: 3/23 (13.0%)
- Cohort 2, Group1:
  - ALT increased: TAF: 3/12 (25.0%), placebo: 1/6 (16.7%)
  - AST increased: TAF: 3/12 (25.0%), placebo: 1/6 (16.7%)
  - Total bilirubin increased: TAF: 0/12 (0%), placebo: 1/6 (16.7%)

Most hepatic laboratory abnormalities were Grade 1 or 2 in severity; however, Grade 3 or 4 ALT abnormalities were also reported for similar percentages of subjects in the Cohort 1 TAF and placebo groups (8.5% and 8.7%, respectively). Of the Cohort 1 TAF group participants with Grade 3 or 4 increased ALT, three were Grade 3 (6.4%) and one was Grade 4 (2.1%). In Cohort 2, Group 1, there were no Grade 3 or 4 ALT or AST laboratory abnormalities.

8.2.8.2 Metabolic Laboratory Parameters

Overall, fasting lipid parameters remained stable from baseline during double-blind treatment in both Cohorts in the TAF and placebo groups at Week 24. No participant in the TAF or placebo group had a Grade 3 or 4 abnormality in any fasting metabolic parameter. Increases in participant body weight, height, and body mass index during double-blind treatment were similar between groups who received TAF and placebo by Week 24.

9 Therapeutic Individualization

9.1 Drug Interactions

The Applicant provided a list of medications that were prohibited or to be used with caution during treatment with TAF (please see VEMLIDY® labeling for further details).

No drug interaction studies with TAF have been conducted in pediatric CHB subjects, since the drug interaction profile of TAF in pediatric CHB patients is not expected to differ from that in CHB adolescents 12 to <18 years old or adults ≥18 years old. No new findings relevant to the coadministration of TAF with other drugs are submitted with this update to the marketing application.

9.2 Pediatric Populations

See Section 7 for discussion regarding efficacy and Section 8 for discussion regarding effects on BMD and linear growth.

On September 13, 2022, the review team for this sNDA presented to the PeRC. The committee agreed with the following recommendations set forth by the Division:

- The safety and efficacy data presented for Cohort 1 (12 to < 18 years old) was acceptable and the drug can be approved for this age group. (b) (4)
- Hence, the PMR 3130-1 would be considered as fulfilled.

(b) (4)

9.3 Pregnancy and Lactation

It is not known whether VEMLIDY® and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. Tenofovir has been shown to be present in the

milk of lactating rats and rhesus monkeys after administration of TDF. It is not known if TAF can be present in animal milk. Prospective study data was added to the Label regarding 800 exposures to TAF-containing regimens during pregnancy (including over 650 exposed in the first trimester and over 150 exposed in the second/third trimester). This data demonstrated a prevalence rate of birth defects in live births of 3.5% (95% CI: 2.3% to 5.2%) and 3.3% (95% CI: 1.1% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

10 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA application.

11 Other Relevant Regulatory Issues

11.1 Submission Quality and Integrity

The quality and integrity of the submission were adequate. From a clinical review perspective, the submission was well organized and reasonable to navigate.

Upon Agency review of the number of subjects enrolled at each site, as well as the list of protocol deviations and discontinuations due to AEs, there were no aberrations identified to warrant any site inspections. No requests were made to the Office of Scientific Investigations (OSI) for site inspections.

11.2 Compliance with Good Clinical Practices

Trial 1092 was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312)], the European Community Directive 2001/20/EC, and other local legislation.

The appropriate approvals from the independent ethics committee (IEC) or institutional review board (IRB) were secured before study initiation. Protocol amendments and all revisions to the consent form after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

12 Financial Disclosures

Gilead Sciences, Inc. submitted Form FDA 3454, which certifies that the Applicant did not enter into any financial relationships with principal or sub-investigators. The form included an attachment containing the names of principal investigators and sub-investigators for study GS-US-320-1092 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3). There were 206 total investigators (59 Principal Investigators and 147 Sub-Investigators), all of whom certified that they are not Gilead employees, received no compensation for conducting the study where the value could be

influenced by the outcome of the study, have no proprietary interest in the product, and have no significant equity interest held in the Applicant of the study.

However, three investigators received significant payments of other sorts valued at >$25,000. All were assessed by Gilead as having minimal potential to introduce bias given the randomized, double-blinded, placebo-controlled nature of the study, the objective nature of the primary and secondary efficacy outcome measurements (i.e., laboratory results), and the presence of Clinical Research Associates and site monitors who are blinded to the treatment assignments. All 3 investigators signed Minimization of Bias forms.

See the Appendix for the Clinical Investigator Financial Disclosure Review Template.

13 Labeling

The USPI and PPI are currently under negotiation; however, the main changes have been agreed to and are summarized below.

Please note that the section numbers here are the section numbers in the label and do not refer to the Section numbers in this review document.

