sNDA 208464/S.16,S.17: Tenofovir alafenamide (VEMLIDY)
Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology, Clinical Virology and Division Director Review

Date	March 6, 2024
From	Virginia Long, DO, MS Medical Officer Division of Antivirals (DAV)
Through	Kimberly Struble, PharmD Team Lead
Subject	Clinical Review
Application Type	Supplemental NDA
NDA/BLA # and Supplement#	208464/ Supplement 16 208464/ Supplement 17
Applicant	Gilead Sciences, Inc.
Date of Submission	September 27, 2023
PDUFA Goal Date	March 27, 2024
Proprietary Name	Vemlidy
Established or Proper Name	Tenofovir alafenamide
Dosage Form(s)	25mg Tablet
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of chronic Hepatitis B virus (HBV) infection in children aged 6 to <12 years and weighing at least 25kg
Applicant Proposed Dosing Regimen(s)	TAF 25 mg oral tablets for pediatric patients aged 6 to <12 years old weighing ≥25 kg
Recommendation on Regulatory Action	Supplement 16: 6 to < 12 years: Approval Supplement 17: 12 to <18 years: Approval with updated Week 96 safety and efficacy data
Recommended Indication(s)/Population(s)	Pediatric patients with CHB aged 6 to <12 years old weighing ≥25 kg
Recommended Dosing Regimen	TAF 25 mg oral tablets for pediatric patients aged 6 to <18 years old weighing ≥25 kg
Cross-Reference	NDA 208464 (S-14) https://www.fda.gov/media/163107/download

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1. Benefit-Risk Integrated Assessment

The Agency's benefit-risk assessment is summarized below.

Benefit-Risk Integrated Assessment

VEMLIDY (tenofovir alafenamide, TAF) is approved for the treatment of chronic Hepatitis B (CHB) in adults and pediatric patients 12 years of age and older. Gilead Sciences, Inc, received an Approval Letter for the 12 to < 18 years of age group on October 17, 2002, based on Week 24 data from Trial GS-US-320-1092, hereafter referred to as Trial 1092. Gilead also received a Complete Response Letter (CRL) for the 6 to < 12 years of age group (Cohort 2, Group 1 from Trial 1092) because the Week 24 clinical data did not provide sufficient evidence that VEMLIDY was effective in this age group. To address this deficiency, efficacy data after longer-term treatment with VEMLIDY was needed. NDA 208464 (S-016) contains the safety and efficacy data through Week 96 to address the deficiencies identified in the CRL. Additionally, NDA 208464 (S-017) includes the Week 96 safety and efficacy data from the 12 to <18-year-old cohort.

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-1 infection in adults and children.

This Clinical Review summarizes the key Week 96 clinical safety and efficacy results from a pivotal pediatric trial evaluating the use of TAF for the treatment of CHB: 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 (CHB) Virus Infection',* which is an ongoing study conducted by Gilead Sciences.

Efficacy

The Week 96 efficacy data from Cohort 1 (pediatric subjects 12 to <18 years of age, henceforth referred to as "adolescents") continues to support the approval of VEMLIDY for the treatment of CHB in children 12 to < 18 years of age, previously approved based on Week 24 data. The Week 96 efficacy data (NDA 208464/S-16) from Cohort 2 Group 1 (corresponding to subjects 6 to <12 years of age) support the approval of VEMLIDY for the treatment of CHB in children 6 to < 12 years of age. Specifically, at Week 96, the proportion of subjects meeting the primary efficacy endpoint of viral suppression (defined as HBV DNA <20 IU/mL) was 50% for the VEMLIDY (TAF) treatment group, compared to 33% for the placebo-TAF treatment group. [Note, the placebo treatment group was switched to TAF treatment after Week 24]. The prior submission of Week 24 efficacy data (NDA 208464/S-14) did not support the extension of the VEMLIDY indication to include pediatric patients younger than 12 years of age because the proportion of subjects who achieved HBV DNA < 20 IU/mL was 8.3% in the VEMLIDY group compared to 0% in the placebo group.

For administrative purposes, the current submission (S-16) was split into two supplements to address each age group:
•Supplement 16: corresponding to longer-term (i.e., Week 96) safety, efficacy, and resistance data in participants 6 to <12 years of age (Cohort 2, Group 1)
•Supplement 17: corresponding to the longer-term (i.e., Week 96) safety and efficacy data for the Cohort 1 (adolescents).

Supplement 16 will be recommended for approval, and Supplement 17 further supports the previously approved Supplement 14 and is recommended for approval.

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 observed 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 96, 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 96-week period. There were two temporary drug interruptions due to AEs reported among adolescents and 1 drug interruption among children 6 to <12 years of age during the 96-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 96 safety data did not reveal any new or unexpected toxicities. The most commonly reported adverse reactions were headache and pyrexia.

Conclusion: benefit and risks assessment
In conclusion, based on the Week 96 data from this clinical trial, the benefit of TAF for the treatment of CHB in children 6 to <12 years of age outweighs the risks, supporting the approval of VEMLIDY for the treatment of CHB infection in children 6 to <12 years of age.

Benefit-Risk Dimensions

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Analysis of Condition</td><td>• 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 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>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, 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>
</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). TAF is a more recent treatment option for patients 12-years of age and older with a more favorable safety profile. However, younger pediatric patients continue to have limited treatment options that provide adequate efficacy with a more favorable safety profile.

The availability of another efficacious oral therapy with a more favorable safety profile for use in younger ages is highly desirable.</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<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>
<tr><td>Tenofovir alafenamide (TAF)</td><td>≥ 12 years of age</td><td>Longer plasma half-life
Better safety profile</td><td>• Not yet approved for younger ages</td></tr>
</table>
</td><td></td></tr>
<tr><td>Benefit</td><td>
• To address the deficiencies in the CRL the Applicant submitted Week 96 efficacy and safety results from a single, Phase 2, randomized, double-blind, placebo-controlled trial. The Week 96 data also support the long term safety and efficacy data in the previously approved 12 to < 18 age group.
• 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 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 with longer term treatment (i.e., Week 96), a significantly greater proportion of subjects in the TAF group of both Cohort 1 and in Cohort 2 Group 1 achieved the primary endpoint of HBV DNA <20 IU/mL at Week 96 compared with the placebo-TAF group.
<table>
<tr><th rowspan="2">HBV DNA <20 IU/mL at Week 96</th><th colspan="2">Cohort 1 (age 12 to <18)</th><th colspan="2">Cohort 2 Group 1 (age 6 to <12)</th></tr>
<tr><th>TAF 25mg (N=47)</th><th>PBO-TAF (N=23)</th><th>TAF 25mg (N=12)</th><th>PBO-TAF (N=6)</th></tr>
<tr><td>Response rate</td><td>30/47 (63.8%)</td><td>12/23 (52.2%)</td><td>6/12 (50%)</td><td>2/6 (33.3%)</td></tr>
<tr><td>95% CI for response rate</td><td>(48.5%, 77.3%)</td><td>(30.6%, 73.2%)</td><td>(21.1%, 78.9%)</td><td>(4.3%, 77.7%)</td></tr>
</table>
HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
95% CIs were calculated using the Clopper-Pearson method.
</td><td>Results from Week 96 demonstrate that TAF was efficacious in suppressing HBV in children 6 to <18 years. The viral suppression in both cohorts led to a higher proportion of subjects with ALT normalization, which is reflective of reduced hepatic inflammation.

The percentage of participants with HBV DNA < 20 IU/mL progressively increased in the TAF group through Week 96 and in the PBO-TAF group from Week 24 to Week 96, after switching to OL TAF (post Week 24), both overall and in the individual cohorts. The Week 96 results support that longer-term TAF treatment leads to HBV viral suppression in the 6 to <12 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 6 to <18 years of age would also lead to fewer complications later in life.</td></tr>
<tr><td>Risk and Risk Management</td><td>• At Week 96, 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 combination ARV treatment for HIV is approved for use in children.</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 significant decrease in BMD or renal toxicity were not observed in this study.

TAF demonstrated an overall favorable safety profile in this</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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; two serious adverse events were reported in the TAF-treatment group (scarlet fever in the double –blind phase and suicidal ideation in the OL phase) and both were unrelated to study drug. • No AEs led to study drug discontinuation or dropout • Three AEs (elevated LFTs, nausea, congenital odontogenic cyst) lead to brief treatment interruption with uncomplicated reinitiation.	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 6 to <12 years of age, weighing at lease 25kg, and who are able to swallow VEMLIDY 25-mg strength tablet. This supplemental new drug applications (sNDA, S-17 and S-16), submitted to the VEMLIDY NDA 208464, contain Week 96 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 pediatric patients aged 12 to <18 years with CHB has previously been established in sNDA 208464/S-14 (see section 2.6 for full submission and regulatory history).

The trial demonstrated that TAF is effective in reducing plasma HBV DNA through Week 96 in pediatric patients 6 to <12 years of age.

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. Without appropriate medical care and vaccinations, 90% of HBV-infected newborns will develop chronic HBV infection. {Health and Human Services (HHS) 2023}. 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.

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 of age. TDF, while highly efficacious, is associated with renal and bone toxicities. TAF has a better safety profile than former available options and was approved for children ≤ 12 years of age in October, 2022. Treatment options for younger pediatric patients are limited as stated above with concerns for rapid development of resistance or significant side effects. 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
Tenofovir alafenamide (TAF)	Vemlidy® (tablet)	25 mg tablet once daily	≥ 12 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 Box 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 Box Warning language. Additionally, TDF carries a (b) (4) 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 (b) (4).

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.

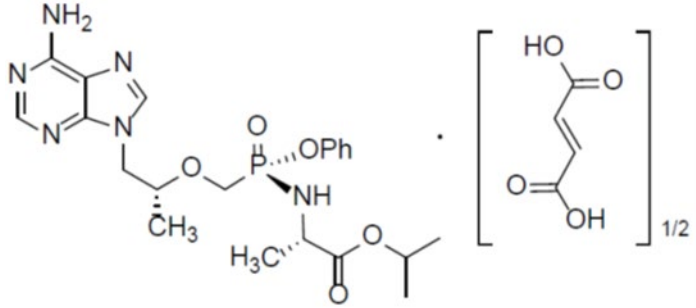
TAF is an oral prodrug of tenofovir (TFV). After absorption, TAF is slowly converted to TFV, which is metabolized intracellularly to the active metabolite, TFV diphosphate, a potent and selective inhibitor of both hepatitis B virus (HBV) polymerase and human immunodeficiency virus type-1 (HIV-1) reverse 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.

At the time of approval (November 10, 2016) of VEMLIDY (tenofovir alafenamide) 25mg tablets, the Agency issued PREA PMRs. 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. (b) (4) 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. On April 19, 2022 sNDA (208464, S-14) was submitted in response to fulfill PREA PMR 3130-1, and to partially address PMR 3130-2 (b) (4).

The current sNDA (208464, S-16/S-17), received on September 17, 2023, was submitted in response to partially address PMR 3130-2 (b) (4).

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 (b) (4) to 24 weeks, and the open-label extension phase was (b) (4) 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. This multidisciplinary 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.

For additional details, please refer to the detailed review by Dr. Takashi Komatsu for the virology considerations.

There is extensive and well characterized safety data with TAF use in pediatric HIV patients. The safety approach for this review is a high-level summary of common adverse events (AEs), serious adverse events (SAEs), death, and discontinuation (DC) as a pooled analysis of children aged 6 to <12 and adolescents aged 12 to <18. The key review issue for this submission relates to the long-term efficacy and safety data in children 6 to < 12 years of age and long-term safety data in adolescents. The 96 weeks submission results support the recommendation to expand the approval to include pediatric patients aged 6 to <12 years.

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

In this submission, no new clinical pharmacology data were submitted. The applicant made minor revision to the non-compartmental analysis (NCA) PK data in TFV exposure. In addition, the Applicant revised the population PK model. Only the revised PK results are included in this review.

Note that the relevant PK data have been previously reviewed in the 2022 review cycle (DARRTS Link) where it was concluded that pediatric CHB patients 6 years of age and older treated with VEMLIDY oral dosage of 25 mg once daily demonstrated no meaningful differences in TAF and TFV exposures, compared to those exposures reported in adult CHB patients receiving the approved VEMLIDY dosage.

5.1. Intensive (NCA) PK Assessment

The minor revision in the current NCA PK data, when compared with the data reviewed in the 2022 review cycle (AUCtau and Ctau were estimated by extrapolating the concentration at 8 hours post-dose), is that the applicant derived TFV AUCtau and Ctau values for the Cohort 1 and Cohort 2 Group 1 using pre next dose concentration. The TAF NCA PK parameters remain unchanged from the data reviewed in 2022. The steady-state exposures of TAF and TFV (revised data) following multiple-dose administration of TAF 25 mg once daily in the intensive PK set of Cohort 2 Group 1 (6 to <12 years of age and weighing at least 25 kg) are presented in Table 3. Mean TAF AUCtau and Cmax in Cohort 2 Group 1 were numerically higher than those in Cohort 1 and in CHB adults.

Table 3. TAF and TFV steady state PK parameters based on intensive PK in Cohort 2 Group 1 vs. in CHB adults and in Cohort 1

PK Parameters	Mean (CV%) Exposure based on Noncompartmental Analysis					
	Cohort 1 (n=13)		Cohort 2 Group 1 (n=5)		CHB Adults (n=8) (Reference)	
	TAF[a]	TFV[b]	TAF	TFV[c]	TAF	TFV
AUCtau (ng*h/mL)	254 (36.4)	244 (28.3)	313 (64.8)	272 (17.5)	270 (47.8)	400 (35.2)
C_{max} (ng/mL)	188 (45.0)	15 (23.5)	388 (96.9)	17 (19.6)	270 (63.3)	30 (20.8)
C_{tau} (ng/mL)	-	7.9 (35.0)	-	8.9 (10.2)	-	10 (39.6)

Source: PK data in CHB adult are from intensive PK analyses in Trials 108 and 110 CSRs
TFV PK data (AUCtau, Ctau) in the Cohort 1 and Cohort 2 Group 1 were derived using pre next dose concentration.

Reviewer Comments:
As the revised TFV PK data are very similar to those previously submitted, TAF PK profile remain unchanged. Therefore, there is no change in the conclusion of clinical pharmacology assessment; based on intensive PK results, there are no meaningful differences in TAF (AUCtau, Cmax) and TFV (AUCtau, Cmax, and Ctau) exposures from VEMLIDY in pediatric subjects of ≥ 6 to <12 years of age who received the 25 mg adult strength tablet compared to the respective exposures in CHB adult and adolescent patients receiving the same Vemlidy dosage.

5.2. Pharmacometrics Assessment

Pharmacometric analyses for Vemlidy was previously conducted by the Applicant to characterize TAF and TFV PK using PK data from pediatric subjects with HIV-1 and from pediatric subjects (including adolescents) with HBV infection. The model-predicted TAF and TFV exposures were compared to adults living with HIV-1 (reference population) (see Clinical Pharmacology review for Supplements 14 and 16 for full details (DARRTS Link).

In this submission, the Applicant revised the population PK model using only data in HBV infected participants (i.e., pediatric and adult subjects). Specifically, the Applicant utilized pre-existing PK data (only intensive), and no new PK data has been submitted. The final dataset for the revised population PK model included a total of 67 patients who contributed 609 and 1,120 PK samples for TAF and TFV, respectively. A summary of treatments, study populations, and intensive PK subjects is provided in Table 4.

Table 4. TAF/TFV PK Data for PopPK Model Development in CHB Subjects

Study	Study Desciption	Treatment	Population	Number of Participants
GS-US-320-1092	A Phase 2, randomized, double-blind evaluation of the PK, safety, and antiviral efficacy of TAF in pediatric participants with CHB virus infection	• Cohort 1: TAF 25 mg • Cohort 2 Group 1: TAF 25 mg	Pediatric participants: • Cohort 1: 12 to < 18 years old, ≥ 35 kg • Cohort 2 Group 1: 6 to < 12 years old, ≥ 25 kg	Cohort 1: N (total) = 47 N (IPK) = 13 Cohort 2 Group 1: N (total) = 12 N (IPK) = 5
GS-US-320-0101	A Phase 1b randomized, open-label, active-controlled study to assess the safety, viral kinetics, and antiviral activity of TAF in treatment-naive adults with CHB infection	TAF 8 mg TAF 25 mg TAF 40 mg TAF 120 mg	Adults	N (total) = 41 N (IPK) = 41
GS-US-320-0108	A Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF versus TDF for the treatment of HBeAg-negative, CHB infection in treatment-naive and treatment-experienced participants	TAF 25 mg	Adults	N (total) = 285 N (IPK) = 1
GS-US-320-0110	A Phase 3, randomized, double-blind study to evaluate the efficacy and safety of TAF versus TDF for the treatment of HbeAg-positive CHB infection in treatment naive and treatment-experienced participants	TAF 25 mg	Adults	N (total) = 581 N (IPK) = 7

CHB = chronic hepatitis B; HbeAg = hepatitis B e antigen; IPK = intensely sampled PK; PK = pharmacokinetic(s); PopPK = population PK; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir.

Source: Applicant's population PK report, Table 1, page 21

Reviewer comments:
While the new pharmacometric analyses in this submission incorporated only HBV subjects for modeling and simulation, there is currently no known literature describing the disease impact (i.e., HIV-1 vs. CHB) on TAF and TFV PK. Furthermore, the Applicant's analyses arrive at the same conclusions as the previous submission regarding exposures. In conclusion, the previous and current analyses support the 25 mg TAF QD dosing regimen in pediatric subjects of 6 to <12 years of age, weighing at least 25kg.

6. Clinical Virology

No treatment-emergent substitutions that have been previously associated with resistance to TAF were detected through 96 weeks of treatment in in adolescent participants or children with CHB in Study GS-US-320-1092. In summary, 24 of 88 (27%) adolescent participants and children with CHB qualified for resistance analysis. Please refer to Dr. Takashi Komatsu's Clinical Virology Review for full details

In Cohort 1, 17 participants (TAF: n=8; PBO−TAF, n=9) qualified for sequence analysis. Sequence analysis showed that a majority (9/13, 69%; n=4 and n=5 in the TAF and PBO-TAF group, respectively) of the participants had no sequence change from baseline. Sequence analysis failed for n=1 and n=3 in the TAF and PBO-TAF group, respectively. Three participants in the TAF group and 1 subject in the PBO-TAF group had treatment-emergent substitutions. These four participants in Cohort 1 qualified for phenotypic analysis due to virologic breakthrough (n=2) or conserved site change (n=2). Phenotypic analysis of the viruses conferred a <2-fold shift in susceptibility compared to baseline/wildtype samples. No HBV pol/RT amino acid substitutions that have been previously associated with resistance to TAF were detected through 96 weeks of treatment.

In Cohort 2 Group 1, 7 participants (TAF, n=4; PBO−TAF, n=3) qualified for sequence analysis. Sequence analysis showed that half (3/6, 50%; n=1 and n=2 in the TAF and PBO-TAF group, respectively) of participants had no sequence change from baseline. Sequence analysis failed for one participant in the TAF group. Two participants in the TAF group and 1 subject in the PBO-TAF group had treatment-emergent substitutions. One participant in PBO−TAF group qualified for phenotypic analysis due to a conserved site change. Phenotypic analysis of the virus conferred a <2-fold shift in susceptibility compared to baseline/wildtype samples. The other viruses having changes from baseline were not phenotyped as they did not satisfy the prespecified phenotypic analysis criteria (i.e., the participants did not experience a virologic breakthrough and the changes were at polymorphic sites observed in only 1 participant for each substitution). No HBV pol/RT amino acid substitutions that have been previously associated with resistance to TAF were detected through 96 weeks of treatment.

7. Clinical/Statistical – Efficacy

7.1 Study Design and Protocol Summary

Study GS-US-320-1092 is a randomized (2:1), placebo-controlled trial to evaluate TAF vs placebo for the treatment of CHB.

The primary study objectives were as follows:
Cohort 1 (adolescents 12 to < 18 years, ≥ 35 kg):

- To evaluate the safety, tolerability, and antiviral activity (hepatitis B virus [HBV] DNA < 20 IU/mL) of TAF 25 mg once daily versus switch to TAF from placebo at Week 24 in adolescent participants with chronic hepatitis B (CHB)

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

- Part A:
  - To evaluate the steady-state pharmacokinetics (PK) of TAF and TAF-metabolite, tenofovir (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

The secondary objectives of this study were as follows:

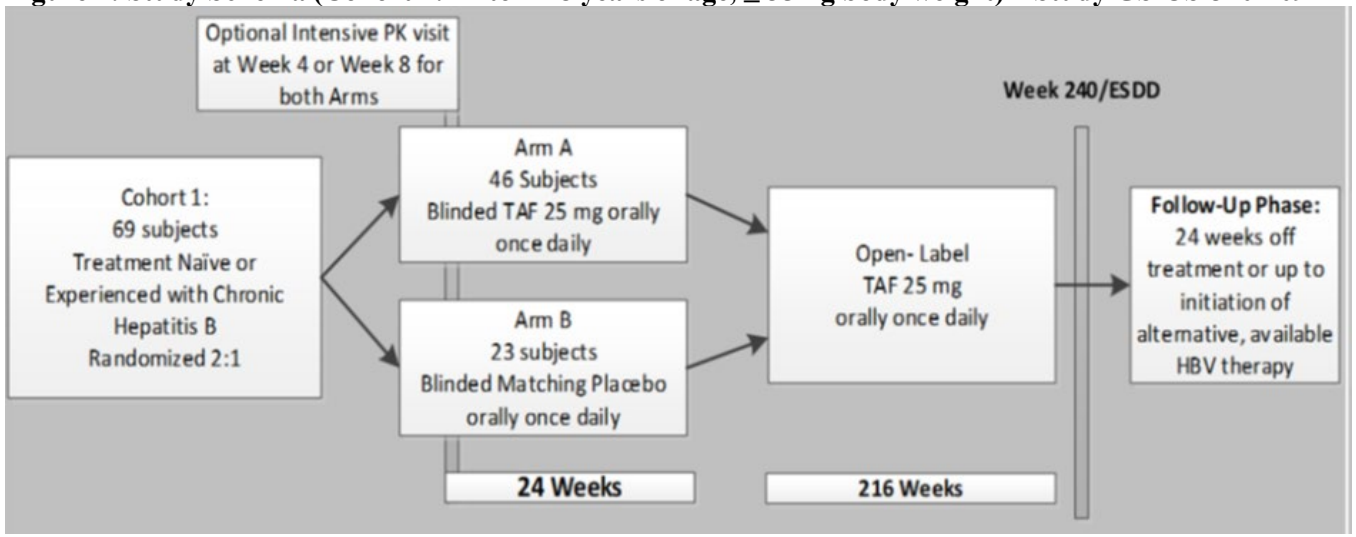
- To evaluate the open-label safety and tolerability of TAF given once daily at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the antiviral activity (HBV DNA < 20 IU/mL) of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the serologic response (loss of hepatitis B e antigen [HBeAg] and seroconversion to antibody against hepatitis B e antigen, and loss of hepatitis B surface antigen (HBsAg) and seroconversion to antibody against hepatitis B surface antigen [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 (alanine aminotransferase [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 formulation 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

The current submission of the supplemental NDA (Supplements 16 and 17) 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 96 visit or prematurely discontinued from the study. Following the initial double-blind treatment period of 24 weeks, all participants were eligible to roll over to receive open-label TAF for a total duration of study treatment of 240 weeks. A brief outline of Study GS-US-320-1092 is presented in Figures 1 and 2.

Of note, Study GS-US-320-1092 is designed to have a PBO arm through Week 24. After Week 24, subjects enrolled in the PBO arm were switched to open label (OL) TAF treatment. Therefore, the PBO treatment arm is referred to as PBO-TAF to indicate the switch to OL TAF after Week 24.

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 sub study 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 sub study, 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 post dose.

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

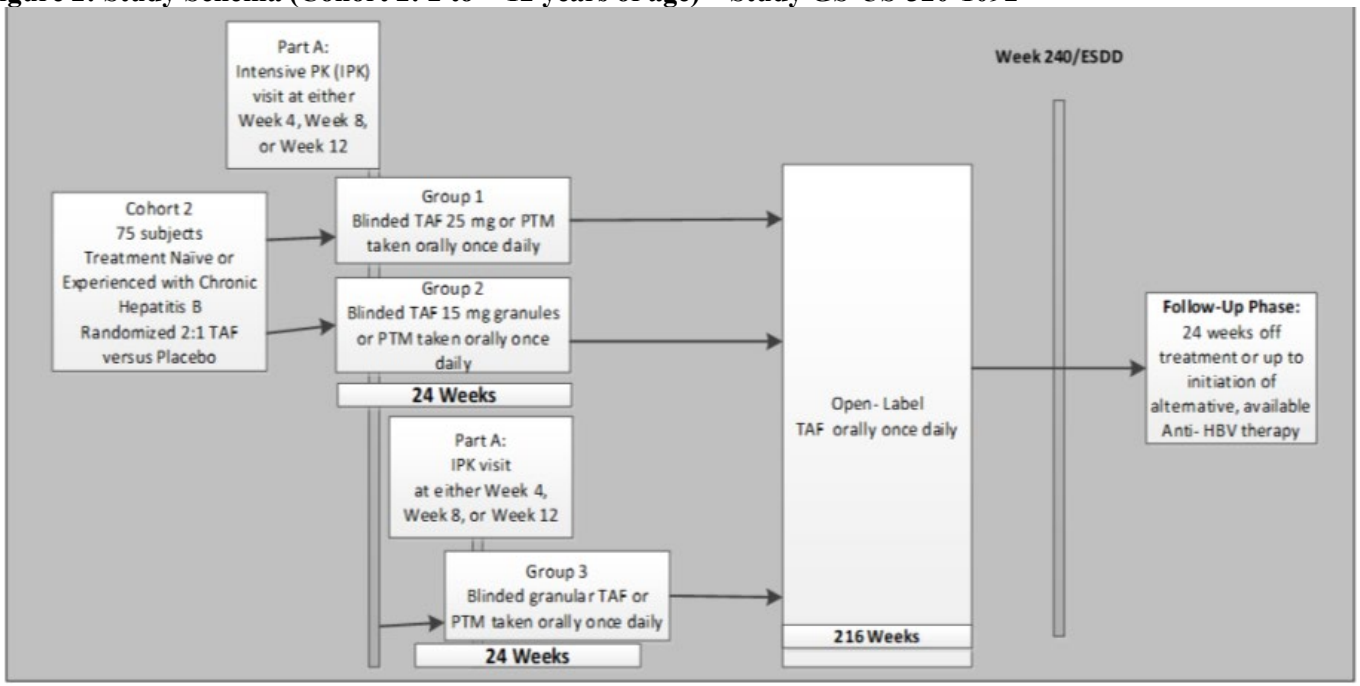


*Source: Applicant's Clinical Study Repo*rt Figure 1 page 33/624

Cohort 2:
At least 75 children were planned to be enrolled in Cohort 2 of the study. Cohort 2 was 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 were to be collected from participants in Part A to confirm the dose of TAF in each dose group and the remaining participants were planned to be enrolled into Part B once dose confirmation was achieved. Part A was 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 was 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 described in Table 5.