Overall Major Change

Based on the Agency's review of the efficacy results at Week 24, the Indication and Usage section were revised to include pediatric patients aged 12 and older (b) (4)

(b) (4)

Section 8.1 Pregnancy

Human Data

This section was updated to include additional study data from 800 exposures (as opposed to 740 exposures in the original Label). The revised paragraph now reads:

> "Based on prospective reports to the APR of over 800 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 650 exposed in the first trimester and over 150 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.5% (95% CI: 2.3% to 5.2%) and 3.3% (95% CI: 1.1% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens."

(b) (4)

(b) (4)

Section 8.4 Pediatric Use

(b) (4)

The section now reads:

"The pharmacokinetics, safety, and effectiveness of VEMLIDY for the treatment of chronic HBV infection have been established in pediatric patients between the ages of 12 to less than 18 years (N=47) in Trial 1092 for 24 weeks. No clinically meaningful differences in pharmacokinetics or safety were observed in comparison to those observed in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)]*.

Safety and effectiveness of VEMLIDY has not been established in pediatric patients with chronic HBV infection who are less than 12 years of age."

Section 12.3 Pharmacokinetics

Specific Populations: *Pediatric Patients*

(b) (4)

, the Clinical Pharmacology team recommended that the Applicant include pharmacokinetic (PK) information derived from non-compartmental analyses to align with the type of analyses utilized for the adult PK information.

Section 12.4 Microbiology

Mechanism of Action

An inadvertently deleted section was restored to the Label.

Resistance in Clinical Trials

This section was revised to include additional information on the proportion of subjects that qualified for sequencing and the proportion for whom results were successfully obtained, with the revised paragraph now reading: "In pediatric Trial 1092, 30/47 subjects aged 12 to less than 18 years receiving VEMLIDY qualified for resistance analysis at Week 24. Results were obtained for 27/30 qualified subjects. No HBV amino acid substitutions known to be associated with resistance to tenofovir alafenamide were detected through 24 weeks of treatment *[see Clinical Studies (14.5)]*."

(b) (4)

14 Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No recommendation for a REMS is indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No new PMRs or PMCs are indicated.

15 Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

16 Patient Experience Data

Patient Experience Data is listed in Table 14 below.

Table 14. Patient Experience Data Relevant to this Application

■	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	■	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		■	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		x	Other: (Please specify) Palatability and acceptability of the VEMLIDY® tablet formulation were assessed in Study GS-US-320-1092	Module 2.5, Section 4.4.2.8 Module 5.3.5.1, GS-US-320-1092 CSR, Section 9.2.7
x	Patient experience data was not submitted as part of this application.			

17 References

Giacomet V, N. P. (2015). Long-term renal effects of tenofovir-disoproxil-fumarate in vertically HIV-infected children, adolescents, and young adults: a 132-month follow-up study. *Clin Drug Investig*, Jul;35(7):419-26.

Health and Human Services (HHS). Hepatitis B Basic Information. 2022.

Terrault NA, L. A. (2018). Update on Prevention, Diagnosis, and Treatment and of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *Hepatology*, 67:1560-99.

VIREAD®, G. S. (2017, April). VIREAD® (tenofovir disoproxil fumarate) tablets, for oral use and powder, for oral use. Foster City, CA, U.S.

World Health Organization (WHO). Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. 2015.

Wright TL. Introduction to chronic hepatitis B infection. Am J Gastroenterol 2006;101:6.

Appendix

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 208464/S.14

Submission Date(s): March 29, 2016

Applicant: Gilead Sciences, Inc.

Product: Tenofovir alafenamide (VEMLIDY®)

Reviewer: Jency Daniel, MD

Date of Review: September 26, 2022

Covered Clinical Study (Name and/or Number):
A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection (Study Number: GS-US-320-1092)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 59 Principal Investigators and 147 Sub-Investigators		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
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: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Assessment:
The Applicant has adequately disclosed financial interests for Trial 1092. Of the 206 total investigators (59 Principal Investigators and 147 Sub-Investigators), all certified that they are not Gilead employees, received no compensation for conducting the study where the value could be influenced by the outcome of the study, have no proprietary interest in the product, and have no significant equity interest held in the Applicant of the study.

Although three investigators received significant payments of other sorts valued at >$25,000, they were all assessed by Gilead as having minimal potential to introduce bias given the randomized, double-blinded, placebo-controlled nature of the study, the objective nature of the primary and secondary efficacy outcome measurements (i.e. laboratory results), and the presence of Clinical Research Associates and site monitors who are blinded to the treatment assignments. All 3 investigators signed Minimization of Bias forms.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENCY M DANIEL
10/10/2022 07:13:47 PM

SAMER S EL-KAMARY
10/10/2022 07:20:31 PM

YODIT BELEW
10/10/2022 09:42:03 PM