Table 5. 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 was 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.

7.2 Enrollment Criteria

7.2.1. Inclusion Criteria

Inclusion criteria for Cohort 1 and Cohort 2 Group 1 were as follows:
1) Males and nonpregnant, nonlactating females

2) Age at screening: 12 to < 18 years old (Cohort 1) and 6 to < 12 years old (Cohort 2 Group 1)
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)
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 analog) OR treatment-experienced participants (defined as participants meeting all entry criteria [including HBV DNA and serum ALT criteria] and > 12 weeks of OAV treatment with any oral nucleos(t)ide analog) were eligible for enrollment. All participants taking OAV treatment were required to 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 CLcr ≥ 80 mL/min/1.73 m2 (using the Schwartz formula; = k × L/sCR) (k = proportionality constant; L = height in centimeters; and sCR = serum creatinine [mg/dL])
10) Normal electrocardiogram (or if abnormal, determined by the investigator not to be clinically significant)
11) Had to be willing and able to comply with all study requirements

7.2.2. Exclusion Criteria

Exclusion criteria for the study were as follows:
1) Pregnant females, females who were breastfeeding or who believed they may wish to become pregnant during the course of the study
2) Males and females of reproductive potential who were unwilling to use an "effective," protocol-specified method(s) of contraception during the study, as specified in Appendix 5 of the study protocol (Appendix 16.1.1).
3) Coinfection with hepatitis C virus (HCV), HIV, or hepatitis delta virus (HDV)
4) Evidence of HCC (Note: if screening alpha fetoprotein [AFP] is ≤ 50 ng/mL no imaging study was needed; however, if the screening AFP is > 50 ng/mL an imaging study was 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/mm3
    d) Aspartate aminotransferase (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 > 1.5 × ULN (unless on stable anticoagulant regimen)
7) Chronic liver disease of non-HBV etiology (eg, hemochromatosis, alpha-1 antitrypsin deficiency, cholangitis)
8) Has received a 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. Participants under evaluation for possible malignancy were 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 participant compliance
14) Participants on prohibited concomitant medications (Section 5.4 of the protocol [Appendix 16.1.1]). Participants on prohibited medications, otherwise eligible, were required to undergo 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 participant unsuitable for the study or unable to comply with dosing requirements.

7.3 Study Endpoints and Analyses

Primary Efficacy Endpoint and Analyses
The primary efficacy endpoint was the percentage of subjects with plasma HBV DNA < 20 IU/mL at Week 24. The superiority of TAF over placebo for the primary efficacy endpoint was tested using stratified Cochran-Mantel-Haenszel (CMH) method adjusted for age at baseline. A Missing=Failure approach was employed wherein all missing data were treated as not achieving the primary endpoint. The Full Analysis Set (FAS), defined as all randomized subjects who receive at least one dose of study drug, was used for the primary efficacy analysis. Subjects were analyzed according to the randomized treatment assignment.

Key Secondary Efficacy Endpoints and Analyses

The key secondary efficacy endpoints were as follows:

- The percentage of subjects with plasma HBV DNA < 20 IU/mL at Weeks 48 and 96
- The change from baseline in HBV DNA (log10 IU/mL) at Weeks 24, 48, and 96
- The percentage of subjects with ALT normalization at Weeks 24, 48, and 96
- ALT (U/L) change from baseline at Weeks 24, 48, and 96
- The percentage of subjects with HBeAg loss and seroconversion to anti-HBe at Weeks 24, 48, and 96 (HBeAg-positive subjects only)
- The percentage of subjects with HBsAg loss and seroconversion to anti-HBs at Weeks 24, 48, and 96

The analyses for the secondary efficacy endpoints were conducted using the FAS, unless otherwise specified. Specifically, for endpoints including ALT normalization, the subset of subjects in the FAS with baseline abnormal ALT were used, for HBeAg loss and HBeAg seroconversion, the Serologically Evaluable FAS for HBeAg Loss/Seroconversion were used, and for HBsAg loss and HBsAg seroconversion, the Serologically

Evaluable FAS for HBsAg Loss/Seroconversion were used. Only descriptive analyses were conducted for these secondary efficacy endpoints. Categorical secondary efficacy endpoints were summarized by number and percentage of subjects that met the endpoint. In addition, log10 HBV DNA (IU/mL), ALT (U/L), and corresponding change from baseline values, were summarized by visit using observed data.

7.4 Disposition

Overall, 161 participants were screened for this study; 88 were randomized (Cohort 1: TAF 47 participants, PBO 23 participants; Cohort 2 Group 1: TAF 12 participants, PBO 6 participants). All 88 randomized participants completed the DB study treatment and entered the OL phase. A total of 9.1% (8/88 participants) prematurely discontinued open-label (OL) TAF (Cohort 1: TAF 10.6% [5/47 participants], PBO-TAF: 8.7% [2/23 participants]; and Cohort 2 Group 1: TAF 8.3% [1/12 participants]). The most common reasons for premature discontinuation of OL TAF were withdrawal of consent (Cohort 1: TAF 4.3% [2/47 participants], PBO-TAF: 4.3% [1/23 participants]) and non-compliance with study drug (Cohort 1 PBO-TAF: 4.3% [1/23 participants], Cohort 2 Group 1: TAF 8.3% [1/12 participant]).

At the time of data cutoff for this report, 20.5% (18/88) participants completed OL TAF treatment and 70.5% (62/88) participants remained on the OL TAF treatment; 21.6% (19/88) participants completed the study (including 1 participant in Cohort 1 TAF group who had HBsAg seroconversion) and 69.3% (61/88) participants were still ongoing.

Table 6. Disposition of Participants (All Screened Participants)

	Cohort 1		Cohort 2 Group 1		Total		Overall
	TAF	PBO-TAF	TAF	PBO-TAF	TAF	PBO-TAF	
Screened	—	—	—	—	—	—	161
Screen failure participants who were not randomized	—	—	—	—	—	—	73
Participants who met all eligibility criteria and were not randomized	—	—	—	—	—	—	3
Covid-19 resulted in temporary halt of enrollment	—	—	—	—	—	—	1
Withdrew consent	—	—	—	—	—	—	2
Randomized Analysis Set	47	23	12	6	59	29	88
Safety Analysis Set	47	23	12	6	59	29	88
Full Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)

Open-label Safety Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Double blind phase							
Completed DB drug	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Open-label phase							
Entered OL phase	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Completed OL drug	12 (25.5%)	6 (26.1%)	0	0	12 (20.3%)	6 (20.7%)	18 (20.5%)
Continuing	30 (63.8%)	15 (65.2%)	11 (91.7%)	6 (100.0%)	41 (69.5%)	21 (72.4%)	62 (70.5%)
Prematurely discontinued	5 (10.6%)	2 (8.7%)	1 (8.3%)	0	6 (10.2%)	2 (6.9%)	8 (9.1%)
Reason for premature discontinuation of OL drug							
Investigator's discretion	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Lack of efficacy	0	0	0	0	0	0	0
Lost to follow-up	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Non-compliance with study drug	0	1 (4.3%)	1 (8.3%)	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Seroconversion	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Participant decision	2 (4.3%)	1 (4.3%)	0	0	2 (3.4%)	1 (3.4%)	3 (3.4%)
Study completion							
Completed study	13 (27.7%)	6 (26.1%)	0	0	13 (22.0%)	6 (20.7%)	19 (21.6%)

Continuing	30 (63.8%)	14 (60.9%)	11 (91.7%)	6 (100.0%)	41 (69.5%)	20 (69.0%)	61 (69.3%)
Prematurely discontinued	4 (8.5%)	3 (13.0%)	1 (8.3%)	0	5 (8.5%)	3 (10.3%)	8 (9.1%)
Reason for premature discontinuation of study							
Adverse event	0	1 (4.3%)	0	0	0	1 (3.4%)	1 (1.1%)
Investigator's discretion	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Lost to follow-	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Non-compliance with study drug	0	1 (4.3%)	1 (8.3%)	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Withdrew consent	2 (4.3%)	1 (4.3%)	0	0	2 (3.4%)	1 (3.4%)	3 (3.4%)T

COVID-19 = coronavirus disease 2019; DB = double blind; eCRF = electronic case report form; FU = follow-up; OL = open label; PBO = placebo; TAF = tenofovir alafenamide

Denominator for percentages was the Safety Analysis Set.

a One participant in Cohort 1 PBO-TAF group completed OL TAF and completed the study per protocol. The site did not complete the 'Study completion' and AE pages page correctly and hence the participant is shown as discontinued the study prior to completion for post-treatment ALT flare.

b One participant in Cohort 1 PBO-TAF group completed OL TAF (b) (6) and completed study; OL study drug completion eCRF is missing.

Two participants from Cohort 1 TAF group have no last OL dose date or OL study drug completion form; but completed study.

Two participants from Cohort 1 TAF group completed OL TAF; ongoing in FU phase [have not completed study].

Source: Applicant's Clinical Study Report Table 4

7.5 Baseline Demographics

Table 7 summarizes subject demographics and baseline characteristics. They are generally balanced in both treatment groups. The median age was 15 years in both TAF and PBO groups in Cohort 1, and 10 years in the TAF group and 8 years in the PBO group in Cohort 2. The majority of participants were male (58%) and Asian (65.9%); 25% were White and 5.7% of the participants were Black or African American. The median weight for subjects in Cohort 1 was 54.6 kg for the TAF group and 55.8 kg for the PBO group; for subjects in Cohort 2 Group 1, the median weight was 37.1 kg for the TAF group and 32.2 kg for the PBO group. The median BMI for subjects in Cohort 1 was 20.4 kg/m^2 for the TAF group and 20.3 kg/m^2 in the PBO group, and for subjects in Cohort 2 Group 1, median BMI was 18.2 kg/m^2 for the TAF group and 16.4 kg/m^2 for the PBO group.

Table 8 summarizes baseline disease characteristics. Baseline disease characteristics were similar for the 2 treatment groups. In Cohort 1, the median baseline HBV DNA value was 7.9 log10 IU/mL for the TAF group and 8.1 log10 IU/mL for the PBO group. In Cohort 2, the median baseline HBV DNA value was 8.0 log10 IU/mL for the TAF group and 8.3 log10 IU/mL for the PBO group. Median (Q1, Q3)HBsAg (log10 IU/mL) for Cohort 1 TAF 4.5 (4.2, 4.9) and PBO-TAF 4.6 (4.2, 5.1); Cohort 2, Group 1 TAF 4.5 (4.3, 4.9) and PBO-TAF 4.7 (4.7, 5.1).

For HBV genotype at baseline, Genotype D was the most common (43.9%), followed by Genotype C (24.4%) and Genotype B (23.2%). The majority of participants (98.9%) were HBeAg-positive at baseline, and 100% of participants were HBsAg-positive.

About 64.8% (57/88 participants) had baseline ALT > 1.5 × ULN based on central laboratory criteria, and the median baseline eGFR by the Schwartz formula was 153.5 mL/min/1.73 m^2 (all participants met these criteria during the screening visit). Overall, 71.6% (63/88 participants) had no previous hepatitis B medication, with 78.4% (69/88 participants) naive to prior oral anti-viral treatment. Participants who had received prior HBV treatment were primarily treated with IFN-α and/or lamivudine.

Table 7. Demographic and Baseline Characteristics (Full Analysis Set)

	Cohort 1		Cohort 2 Group 1		Total		Overall (N = 88)
	TAF (N = 47)	PBO-TAF (N = 23)	TAF (N =12)	PBO-TAF (N = 6)	TAF (N =59)	PBO-TAF (N = 29)	
Age (years)							
N	47	23	12	6	59	29	88
Mean (SD)	15 (1.9)	15 (1.5)	10 (1.3)	8 (0.8)	14 (2.7)	13 (3.0)	14 (2.8)
Median	15	15	10	8	14	14	14
Q1, Q3	13, 17	14, 16	10, 11	8, 9	12, 16	12, 16	12, 16
Min, max	12, 17	12, 17	7, 11	7, 9	7, 17	7, 17	7, 17
Sex at birth							
Female	20 (42.6%)	7 (30.4%)	5 (41.7%)	5 (83.3%)	25 (42.4%)	12 (41.4%)	37 (42.0%)
Male	27 (57.4%)	16 (69.6%)	7 (58.3%)	1 (16.7%)	34 (57.6%)	17 (58.6%)	51 (58.0%)
Race							
Asian	33 (70.2%)	18 (78.3%)	4 (33.3%)	3 (50.0%)	37 (62.7%)	21 (72.4%)	58 (65.9%)
Black or African American	2 (4.3%)	2 (8.7%)	1 (8.3%)	0	3 (5.1%)	2 (6.9%)	5 (5.7%)

Native Hawaiian Or Other Pacific Islander	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
White	9 (19.1%)	3 (13.0%)	7 (58.3%)	3 (50.0%)	16 (27.1%)	6 (20.7%)	22 (25.0%)
Other	2 (4.3%)	0	0	0	2 (3.4%)	0	2 (2.3%)
Ethnicity							
Hispanic or Latino	2 (4.3%)	0	0	0	2 (3.4%)	0	2 (2.3%)
Not Hispanic or Latino	44 (93.6%)	22 (95.7%)	12 (100.0%)	6 (100.0%)	56 (94.9%)	28 (96.6%)	84 (95.5%)
Not permitted	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Region							
Asia	17 (36.2%)	11 (47.8%)	1 (8.3%)	2 (33.3%)	18 (30.5%)	13 (44.8%)	31 (35.2%)
Europe or North America	30 (63.8%)	12 (52.2%)	11 (91.7%)	4 (66.7%)	41 (69.5%)	16 (55.2%)	57 (64.8%)
Weight (kg)							
N	47	23	12	6	59	29	88
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)	50.9 (12.86)
Median	54.6	55.8	37.1	32.2	52.2	52.0	52.1
Q1, Q3	46.2, 61.1	50.4, 64.3	30.7, 43.7	25.6, 34.5	42.1, 57.5	36.5, 59.5	41.8, 59.0
Min, max	36.3, 87.5	35.0, 78.5	29.0, 54.1	24.0, 36.5	29.0, 87.5	24.0, 78.5	24.0, 87.5
Height (cm)							
N	47	23	12	6	59	29	88
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)	158.0 (13.25)
Median	160.5	166.5	140.2	136.4	156.4	161.3	159.9
Q1, Q3	153.4, 171.1	159.9, 172.0	135.5, 148.6	133.0, 141.0	150.5, 169.0	147.5, 170.5	148.7, 169.5
Min, max	143.0, 183.0	144.8, 179.5	125.0, 155.0	130.0, 144.0	125.0, 183.0	130.0, 179.5	125.0, 183.0
Body mass index (kg/m^2)							
N	47	23	12	6	59	29	88
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)	20.0 (2.93)
Median	20.4	20.3	18.2	16.4	20.1	19.7	20.0

Q1, Q3	18.7, 22.1	19.7, 22.1	16.6, 21.0	15.1, 17.4	18.0, 21.8	17.3, 21.4	17.8, 21.7
Min, max	15.5, 29.4	16.0, 27.3	15.8, 24.3	13.6, 19.7	15.5, 29.4	13.6, 27.3	13.6, 29.4

PBO = placebo; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide
Denominator for percentages was the number of participants in the Safety Analysis Set.
P values were based on 2-sided Wilcoxon rank-sum test for continuous data or Cochran-Mantel-Haenszel test for categorical data.
P value for race used the categories: Asian and non-Asian.
Body mass index (kg/m2) = (Weight [kg]/Height [cm]2) X 10,000.
Age (in years) was calculated from the date of the first dose of study drug.
Source: Applicant's Clinical Study Report Table 6

Table 8. Baseline Disease Characteristics (Full Analysis Set)

	Cohort 1		**Cohort 2 Group 1**		**Total**		**Overall (N = 88)**
	TAF (N = 47)	**PBO-TAF (N = 23)**	**TAF (N = 12)**	**PBO-TAF (N = 6)**	**TAF (N = 59)**	**PBO-TAF (N = 29)**	
HBV DNA (log_{10} IU/mL)							
N	47	23	12	6	59	29	88
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)	8.0 (1.01)
Median	8.1	8.3	8.1	8.3	8.1	8.3	8.1
Q1, Q3	7.4, 8.6	7.6, 8.6	7.9, 8.6	8.1, 8.5	7.7, 8.6	7.9, 8.6	7.8, 8.6
Min, max	2.5, 9.2	5.4, 9.2	5.0, 9.2	7.8, 8.6	2.5, 9.2	5.4, 9.2	2.5, 9.2
HBV DNA (log_{10} IU/mL) category							
< 8 log_{10} IU/mL	17 (36.2%)	7 (30.4%)	3 (25.0%)	1 (16.7%)	20 (33.9%)	8 (27.6%)	28 (31.8%)
≥ 8 log_{10} IU/mL	30 (63.8%)	16 (69.6%)	9 (75.0%)	5 (83.3%)	39 (66.1%)	21 (72.4%)	60 (68.2%)
HBsAg (log_{10} IU/mL)							
N	47	23	12	6	59	29	88
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)	4.5 (0.57)
Median	4.5	4.6	4.5	4.7	4.5	4.7	4.5
Q1, Q3	4.2, 4.9	4.2, 5.1	4.3, 4.9	4.7, 5.1	4.2, 4.9	4.4, 5.1	4.2, 4.9

Min, max	3.3, 5.1	2.9, 5.1	2.0, 5.1	3.8, 5.1	2.0, 5.1	2.9, 5.1	2.0, 5.1
HBeAg status							
Negative	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Positive	46 (97.9%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	58 (98.3%)	29 (100.0%)	87 (98.9%)
HBeAb status							
Positive	1/1 (100.0%)	0	0	0	1/1 (100.0%)	0	1/1 (100.0%)
Years positive for HBV							
N	47	23	12	6	59	29	88
Mean (SD)	7 (5.4)	6 (5.1)	6 (3.9)	5 (3.3)	7 (5.1)	6 (4.7)	7 (5.0)
Median	7	4	6	7	6	5	6
Q1, Q3	2, 13	1, 10	2, 10	1, 7	2, 12	1, 8	2, 11
Min, max	1, 18	1, 15	1, 12	1, 8	1, 18	1, 15	1, 18
HBV genotype							
Genotype A	4 (9.3%)	1 (4.8%)	1 (8.3%)	0	5 (9.1%)	1 (3.7%)	6 (7.3%)
Genotype B	10 (23.3%)	5 (23.8%)	3 (25.0%)	1 (16.7%)	13 (23.6%)	6 (22.2%)	19 (23.2%)
Genotype C	11 (25.6%)	7 (33.3%)	1 (8.3%)	1 (16.7%)	12 (21.8%)	8 (29.6%)	20 (24.4%)
Genotype D	17 (39.5%)	8 (38.1%)	7 (58.3%)	4 (66.7%)	24 (43.6%)	12 (44.4%)	36 (43.9%)
Mixed genotype detected	1 (2.3%)	0	0	0	1 (1.8%)	0	1 (1.2%)
ALT (U/L)							
N	47	23	12	6	59	29	88
Mean (SD)	112 (134.4)	110 (110.5)	85 (69.0)	96 (94.0)	106 (123.9)	107 (105.9)	107 (117.6)
Median	68	76	59	60	65	66	66
Q1, Q3	50, 109	56, 91	46, 112	50, 75	50, 109	54, 89	52, 103
Min, max	19, 793	20, 502	22, 274	43, 286	19, 793	20, 502	19, 793

ALT level based on central laboratory range

≤ 1.5 × ULN	18 (38.3%)	5 (21.7%)	6 (50.0%)	2 (33.3%)	24 (40.7%)	7 (24.1%)	31 (35.2%)
> 1.5 × ULN to −5 × ULN	23 (48.9%)	15 (65.2%)	5 (41.7%)	3 (50.0%)	28 (47.5%)	18 (62.1%)	46 (52.3%)
> 5 × ULN to −10 × ULN	4 (8.5%)	2 (8.7%)	1 (8.3%)	1 (16.7%)	5 (8.5%)	3 (10.3%)	8 (9.1%)
> 10 × ULN	2 (4.3%)	1 (4.3%)	0	0	2 (3.4%)	1 (3.4%)	3 (3.4%)
ALT level based on AASLD range							
≤ 1.5 × ULN	8 (17.0%)	2 (8.7%)	3 (25.0%)	1 (16.7%)	11 (18.6%)	3 (10.3%)	14 (15.9%)
> 1.5 × ULN to −5 × ULN	32 (68.1%)	17 (73.9%)	8 (66.7%)	4 (66.7%)	40 (67.8%)	21 (72.4%)	61 (69.3%)
> 5 × ULN to −10 × ULN	3 (6.4%)	2 (8.7%)	1 (8.3%)	1 (16.7%)	4 (6.8%)	3 (10.3%)	7 (8.0%)
> 10 × ULN	4 (8.5%)	2 (8.7%)	0	0	4 (6.8%)	2 (6.9%)	6 (6.8%)
Baseline fibrosis score group							
0.00 to 0.48	43 (95.6%)	21 (95.5%)	11 (91.7%)	6 (100.0%)	54 (94.7%)	27 (96.4%)	81 (95.3%)
0.49 to 0.74	2 (4.4%)	1 (4.5%)	1 (8.3%)	0	3 (5.3%)	1 (3.6%)	4 (4.7%)
Previous hepatitis B medication exposure							
No	32 (68.1%)	20 (87.0%)	7 (58.3%)	4 (66.7%)	39 (66.1%)	24 (82.8%)	63 (71.6%)
Yes	15 (31.9%)	3 (13.0%)	5 (41.7%)	2 (33.3%)	20 (33.9%)	5 (17.2%)	25 (28.4%)
Previous oral antiviral treatment status							
Treatment experienced	11 (23.4%)	3 (13.0%)	3 (25.0%)	2 (33.3%)	14 (23.7%)	5 (17.2%)	19 (21.6%)
Treatment naive	36 (76.6%)	20 (87.0%)	9 (75.0%)	4 (66.7%)	45 (76.3%)	24 (82.8%)	69 (78.4%)
Corrected BMD for spine (g/cm^2)							
N	42	21	12	6	54	27	81
Mean (SD)	1.0 (0.17)	1.0 (0.17)	0.7 (0.13)	0.7 (0.10)	0.9 (0.19)	0.9 (0.19)	0.9 (0.19)
Median	1.0	1.0	0.7	0.7	0.9	0.9	0.9
Q1, Q3	0.8, 1.1	0.9, 1.0	0.7, 0.8	0.7, 0.8	0.8, 1.1	0.8, 1.0	0.8, 1.1
Min, max	0.6, 1.3	0.6, 1.4	0.5, 1.0	0.6, 0.9	0.5, 1.3	0.6, 1.4	0.5, 1.4

Corrected BMD for whole body (g/cm^2)							
N	44	21	12	6	56	27	83
Mean (SD)	0.9 (0.10)	0.9 (0.12)	0.7 (0.07)	0.7 (0.07)	0.9 (0.12)	0.9 (0.15)	0.9 (0.13)
Median	0.9	0.9	0.7	0.7	0.9	0.9	0.9
Q1, Q3	0.8, 1.0	0.9, 1.0	0.7, 0.7	0.6, 0.7	0.8, 1.0	0.8, 1.0	0.8, 1.0
Min, max	0.7, 1.1	0.7, 1.2	0.6, 0.9	0.6, 0.8	0.6, 1.1	0.6, 1.2	0.6, 1.2
Corrected Z-scores for spine							
N	42	21	12	6	54	27	81
Mean (SD)	−0.2 (1.01)	0.0 (1.18)	0.2 (1.08)	0.7 (0.93)	−0.1 (1.02)	0.1 (1.15)	0.0 (1.06)
Median	−0.3	−0.2	0.4	0.5	−0.2	−0.1	−0.1
Q1, Q3	−0.7, 0.6	−0.7, 0.3	−0.6, 0.8	−0.1, 1.3	−0.7, 0.7	−0.7, 1.0	−0.7, 0.7
Min, max	−2.6, 1.6	−1.5, 3.3	−1.6, 1.8	−0.3, 2.0	−2.6, 1.8	−1.5, 3.3	−2.6, 3.3
Corrected Z-scores for whole body							
N	44	21	11	5	55	26	81
Mean (SD)	−0.4 (0.82)	−0.3 (1.04)	−0.2 (1.03)	0.4 (1.41)	−0.3 (0.86)	−0.2 (1.13)	−0.3 (0.95)
Median	−0.4	−0.6	−0.3	0.8	−0.3	−0.6	−0.4
Q1, Q3	−0.8, 0.1	−1.1, 0.6	−1.0, 0.5	−0.7, 1.3	−0.8, 0.2	−1.1, 0.6	−0.8, 0.4
Min, max	−2.4, 1.4	−2.3, 1.8	−2.2, 1.4	−1.3, 2.1	−2.4, 1.4	−2.3, 2.1	−2.4, 2.1
Estimated GFR by the Schwartz formula (mL/min/1.73 m^2)							
N	47	23	12	6	59	29	88
Mean (SD)	154.8 (30.37)	157.5 (32.49)	154.6 (21.10)	167.0 (24.67)	154.8 (28.57)	159.4 (30.88)	156.3 (29.26)
Median	154.0	145.0	153.5	173.0	154.0	149.0	153.5
Q1, Q3	137.0, 169.0	142.0, 175.0	142.0, 168.5	152.0, 189.0	137.0, 169.0	143.0, 180.0	138.0, 170.5

Min, max	85.0, 270.0	119.0, 254.0	122.0, 193.0	126.0, 189.0	85.0, 270.0	119.0, 254.0	85.0, 270.0
Fasting serum creatinine (mg/dL)							
N	47	21	12	6	59	27	86
Mean (SD)	0.7 (0.13)	0.7 (0.15)	0.5 (0.09)	0.5 (0.07)	0.6 (0.14)	0.7 (0.17)	0.7 (0.15)
Median	0.7	0.7	0.5	0.4	0.6	0.6	0.6
Q1, Q3	0.6, 0.8	0.6, 0.8	0.4, 0.6	0.4, 0.5	0.5, 0.8	0.5, 0.8	0.5, 0.8
Min, max	0.4, 1.0	0.4, 1.0	0.4, 0.7	0.4, 0.6	0.4, 1.0	0.4, 1.0	0.4, 1.0
Baseline proteinuria toxicity grade							
Grade 0	43 (91.5%)	15 (65.2%)	12 (100.0%)	6 (100.0%)	55 (93.2%)	21 (72.4%)	76 (86.4%)
Grade 1	3 (6.4%)	8 (34.8%)	0	0	3 (5.1%)	8 (27.6%)	11 (12.5%)
Grade 2	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)

AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; BMD = bone mineral density; DNA = deoxyribonucleic acid; GFR = glomerular filtration rate; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; N/A = not applicable; PBO = placebo; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide; ULN = upper limit of normal; vs = versus
P values were based on 2-sided Wilcoxon rank-sum test for continuous data or Cochran-Mantel-Haenszel test for categorical data.
The ALT ULN for the central laboratory was defined as 34 U/L for females aged 2 or older or males aged 1 to 9 years old and 43 U/L for males aged older than 9 years old. The ULN for the AASLD was defined as 30 U/L for pediatric participants.
Participants with genotype undetermined were not included in the analysis.
Bone mineral density measurements and corresponding Z-scores were corrected for longitudinal changes in the scanner calibration. The HBeAb was a reflex test performed if HBeAg was negative.
Source: Applicant's Clinical Study Report Table 7

7.6 Results Primary Efficacy Analysis

Primary Efficacy Endpoint Analysis Result

The primary endpoint, proportion of subjects with HBV DNA < 20 IU/mL at Week 24, was reviewed in detail and presented in the sNDA review (NDA 20846/S-14). The Week 24 data supported the approval in adolescents. The results showed that 21.3% of the subjects in the VEMLIDY arm achieved HBV DNA <20 IU/mL versus 0% in the placebo arm in this age cohort (treatment difference and 95% CI: 21.3% (6.3%, 36.2; p=0.0199)). However, Week 24 efficacy data did not support the extension of the VEMLIDY indication to include pediatric patients 6 to less than12 years of age because the proportion of subjects who achieved HBV DNA < 20 IU/mL was 8.3% in the VEMLIDY group compared to 0% in the placebo group (treatment difference and 95% CI: 8.3% (-19.8, 36.5%)).

Gilead received a Complete Response Letter (CRL) for the 6 to < 12 years of age group (Cohort 2, Group 1) because the Week 24 clinical data did not provide sufficient evidence that VEMLIDY was effective in this age group. To address this deficiency, efficacy data after longer-term treatment with VEMLIDY was needed. Gilead submitted the efficacy data through Week 96 to address the deficiencies identified in the CRL together with longer-term treatment data from the 12 to <18-year-old cohort. These data are summarized in Section 7.7.

7.7 Results of Secondary, Exploratory and Key Subgroup Analyses

Percentage of Participants With HBV DNA < 20 IU/mL

Table 9 summarizes the percentage of participants with HBV DNA < 20 IU/mL by visit. The overall percentage of participants with HBV DNA < 20 IU/mL progressively increased for both groups. These data support the approval for the 6 to < 12 years of age cohort and support the longer term (Week 96) efficacy in adolescents. Of note, during the first 24 weeks of treatment (i.e., double-blind) phase, subjects in the PBO arm received placebo. During the open label (OL) phase (i.e., after Week 24), participants who received placebo during the double-blind (DB) phase initiated TAF treatment, hence referred to as the PBO-TAF treatment group. Therefore, both the TAF and PBO-TAF treatment arms received TAF during the OL phase.

In Cohort 2 Group 1, the percentage of participants with HBV DNA < 20 IU/mL in the TAF group increased from 8.3% at Week 24 to 50.0% at Week 96 and in the PBO-TAF group it increased from 0% at Week 24 to 33.3% at Week 96. These results indicate that participants in this age group may take a relatively longer time to achieve the similar response rate compared to adolescent cohort. In addition, the Week 96 response rate was numerically much higher than that in the PBO-TAF group at Week 24 and it is generally unlikely that these participants will have improvement if left untreated.

In Cohort 1, the percentage of participants with HBV DNA < 20 IU/mL in the TAF group increased from from 21.3% at Week 24 to 63.8% at Week 96 and in the PBO-TAF group it increased from 0% at Week 24 to 52.2% at Week 96.

The percentage of participants with HBV DNA < 20 IU/mL is relatively lower in the Cohort 2 Group 1 compared to Cohort 1 at each corresponding timepoint. A few baseline factors were identified as the potential reasons to explain this difference.

- Genotype D: Cohort 1 (TAF 39.5%, PBO 38.1%), Cohort 2 Group 1 (TAF 58.3%, PBO 66.7%)
- HBV DNA ≥ 8 log10 IU/mL: Cohort 1 (TAF 63.8%, PBO 69.6%), Cohort 2 Group 1 (TAF 75.0%, PBO 83.3%)
- ALT: Median: Cohort 1 (TAF 68 U/L, PBO 76 U/L), Cohort 2 Group 1 (TAF 59 U/L, PBO 60 U/L)

Table 9. Percentage of Participants With HBV DNA < 20 IU/mL By Visit (Missing = Failure) (Full Analysis Set)

	Cohort 1		Cohort 2 Group 1	
	TAF (N = 47)	**PBO-TAF (N = 23)**	**TAF (N = 12)**	**PBO-TAF (N = 6)**
HBV DNA at Week 24				
< 20 IU/mL	10/47 (21.3%)	0/23	1/12 (8.3%)	0/6
95% CI	(10.7%, 35.7%)	(0.0%, 14.8%)	(0.2%, 38.5%)	(0.0%, 45.9%)
HBV DNA at Week 48				
< 20 IU/mL	19/47 (40.4%)	5/23 (21.7%)	3/12 (25.0%)	1/6 (16.7%)
95% CI	(26.4%, 55.7%)	(7.5%, 43.7%)	(5.5%, 57.2%)	(0.4% to 64.1%)
HBV DNA at Week 96				
< 20 IU/mL	30/47 (63.8%)	12/23 (52.2%)	6/12 (50.0%)	2/6 (33.3%)
95% CI	(48.5%, 77.3%)	(30.6%, 73.2%)	(21.1%, 78.9%)	(4.3%, 77.7%)

Source: Reviewer's Analysis

Table 10 summarizes the change from baseline in HBV DNA (log10 IU/mL) by visit. HBV DNA decreased continually from baseline over time for the TAF group. Decreases from baseline in HBV DNA in the PBO group was observed once subjects were switched to OL TAF.

Table 10. Change From Baseline in HBV DNA (log10 IU/mL) by Visit (Full Analysis Set)

	Cohort 1		Cohort 1 Group 2	
	TAF (N = 47)	**PBO-TAF (N = 23)**	**TAF (N = 12)**	**PBO-TAF (N = 6)**
HBV DNA Change at Week 24				
N	46	22	12	5
Mean (SD)	−5.04 (1.544)	−0.13 (0.689)	−4.76 (1.466)	0.00 (0.346)
Median	−5.26	−0.01	−4.87	−0.04
Q1, Q3	−6.01, −4.48	−0.18, 0.24	−5.80, −4.10	−0.16, 0.18
Min, max	−6.98, 0.16	−2.48, 1.06	−6.59, −1.20	−0.45, 0.47
HBV DNA Change at Week 48				
N	45	23	12	6
Mean (SD)	−5.65 (1.779)	−5.06 (1.703)	−5.88 (0.861)	−4.16 (2.445)
Median	−6.10	−5.75	−5.98	−4.91
Q1, Q3	−6.76, −5.43	−6.38, −4.12	−6.47, −5.66	−5.70, −3.03
Min, max	−7.71, 0.04	−6.89, −0.93	−6.92, −3.75	−6.55, 0.13
HBV DNA Change at Week 96				
N	43	23	11	6
Mean (SD)	−6.16 (1.589)	−5.76 (1.963)	−6.24 (1.110)	−6.56 (0.298)
Median	−6.79	−6.22	−6.74	−6.61
Q1, Q3	−7.01, −5.49	−6.99, −5.75	−6.92, −6.01	−6.82, −6.43
Min, max	−7.88, 0.38	−7.46, 0.18	−7.73, −3.75	−6.83, −6.04

DNA = deoxyribonucleic acid; HBV = hepatitis B virus; PBO = placebo; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide; vs = versus
HBV DNA samples collected through Week 96 were analyzed using Roche COBAS Ampliprep/COBAS Taqman HBV test, Version 2.0.
Change = change from baseline. Baseline value was the last available value collected on or prior to first dose of blinded study drug.
HBV DNA values below the lower limit of quantification were imputed as 19 IU/mL.
Source: Reviewer's Analysis

Percentage of participants with normalized ALT

Table 11 summarizes the Percentage of participants with normalized ALT by visit. In the TAF group, the percentage of participants with Normalized ALT (per AASLD criteria) in Cohort 1 increased from 43.5% at Week 24 to 56.5% at Week 96 and in Cohort 2 Group 1 it decreased from 50.0% at Week 24 to 40.0% at Week 96. In the PBO group, the percentage of participants with Normalized ALT (AASLD) in Cohort 1 increased from 0% at Week 24 to 63.3% at Week 96 and in Cohort 2 Group 1 it increased from 0% at Week 24 to 33.3% at Week 96.

Table 11. Percentage of Participants With Normalized ALT (AASLD) by Visit (Full Analysis Set With Baseline Abnormal ALT)

	Cohort 1		Cohort 2 Group 1	
	TAF	**PBO-TAF**	**TAF (N = 12)**	**PBO-TAF (N = 6)**
Week 24	20/46 (43.5%)	0/22	5/10 (50.0%)	0/6
Week 48	25/46 (54.3%)	9/22 (40.9%)	5/10 (50.0%)	2/6 (33.3%)
Week 72	26/46 (56.5%)	10/22 (45.5%)	3/10 (30.0%)	2/6 (33.3%)
Week 96	26/46 (56.5%)	14/22 (63.6%)	4/10 (40.0%)	2/6 (33.3%)

Source: Reviewer's Analysis

ALT (U/L) and Change from Baseline

Table 12 summarizes the ALT (U/L) and Change from Baseline by visit. ALT(U/L) decreased continually from baseline over time for the TAF group. Decreases from baseline in ALT(U/L) in the PBO group was more obvious once subjects were switched to OL TAF.

Table 12. ALT (U/L) Change from Baseline by Visit (Full Analysis Set)

	Cohort 1		Cohort 2 Group 1	
	TAF (N = 47)	**PBO-TAF (N = 23)**	**TAF (N = 12)**	**PBO-TAF (N = 6)**
ALT Change at Week 24				
N	45	21	12	5
Mean (SD)	-73.9 (133.52)	-14.4 (110.87)	-53.6 (74.89)	-37.8 (75.29)
Median	-32.0	1.0	-29.0	-12.0
Q1, Q3	-63.0, -13.0	-10.0, 25.0	-81.0, -5.5	-22.0, -2.0
Min, Max	-762.0, 29.0	-437.0, 140.0	-256.0, 25.0	-170.0, 17.0
ALT Change at Week 48				
N	46	23	12	6

Mean (SD)	-72.4 (140.02)	-66.1 (114.25)	-54.3 (75.57)	-58.7 (80.44)
Median	-38.0	-26.0	-30.0	-30.5
Q1, Q3	-70.0, -12.0	-55.0, -9.0	-82.0, -2.5	-53.0, -12.0
Min, Max	-774.0, 201.0	-485.0, 13.0	-258.0, 11.0	-219.0, -7.0
ALT Change at Week 96				
N	41	22	11	6
Mean (SD)	-81.7 (140.97)	-77.8 (119.63)	-55.0 (78.35)	-62.7 (97.28)
Median	-41.0	-47.5	-24.0	-31.5
Q1, Q3	-82.0, -17.0	-64.0, -24.0	-83.0, -12.0	-60.0, -1.0
Min, Max	-773.0, 64.0	-480.0, 69.0	-260.0, 14.0	-255.0, 3.0

Source: Reviewer's Analysis

Percentage of Participants With HBeAg Loss

Table 13 summarizes the percentage of participants with HBeAg loss by visit. In the TAF group, the percentage of participants with HBeAg loss in Cohort 1 increased from 6.5% at Week 24 to 26.1% at Week 96 and in Cohort 2 Group 1 it increased from 8.3% at Week 24 to 16.7% at Week 96. In the PBO group, the percentage of participants with HBeAg loss in Cohort 1 increased from 4.3% at Week 24 to 17.4% at Week 96 and in Cohort 2 Group 1 it increased from 0% at Week 24 to 16.7% at Week 96. In comparison HBeAg loss is approximately 14% in adults.

Table 13. Percentage of Participants With HBeAg Loss by Visit (Missing = Failure) (Serologically Evaluable Full Analysis Set for HBeAg Loss)

	Cohort 1		**Cohort 2 Group 1**	
	TAF	**PBO-TAF**	**TAF (N = 12)**	**PBO-TAF (N = 6)**
Week 24	3/46 (6.5%)	1/23 (4.3%)	1/12 (8.3%)	0/6
Week 48	8/46 (17.4%)	2/23 (8.7%)	3/12 (25.0%)	0/6
Week 72	11/46 (23.9%)	4/23 (17.4%)	3/12 (25.0%)	0/6
Week 96	12/46 (26.1%)	4/23 (17.4%)	2/12 (16.7%)	1/6 (16.7%)

Source: Reviewer's Analysis

Percentage of Participants With HBsAg Loss

One participant in Cohort 1 TAF group achieved HBsAg loss at Week 96.

7.8 Conclusions on Effectiveness

The results from the primary endpoint Week 24 analysis of Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg) and the longer-term Week 96 results from Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg) in Study GS-US-320-1092 show that TAF is effective for the treatment of chronic HBV infection in the combined cohorts of children and adolescents aged 6 to < 18 years and weighing ≥ 25 kg.

The Week 96 data provided in this supplement showed progressive decrease in plasma HBV DNA with 50% of participants in Cohort 1 Group 2 achieving HBV DNA < 20 IU/mL by Week 96 (see Table 9) supporting the use of TAF for the treatment of chronic HBV infection in children aged 6 to <12 years weighing ≥ 25kg. Additionally, an increase in the percentage of participants with HBV DNA < 20 IU/mL was observed once PBO participants switched to OL TAF after the Week 24 visit. The progressive decrease in HBV DNA over time is highlighted in the label with inclusion of Week 24, 48 and 96 data to prevent premature discontinuation of the drug and provide reassurance that treatment for 96 weeks or longer may be needed for patients' HBV viral loads to become undetectable.

8. Safety

Trial 1092 demonstrated that TAF is a well-tolerated treatment for CHB in children aged 6 to < 18 years weighing at least 25kg. 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 participants in either Cohort 1 or Cohort 2, Group 1. Overall, there were no remarkable changes in spine and whole-body bone mineral density (BMD), and no significant differences in spine and whole-body BMD were observed between the TAF and PBO-TAF treatment groups over 96 weeks. Renal toxicity was not observed in this study as no patients demonstrated a significant decline in glomerular function or renal tubule injury. The TAF safety data with the longer duration of exposure in pediatric (children and adolescents) participants remained unchanged relative to the initial sNDA submission.

The most commonly reported adverse reactions during the OL phase Trial 1092 were headache and pyrexia. One participant in Cohort 1 TAF experienced a serious adverse event (SAE) during the OL phase (suicidal ideation) and was determined to be unrelated to the study drug. Overall, the safety review did not reveal new signals to monitor or warrant any changes to the product labeling. Further details regarding adverse events and safety monitoring are described in Section 8.2

8.1 Approach to Safety Review

8.1.1 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 aged 6 to <18 years old infected with HBV 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 96-week open label (OL) treatment phase.

The source of data for the safety review is from Trial 1092, for which 96 weeks on study translates to 96 weeks of treatment for the TAF group and 72 weeks of treatment for the PBO-TAF group. Data from the double-blind treatment phase (through Week 24) for Cohort 1 and Cohort 1 Group 2 is described in the prior Supplement (S-14). This review will analyze data obtained from the open label phase of Trial 1092 (Week 25 - Week 96). Using the Applicant's STDM and ADAM datasets, the primary clinical reviewer conducted all safety analyses presented in this section using JMP Clinical 8.0, unless otherwise specified.

8.1.2 Categorization of Adverse Events

Investigator-reported verbatim terms were translated into preferred terms using the MedDRA dictionary Version 25.1 used by the Applicant. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms.

8.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

Not applicable

8.2 Safety Findings

This section will focus on the safety findings after the Week 24 timepoint and through Week 96 of Trial 1092. Please refer to the prior approval efficacy supplement review for safety analysis of the double blind treatment phase (through Week 24) for Cohort 1 and Cohort 2, Group 1. Of note, participants who received placebo during the double-blind (DB) treatment phase were switched to TAF after Week 24 (i.e., during the OL phase), hence referred to as PBO-TAF treatment arm. Therefore, both the TAF and PBO-TAF treatment arms received TAF during the OL phase.

8.2.1 Treatment Emergent Adverse Events and Adverse Drug Reactions

Table 14 presents an overall summary of AEs by treatment group during the OL phase. Overall, the incidence of AEs reported during the OL phase was similar between TAF and PBO-TAF treatment groups. In total, in both cohorts, 69.5% (41 participants) in the TAF group and 75.9% (22 participants) in the PBO-TAF group experienced at least 1 AE during the OL phase.

Table 15 presents an overall summary of AEs reported in ≥ 5% of participants in either treatment group during the OL phase, in descending overall incidence. The AEs with the highest incidence in the total TAF group were headache and pyrexia (13.6% each). Other AEs reported in ≥ 5% of participants in the total TAF group were nasopharyngitis and diarrhea (10.2% each), URI, COVID-19, and cough (8.5% each), and viral respiratory tract infection, and upper abdominal pain (9.8% each). Table 16 presents the summary of three participants who experienced a TEAE of Grade 3 or higher. Two participants were in Cohort 1 and one participant was in Cohort 2.

Cohort 1

During the OL phase a total of 33 subjects (70.2%) in the TAF treatment group and 18 subjects (78.3%) in the PBO-TAF treatment group were assessed as having Treatment-Emergent AEs (TEAEs). Of those, 10 subjects in the TAF group and 4 subjects in the PBO-TAF group had TEAEs assessed as related to the study drug by the investigator. In the TAF treatment group, the TEAEs considered related to the study drug were Grade 1 or 2. The most common treatment-related AE which occurred in >1 subject in the Cohort 1 TAF group was upper abdominal pain (2/47, 4.3%); the remainder of treatment-related AEs occurred in 1 participant each and included diarrhea, rectal discharge, vomiting, pyrexia, cholestasis, jaundice and hyperbilirubinemia (in the same subject), elevated blood cholesterol, bone AEs (see section 8.2.6.1), headache, renal nephrolithiasis, acne and pityriasis rosea. In the Cohort 1 PBO-TAF group none of the treatment-related AEs occurred in > 1 subject and included bone density abnormal and osteoporosis (see section 8.2.6.1 for further detail), metabolic nephropathy and allergic dermatitis. See section 8.2.1 for further discussion of Renal AEs.

Two subjects in the TAF group experienced an AE of Grade 3 or 4 in severity. One subject had Grade 3 infectious mononucleosis with no action taken for the study drug. The event was considered unrelated to the study drug. One subject had a Grade 3 AE of antisocial behavior and Grade 4 AE of suicidal ideation with no action taken for the study drug (see section 8.4.2 for further details).

Cohort 2, Group 1

During the OL phase a total of 8 (66.7%) subjects in the TAF treatment group and 4 (66.7%) subjects in the PBO-TAF group were assessed as having TEAEs. Of those, 2 subjects in the TAF group and 0 of subjects in the PBO-TAF group had TEAEs assessed as related to the study drug by the investigator. The TEAEs in the TAF-treatment group considered related to the study drug were Grade 1 or 2. None of the treatment-related AEs occurred in > 1 subject of Cohort 2, Group 1 and included abdominal pain, atopic dermatitis, UTI, metabolic nephropathy and hematuria (in the same subject). See section 8.1.1 for further discussion of Renal AE.

One Subject in the TAF Group had a Grade 3 AE of tibia fracture with no action taken for the study drug. The event was considered unrelated to the study drug (see Section 8.7.2.2 for further details).

The majority of reported AEs were considered mild or moderate in severity. No AE led to treatment discontinuation.

8.2.1.1 Renal Treatment-Related AEs, Non-laboratory Abnormalities

Overall, in the OL phase, 3 participants experienced treatment-associated renal AEs (2 participants in the TAF group [1 each in Cohort 1 and Cohort 2 Group 1] and 1 participant in the Cohort 1 PBO-TAF group) as noted above.

- Metabolic Nephropathy: Two participants experienced Grade 1 non-serious metabolic nephropathy. Both participants were from the same site and met diagnostic criteria of "deviations in urinalysis." The participant from Cohort 1 PBO-TAF group had a medical history significant for rachitis (rickets). The participant from Cohort 2 Group 1 TAF group had a medical history significant for mild rickets with additional AEs of urinary tract infection, pyelocaliectasis, and hematuria.

- Nephrolithiasis: One participant in Cohort 1 TAF group and had a Grade 1 non-serious AE of nephrolithiasis with past medical history significant for oxalate crystals in the urine.

All three events were determined by the site investigator to be related to the study drug and no action was taken with the study drug. None of the renal AEs lead to study interruption or premature discontinuation.

Clinical Reviewer Comments:

With regard to the participants with metabolic nephropathy we agree that the AEs are likely related to the study drug as neither participant had a history of renal abnormalities prior to initiation of the study drug. It is unclear if the renal AE of nephrolithiasis is related to the study drug given participant medical history of calcium oxalate crystals and that calcium oxalate stones are the most common form of kidney stone. Therefore, we are unable to determine if this participant's development of nephrolithiasis was related to the study drug versus an existing condition.

Table 14: GS-US-320-1092: Overall Summary of Adverse Events (Open-Label Safety Analysis Set, Open-Label Phase)

Participants Experiencing, n (%)	Cohort 1		Cohort 2 Group 1		Total		Overall (N = 88)
	TAF (N = 47)	PBO-TAF (N = 23)	TAF (N = 12)	PBO-TAF (N = 6)	TAF (N = 59)	PBO-TAF (N = 29)	
Any AE	33 (70.2%)	18 (78.3%)	8 (66.7%)	4 (66.7%)	41 (69.5%)	22 (75.9%)	63 (71.6%)
Any Grade 3 or 4 AE	2 (4.3%)	0	1 (8.3%)	0	3 (5.1%)	0	3 (3.4%)
Any Grade 2, 3, or 4 AE	13 (27.7%)	6 (26.1%)	4 (33.3%)	3 (50.0%)	17 (28.8%)	9 (31.0%)	26 (29.5%)
Any study drug–related AE	10 (21.3%)	4 (17.4%)	2 (16.7%)	0	12 (20.3%)	4 (13.8%)	16 (18.2%)
Any Grade 3 or 4 study drug–related AE	0	0	0	0	0	0	0
Any Grade 2, 3, or 4 study drug–related AE	2 (4.3%)	1 (4.3%)	1 (8.3%)	0	3 (5.1%)	1 (3.4%)	4 (4.5%)
Any SAE	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Any study drug–related SAE	0	0	0	0	0	0	0
Any AE leading to premature study drug discontinuation	0	0	0	0	0	0	0
Any AE leading to dose modification or study drug interruption	2 (4.3%)	0	0	0	2 (3.4%)	0	2 (2.3%)
Death	0	0	0	0	0	0	0

Source: Reviewer analyzed of *Table 24 in Applicant CSR (page 114)*
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; SAE = serious adverse event; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA 25.1.
Severity grades were defined by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1, April 2015.
Death includes any death that occurred during the study.
Treatment-emergent events during the open-label phase began on or after the open-label study drug first dose date up to 3 days after permanent discontinuation of the open-label study drug or all data if ongoing on the open-label study drug.

Table 15: GS-US-320-1092: Adverse Events Reported in ≥ 5% Participants Overall (Open-Label Safety Analysis Set, Open Label Phase)

	Cohort 1		Cohort 2 Group 1		Total		Overall (N=88)
	TAF (N = 47)	PBO-TAF (N = 23)	TAF (N = 12)	PBO-TAF (N = 6)	TAF 25 mg (N = 59)	PBO-TAF (N = 29)	
Preferred Term							
Nasopharyngitis	5 (10.6%)	3 (13.0%)	1 (8.3%)	2 (33.3%)	6 (10.2%)	5 (17.2%)	11 (12.5%)
Headache	7 (14.9%)	0	1 (8.3%)	1 (16.7%)	8 (13.6%)	1 (3.4%)	9 (10.2%)
COVID-19	4 (8.5%)	3 (13.0%)	1 (8.3%)	0	5 (8.5%)	3 (10.3%)	8 (9.1%)
Pyrexia	7 (14.9%)	0	1 (8.3%)	0	8 (13.6%)	0	8 (9.1%)
Diarrhea	6 (12.8%)	1 (4.3%)	0	0	6 (10.2%)	1 (3.4%)	7 (8.0%)
Upper respiratory tract infection	4 (8.5%)	1 (4.3%)	1 (8.3%)	1 (16.7%)	5 (8.5%)	2 (6.9%)	7 (8.0%)
Cough	5 (10.6%)	1 (4.3%)	0	0	5 (8.5%)	1 (3.4%)	6 (6.8%)
Respiratory tract infection viral	3 (6.4%)	0	1 (8.3%)	2 (33.3%)	4 (6.8%)	2 (6.9%)	6 (6.8%)
Abdominal pain upper	2 (4.3%)	0	2 (16.7%)	1 (16.7%)	4 (6.8%)	1 (3.4%)	5 (5.7%)

Source: Reviewer analyzed of *Table 19 in Applicant CSR (page 115)*
AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; OL = open label; PBO = placebo; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA, Version 25.1.
Multiple AEs were counted only once per participant for each system organ class, high-level term, and preferred term. Treatment-emergent events during the OL phase began on or after the OL study drug first dose date up to 3 days after permanent discontinuation of the OL study drug or all data if ongoing on the OL study drug.

Table 16: GS-US-320-1092: Grade 3 or Grade 4 Adverse Events (Open-Label Safety Analysis Set, Open-Label Phase)

	Cohort 1		Cohort 2 Group 1		Total		Overall (N = 88)
	TAF (N = 47)	PBO-TAF (N = 23)	TAF (N = 12)	PBO-TAF (N = 6)	TAF (N = 59)	PBO-TAF (N = 29)	
Participants experiencing any Grade 3 or 4 AE, n (%)	2 (4.3%)	0	1 (8.3%)	0	3 (5.1%)	0	3 (3.4%)
By highest grade							
Grade 3 (severe)	1 (2.1%)	0	1 (8.3%)	0	2 (3.4%)	0	2 (2.3%)
Grade 4 (life-threatening)	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)

Infectious mononucleosis (Grade 3)[a]	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Tibia fracture (Grade 3)	0	0	1 (8.3%)	0	1 (1.7%)	0	1 (1.1%)
Antisocial behavior (Grade 3)[a]	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Affective disorder (Grade 3)	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Suicidal ideation (Grade 4)[a]	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)

Source: Reviewer analyzed of *Table 20 in Applicant CSR (page 116)*
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA, Version 25.1. a Adverse events occurred for the same participant
Severity grades were defined by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1, April 2015.
Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term. Preferred terms were presented by descending order of the total frequencies.
Treatment-emergent events during the open-label phase began on or after the open-label study drug first dose date up to 3 days after permanent discontinuation of the open-label study drug or all data if ongoing on the open-label study drug.

8.3 Deaths

No deaths occurred up to 96 weeks of treatment

8.4 Serious Adverse Events

Overall, through 96 weeks (DB and OL) of treatment, 4 participants, all in Cohort 1, experienced an SAE. Three SAEs occurred during the double-blind treatment phase and were reviewed and assessed in the supplemental NDA (S-14), an NDA that approved VEMLIDY for pediatric patients 12 to less than 18 years of age. One participant in Cohort 1 experienced an SAE during the OL phase.

8.4.1 Brief Summary of SAEs during double-blind treatment phase

1. 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.
2. Two participants (both placebo group, and receiving placebo at the time of event) experienced an SAE:
    a. Grade 3 ankle fracture (Day 7, trauma-related)
    b. Grade 3 ALT increased (Day 27, considered related to underlying HBV infection).
        i. Study drug briefly interrupted and resumed without further interruption.
        ii. This same participant who had Grade 3 elevated ALT on Day 27 also had a concurrent HBV DNA viral load of >7.0 log10 IU/mL although it did not appreciably increase on or around Study Day 27; however, by Study Day 108 when the HBV DNA fell to 5.07 log10 IU/mL, the ALT also began to normalize.

8.4.2 Summary of SAE during OL phase

One participant in Cohort 1 (TAF) experienced an SAE of Grade 4 suicidal ideation on day 256. The participant was a 13-year-old, white, female with past medical history of perinatal brain injury, insomnia, disturbance in attention, and mood swings. Three months prior to the initiation of the study drug the participant experienced suicidal ideation. In addition to the Grade 4 SAE of suicidal ideation the participant also experienced a Grade 3 AE of antisocial behavior. The SAE was considered not related to the study drug; no action was taken with study drug. The event resolved on day 272.

Clinical Reviewer comments:
The clinical team agrees with the Investigator that the event of suicidal ideation was not related to study drug. The participant had a history of mental illness, including suicidal ideation, prior to initiation of the study drug, which was received throughout and after the resolution of the event.

8.5 Dropout and/or Discontinuations Due to Adverse Events

Throughout the DB and OL phases of Trial 1092 there were no AEs leading to premature study discontinuation or study dropout. Three AEs lead to brief treatment interruption and subsequent reinitiation. During the double-blind treatment phase one participant, 12-year-old male, in Cohort 1 experienced elevated LFTs leading to treatment interruption (see section 8.3.1). During the OL treatment phase one participant, 17-year-old female, in Cohort 1 experienced nausea leading to brief treatment disruption. One participant, 13-year-old male, in Cohort 1 experienced a congenital odontogenic cyst leading to brief treatment disruption. Treatment was resumed in all participants and no further interruptions were necessary.

8.6 Graded Laboratory Abnormalities

The majority of participants had a post OL baseline graded laboratory abnormality during the OL phase (TAF 88.1% (52/59 participants); PBO-TAF 89.7% (26/29 participants). The graded abnormalities in both treatment groups were mainly Grade 1 or 2. A similar percentage of participants in each treatment group had Grade 3 or 4 laboratory abnormalities (TAF 22.0% [13/59 participants]; PBO-TAF 17.2% [5/29 participants]). Participants in Cohort 1 had a higher incidence of Grade 3 or 4 laboratory abnormalities (TAF 25.5% [12/47 participants]; PBO-TAF 21.7% [5/23 participants]) compared to Cohort 2 Group 1 (TAF 8.3% [1/12 participants]; PBO-TAF [0/6 participants]) during the OL phase. Table 17 summarizes the incidence of Graded laboratory abnormalities at Week 96.

Table 17: Treatment-Emergent Laboratory Abnormalities Toxicity Grade Week 96

Maximum Postbaseline Toxicity Grade	Cohort 1		Cohort 2 Group 1		Total		Overall (N=88)
	TAF (N=47)	PBO-TAF (N=23)	TAF (N=12)	PBO-TAF (N=6)	TAF (N=59)	PBO-TAF (N=29)	
Subjects with Postbaseline Value at Week 96	47	23	12	6	59	29	88
Any Grade 1 or Higher	43 (92%)	20 (87%)	9 (75%)	6 (100%)	52 (88%)	26 (90%)	78 (89%)
Grade 1	18 (38%)	8 (53%)	6 (50%)	3 (50%)	24 (41%)	11 (38%)	35 (40%)
Grade 2	13 (28%)	7 (30%)	2 (17%)	3 (50%)	15 (25%)	10 (35%)	25 (29%)
Grade 3	8 (17%)	4 (17%)	1 (8%)	0	9 (15%)	4 (14%)	13 (14%)
Grade 4	4 (9%)	1 (4%)	0	0	4 (7%)	1 (3%)	5 (6%)

Source: Reviewer analysis
PBO = placebo, TAF = tenofovir alafenamide
Grade 1 (mild); Grade 2 (moderate); Grade 3 (severe); Grade 4 (life-threatening).

8.6.1 Hematology Laboratory Abnormalities

No graded hematology laboratory abnormalities were reported for Cohort 2 in either treatment arm.

For Cohort 1, no clinically relevant changes from baseline hematology were noted within the TAF group, and median values were within normal ranges. The majority of hematology abnormalities were mainly Grade 1 or 2 across all study participants. Grade 3 or 4 hematology abnormalities are summarized in Table 18 and included decreased hemoglobin, decreased neutrophils, decreased platelets (1 participant each in Cohort 1 TAF group), and decreased lymphocytes (1 participant in Cohort 1 PBO-TAF group). All Grade 3 or 4 hematologic abnormalities were transient and improved during subsequent visits. No hematologic laboratory abnormalities in the OL phase led to premature study discontinuation, dropout, or study drug disruption.

8.6.2 Chemistry Laboratory Abnormalities

No graded chemistry laboratory abnormalities were reported for Cohort 2 in either treatment arm.

No clinically relevant changes from baseline chemistry were noted within the Cohort 1 TAF group, and median values were within normal ranges. Grade 3 or 4 chemistry abnormalities are summarized in Table 18. Abnormalities occurring in > 1 participant included increased ALT (1 participant each in Cohort 1 TAF group and Cohort 1 PBO-TAF group), increased creatine kinase (2 participants in Cohort 1 TAF group and 1 participant in Cohort 1 PBO-TAF group). These Grade 3 or 4 chemistry abnormalities were transient and improved to Grade 1 or normal values during subsequent visits. No chemistry laboratory abnormalities in the OL phase led to premature study discontinuation, dropout, or study drug disruption.

8.6.3 Renal Laboratory Abnormalities

The majority of urinalysis abnormalities were mainly Grade 1 or 2 across all study participants. Grade 3 or 4 urinalysis abnormalities are summarized in Table 18 and included occult blood (4 participants in Cohort 1 TAF group, 1 participant in Cohort 2 Group 1 TAF group and 2 participants in Cohort 1 PBO-TAF group), and urine RBCs (3 participants in Cohort 1 TAF group, 1 participant in Cohort 2 Group 1 TAF group and 1 participant in Cohort 1 PBO-TAF group). Of these, 3 participants (1 each in Cohort 1 TAF, Cohort 2 Group 1 TAF and Cohort 1 PBO-TAF groups) had both occult blood and urine RBCs Grade 3 or 4 abnormalities that improved on subsequent visits. Notably, all participants but 1 were female adolescents, and the Cohort 2 participant was a 11-year-old female at baseline (approximately 13 years of age at the time of the AE occurrence). No renal laboratory abnormalities in the OL phase led to premature study discontinuation, dropout, or study drug disruption. Please refer to section 8.7 for additional summary of renal toxicity.

Table 18: GS-US-320-1092: Grade 3 or 4 Laboratory Abnormalities (Open-Label Safety Analysis Set, Open-Label Phase)

Maximum Postbaseline Toxicity Grade	Cohort 1		Cohort 2 Group 1		Total		Overall (N = 88)
	TAF (N = 47)	PBO- TAF (N = 23)	TAF (N = 12)	PBO- TAF (N = 6)	TAF (N = 59)	PBO- TAF (N = 29)	
Participants with postbaseline value	47	23	12	6	59	29	88
Any Grade 3 or higher	12 (25.5%)	5 (21.7%)	1 (8.3%)	0	13 (22.0%)	5 (17.2%)	18 (20.5%)
Grade 3	8 (17.0%)	4 (17.4%)	1 (8.3%)	0	9 (15.3%)	4 (13.8%)	13 (14.8%)
Grade 4	4 (8.5%)	1 (4.3%)	0	0	4 (6.8%)	1 (3.4%)	5 (5.7%)
Hematology							
Participants (n) with hematologic data	**47**	**23**	**12**	**6**	**59**	**29**	**88**
Hemoglobin (decreased)							
Any Grade 3 or higher	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Grade 3	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Lymphocytes (decreased)							
Any Grade 3 or higher	0	1 (4.3%)	0	0	0	1 (3.4%)	1 (1.1%)
Grade 4	0	1 (4.3%)	0	0	0	1 (3.4%)	1 (1.1%)
Neutrophils (Decreased)							
Any Grade 3 or Higher	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Grade 4	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Platelets (decreased)							
Any Grade 3 or higher	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Grade 4	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Chemistry							

Participants (n) with chemistry data	**47**	**23**	**12**	**6**	**59**	**29**	**88**
ALT (increased)							
Any Grade 3 or higher	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Grade 3	0	1 (4.3%)	0	0	0	1 (3.4%)	1 (1.1%)
Grade 4	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Creatine kinase (increased)							
Any Grade 3 or higher	2 (4.3%)	1 (4.3%)	0	0	2 (3.4%)	1 (3.4%)	3 (3.4%)
Grade 3	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Grade 4	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Serum potassium (hyperkalemia)	47	23	12	6	59	29	88
Any Grade 3 or higher	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Grade 4	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Urinalysis							
Participants (n) with urinalysis data	**47**	**23**	**12**	**6**	**59**	**29**	**88**
Occult blood							
Any Grade 3 or higher	4 (8.5%)	2 (8.7%)	1 (8.3%)	0	5 (8.5%)	2 (6.9%)	7 (8.0%)
Grade 3	4 (8.5%)	2 (8.7%)	1 (8.3%)	0	5 (8.5%)	2 (6.9%)	7 (8.0%)
Participants (n) with Urine RBCdata	**43**	**19**	**9**	**5**	**52**	**24**	**76**
Urine RBC (hematuria, quantitative)							
Any Grade 3 or higher	3 (7.0%)	1 (5.3%)	1 (11.1%)	0	4 (7.7%)	1 (4.2%)	5 (6.6%)
Grade 3	3 (7.0%)	1 (5.3%)	1 (11.1%)	0	4 (7.7%)	1 (4.2%)	5 (6.6%)

Source: Reviewer analysis of Table 29 in CSR (page 141)
ALT = alanine aminotransferase; OL = open-label; PBO = placebo; RBC = red blood cell; TAF = tenofovir alafenamide Denominator for percentages was the number of participants in the OL Safety Analysis Set with at least 1 post OL baseline laboratory value for each test.
Severity grades were defined by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1 (01 April 2015).
Severity grading scale: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening.
For maximum postbaseline toxicity grade, the most severe graded abnormality during OL phase was counted for each participant. For each individual laboratory test, the most severe graded abnormality for that test during OL phase was counted for a participant.
Treatment-emergent laboratory abnormalities during open-label phase were defined as an increase of at least 1 toxicity grade from OL baseline at any time post OL baseline up to and including the last dose date of OL study drug + 3 days.

8.7 Adverse Events of Special Interest

8.7.1 Exacerbation of Hepatitis and ALT Flairs

During the double-blind treatment phase (through Week 24) of the study 3 participants in Cohort 1, 1 participant in the TAF group and 2 participants in the PBO group, met criteria for ALT elevation. The two participants in the Cohort 1 PBO group experienced an ALT flare defined as ALT elevations at two consecutive post-baseline visits, 1 of which was considered serious leading to study interruption (See section 8.4.1.b).

No participant experienced treatment-emergent ALT elevation or flare during OL phase noted in the Week 96 data.

8.7.2 Bone-related Safety Analysis

A decline in bone mineral density (BMD) in adults and slower gain in adolescents are well-described 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 96 weeks of double-blind treatment (see Tables 19 and 20).

8.7.2.1 Bone laboratory Parameters

During the double-blind treatment phase, noted in Week 24 data, 9 of 88 participants (10.2%) experienced a bone related event including 3 fracture events in the placebo group of Cohort 1 (see section 8.6.2.2). Two 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. Four participants in the TAF group of Cohort 2, Group 1had a $\geq 4\%$ decrease in spine BMD (3 participants) or whole-body BMD (1 participant), but Z-scores for these participants remained within normal range for their age and gender. Please refer to prior sNDA S-14 for full review and analysis of these events.

During the OL phase, noted in the Week 96 data, 9 of 88 (10.2%) participants experienced a bone event during the OL phase, including 3 fracture events (discussed in section 8.6.2.2). One participant in the Cohort 1 TAF group was reported to have a Grade 1 calcium metabolism disorder and had low vitamin D levels at baseline and during the study. The diagnostic criteria for calcium metabolism disorder according to the investigator were hypercalcemia and hyperphosphatemia based on local laboratory data. The participant had a transient whole body BMD decrease from baseline of 4.1% at Week 48 and no longer met $\geq 4\%$ decrease from baseline threshold at the subsequent visit. Additionally, one participant in the Cohort 1 TAF group was reported to have Grade 1 AE of osteopenia. In the Cohort 1 PBO-TAF group 2 participants were reported to have Grade 1 AE of osteoporosis and 2 participants were reported to have Grade 1 AE of bone density abnormal. It is unclear why the investigator labeled the aforementioned participants as AEs given that none of them met the 2019 ISCD criteria for osteoporosis or had abnormal BMD Z-scores for age. Of note, one of the participants who experienced an AE of osteoporosis (participant (b) (6); randomized to PBO during DB phase) and one of the participants who experienced and AE of bone density abnormal (participant (b) (6); randomized to PBO during DB phase) both had fracture events reported during the DB phase that were determined to be trauma related (see section 8.6.2.2) No participant in Cohort 2 Group 1 experienced an adverse event of osteoporosis, osteopenia, or bone mineral density abnormality. There were no reports of abnormal whole-body or spine BMD Z-scores for age in any participant across both cohorts.

Table 19. Summary of Percent Change From Baseline in Spine BMD and Whole Body BMD by Visit (Spine and Whole Body DXA Analysis Sets)

			Cohort 1		Cohort 2 Group 1	
			TAF (N = 47)	PBO-TAF (N = 23)	TAF (N=12)	PBO-TAF (N=6)
Spine BMD	% Change at Week 24	N	37	18	11	5
		Mean (SD)	2.389 (3.3223)	1.925 (3.0776)	−1.216 (8.5533)	1.896 (1.6566)
	% Change at Week 48	N	40	21	12	6
		Mean (SD)	4.007 (4.5409)	2.039 (3.4617)	3.167 (11.1945)	5.650 (11.2564)
	% Change at Week 96	N	36	20	10	6
		Mean (SD)	6.131 (6.7944)	5.306 (7.6967)	7.467 (14.9592)	15.417 (17.2283)
Whole Body BMD	% Change at Week 24	N	39	18	11	5
		Mean (SD)	1.489 (2.2592)	1.855 (2.5644)	3.207 (3.4900)	2.670 (2.6816)
	% Change at Week 48	N	42	21	12	6
		Mean (SD)	2.248 (3.7602)	2.346 (3.2809)	5.342 (3.7372)	8.428 (5.1777)
	% Change at Week 96	N	40	21	10	6
		Mean (SD)	5.739 (6.5195)	4.525 (5.1791)	9.945 (7.2239)	16.060 (5.7378)

Table 20. Change From Baseline in Spine and Whole Body Bone Mineral Density Z-Scores by visit (Spine and Whole Body DXA Analysis Sets)

			Cohort 1		Cohort 2 Group 1	
			TAF (N = 47)	PBO-TAF (N = 23)	TAF (N=12)	PBO-TAF (N=6)
Spine BMD	Change 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)
	Change at Week 48	N	40	21	12	6
		Mean (SD)	−0.10 (0.298)	−0.25 (0.391)	0.13 (0.475)	0.33 (0.360)
	Change at Week 96	N	36	20	10	6

		Mean (SD)	−0.26 (0.399)	−0.36 (0.703)	−0.07 (0.731)	0.45 (0.527)
Whole Body BMD	Change 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)
	Change at Week 48	(N)	42	21	11	5
		Mean (SD)	−0.16 (0.280)	−0.12 (0.298)	−0.10 (0.297)	0.12 (0.547)
	Change at Week 96	N	40	21	9	5
		Mean (SD)	−0.14 (0.395)	−0.21 (0.450)	−0.25 (0.681)	0.20 (0.615)

Table 21. Incidence of ≥ 4% Decrease From Baseline in Spine or Whole Body BMD by Visit (Spine and Whole Body DXA Analysis Sets)

		Cohort 1		Cohort 2 Group 1	
		TAF (N = 47)	**PBO-TAF (N = 23)**	**TAF (N = 12)**	**PBO-TAF (N = 6)**
Spine BMD, n/N (%)	Week 24	0/37	0/18	3/11 (27.3%)	0/5
	Week 48	0/40	0/21	2/12 (16.7%)	1/6 (16.7%)
	Week 96	1/36 (2.8%)	1/20 (5.0%)	2/10 (20.0%)	1/6 (16.7%)
Whole Body BMD, n/N (%)	Week 24	0/39	0/18	1/11 (9.1%)	0/5
	Week 48	1/42 (2.4%)	1/21(4.8%)	0/12	0/6
	Week 96	0/40	0/21	1/10 (10.0%)	0/6

8.7.2.2. Fracture events

Three facture events occurred during the double-blind treatment phase noted in the Week 24 data. All participants experiencing a fracture were in the Cohort 1 PBO group. One participant, 13-year-old Asian female, experienced a grade 1 hand fracture. One participant, 16-year-old Asian female, experienced a grade 1 ankle fracture. One participant, 16-year-old Asian male, experienced a grade 3 fibula fracture and grade 3 ankle fracture. All fractures were trauma related and no action was taken with the study drug. All participants had spine and whole-body BMD Z-scores within the expected range for age. No participant in Cohort 2 Group 1 experienced a fracture event during the double-blind treatment phase.

Three fracture events occurred during the OL treatment phase noted in the Week 96 data, two participants in Cohort 1 and one participant in Cohort 2 Group 1. One participant 16-year-old white male, in the Cohort 1 TAF group experienced a grade 2 patella fracture. One participant 14-year-old Asian male, in the Cohort 1 PBO-TAF group experienced a grade 1 thumb fracture. One participant 10-year-old white male, in the Cohort 2 Group 1 TAF group experienced a grade 3 tibia fracture. All fractures were trauma related and no action was taken with study drug due to these fractures. All participants had spine and whole-body BMD Z-scores within the expected range for age.

8.7.3. Renal Toxicity

Renal Clinical Adverse Events

During the DB phase 1 participant in the Cohort 2 Group 1 TAF group experienced Grade 1 proteinuria on Day 2 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 other participants in either Cohort 1 or Cohort 2 Group 1 experienced a renal clinical event during the DB phase of treatment.

All 88 participants had at least 1 post OL baseline urine protein value collected during the OL phase. The majority of participants (TAF: 64.4% [38/59 participants]; PBO-TAF 51.7% [15/29 participants]) did not have any treatment-emergent proteinuria, as assessed by dipstick analysis. Overall, most of the occurrences of proteinuria by dipstick were Grade 1 (TAF 33.9% [20/59 participants]; PBO-TAF 41.4% [12/29 participants]). A numerically higher percentage of participants in Cohort 1 had Grade 1 proteinuria by dipstick (TAF 38.3% [18/47 participants; PBO-TAF 43.5% 10/23 participants]) compared to participants in Cohort 2 Group 1 (TAF 16.7% [2/12 participants]; PBO-TAF 33.3% [2/6 participants]).

One participant in the Cohort 1 TAF, Cohort 1 PBO-TAF and Cohort 2 Group 1 PBO-TAF groups, each had Grade 2 proteinuria by dipstick, while no participant in either treatment group had Grade 3 proteinuria by dipstick.

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). During the DB treatment phase the serum creatinine remained similar to baseline 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.

Serum creatinine of participants in the TAF group remained stable through 96 weeks of treatment, with small mean (SD) increases from baseline to Week 48 and Week 96. When evaluated by cohort, at Week 48, increase in mean serum creatinine was similar between the TAF and PBO-TAF groups. At Week 96 there was a greater increase in mean serum creatinine noted in the TAF groups compared with PBO-TAF.

Week 48

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

Week 96

- Cohort 1 mean increase from baseline of 0.09 mg/dL and 0.07 mg/dL for TAF and PBO-TAF, respectively
- Cohort 2 Group 1 mean increase from baseline of 0.07 mg/dL and a 0.05 mg/dL for TAF and PBO-TAF, respectively

Estimated Glomerular Filtration Rate (eGFR)

At baseline, the median (Q1, Q3) overall estimated glomerular filtration rate (eGFR, creatinine clearance [CLcr] 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 m2, placebo 145 [142, 175] mL/min/1.72 m2).
- Cohort 2, Group 1, Baseline: TAF and placebo groups (TAF 154 [142, 169] mL/min/1.72 m2, placebo 173 [152, 189] mL/min/1.72 m2).

During the DB treatment phase there was a significant overall median decrease from baseline in eGFR (CLcr) in the TAF treatment group compared to PBO treatment group (TAF -9 (−19, 2) mL/min; placebo −1 (−7, 7) mL/min; P = 0.0303). However, the median eGFR remained within normal range in all subjects, and no participant had an eGFR < 70 mL/min at 2 consecutive postbaseline visits.

For both the TAF and PBO-TAF groups, fluctuations in median eGFR were noted in the OL phase with a greater decrease in median eGFR at Week 96 for the TAF and PBO-TAF groups compared to week 48; the difference in eGFR median change from baseline (Q1, Q3) was not statistically significant between the TAF and the PBO-TAF groups.

Week 48

- Cohort 1: TAF group (-12 [−20, 2] mL/min/1.72 m2) compared to the PBO-TAF group (-2 [-20, 7] mL/min/1.72 m2)
- Cohort 2, Group 1: TAF group (4 [−4, 42] mL/min/1.72 m2) compared to the PBO-TAF group (-2 [-4, 3] mL/min/1.72 m2)

Week 96

- Cohort 1: TAF group (-17 [-32, 10] mL/min/1.72 m2) compared to the PBO-TAF group (-12 [-30, 2] mL/min/1.72 m2)
- Cohort 2, Group 1: TAF group (-3 [-12, 29] mL/min/1.72 m2) compared to the PBO-TAF group (-4 [-12, 1] mL/min/1.72 m2)

Median eGFR remained within normal range at Week 48 and Week 96 in both groups. No participant had an eGFR < 70 mL/min/1.73 m2 at 2 consecutive post-baseline visits. No participant had eGFR value below the normal range cutoff of 90 mL/min/1.73 m2 through Week 96.

'Confirmed' Renal Abnormalities

Confirmed renal abnormalities were defined as an increase from OL baseline in sCR ≥ 0.3 mg/dL, an increase from OL baseline in sCR ≥ 0.5 mg/dL, occurrence of serum phosphorous below 2.0 mg/dL, CLcr estimated according to the Schwartz formula (eGFRSchwartz) < 50 mL/min, or eGFRSchwartz < 70 mL/min at 2 consecutive postbaseline visits. No participant had a confirmed renal abnormality through Week 24, during the double-blind treatment phase. Four participants in Cohort 1 (3 participants in the treatment TAF group and 1 participant in the PBO-TAF group) had a renal abnormality of confirmed increase in sCR of ≥ 0.3 mg/dL above OL baseline. No (clinical) renal AEs were reported for these 4 participants and eGFR was above 135 mL/min/1.73 m2 at Week 96. No participant met other confirmed renal abnormalities criteria during OL phase.

Renal treatment emergent, treatment-related AEs are discussed in section 8.2.1.1 and renal laboratory AEs are discussed in section 8.5.3. Please refer to sNDA S-14 for full review and analysis of Renal Toxicity events during the DB treatment phase.

Based on these data, additional changes to the product labeling are not warranted.

8.7.4 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. Median body weight Z-scores decreased slightly overall in both the TAF and PBO-TAF groups at Weeks 48 and 96 and Z-scores remained normal for the age (> −2) overall for TAF and PBO-TAF groups, and each group in Cohort 1 and Cohort 2 Group 1. During 96 weeks of treatment, Z-scores fluctuated slightly for both TAF and PBO-TAF groups and the change from baseline at Weeks 48 and 96 was not significantly different between the treatment groups. During 96 weeks of treatment, Z-scores fluctuated slightly for both TAF and PBO-TAF groups, with statistical difference between the change from baseline at Week 96 observed between TAF and PBO-TAF groups, while median Z-scores remained normal for the age (> −2) for the TAF and PBO-TAF groups.

8.7.5 Tanner Staging

As expected for the study population of Cohort 1 (adolescent participants aged 12 to < 18 years), the majority of males and females were categorized at Tanner Stage 3 through 5 at baseline, with the number of participants categorized at Tanner Stage 3 through 5 increasing at Weeks 48 and 96.

For participants in 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) at baseline through Week 96.

Overall body weight changes and tanner staging were appropriate during the trial and additional labeling is not warranted.

8.8 Conclusions of Safety

Overall, through the Week 96 data cut-off date, treatment with TAF in pediatric and adolescent participants with CHB was generally safe and well tolerated. The adverse events seen in the pediatric populations studied are similar to those seen in adults, and no new safety concerns were identified. Longer term treatment of these participants through Week 240 is ongoing.

9. Advisory Committee Meeting

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

10. Pediatrics

See Section 7 for discussion regarding efficacy and Section 8 for discussion regarding general safety and effects on BMD.

On February 27, 2024, the review team for this sNDA presented to the PeRC. The committee agreed with the review team assessment and no further recommendations were set forth by the Division.

11. Other Relevant Regulatory Issues

- *Financial disclosures*

  Financial certification and disclosure information that have remained the same since the submission of the sNDA on 19 April 2022. No new investigator who participated or is participating in the covered clinical study since the submission of the sNDA has disclosable financial interests or arrangements as described in 21 CFR 54.4(a)(3). The investigators with disclosable financial interest or arrangements were included in the m1.3.4 submitted with the prior sNDA and have updated financial disclosures for this sNDA resubmission.

A summary of the previously submitted information is provided in the Financial Certification and Disclosure document submitted with the sNDA (NDA 208464, SN0130, m1.3.4). is provided below:
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.

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.

- *Other Good Clinical Practice (GCP) issues*

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.

- *Office of Scientific Investigations (OSI) audits*

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

- *Office of Study Integrity and Surveillance (OSIS) audits*

No requests were made to the Office of Study Integrity and Surveillance (OSIS) for site inspections

12. Labeling

Prescribing Information

Overall Major Change

Based on the Agency's review of the efficacy results at Week 96, the Indication and Usage section was revised to include pediatric patients aged 6 years and older. The weight requirement was lowered to ≥ 25 kg to include the younger children. All summaries of safety and efficacy in the labeling were revised to include the updated results from the 6 to <12-year-old and 12 to <18-year-old age groups.

Section 6.1 Clinical Trials Experience

Adverse Reactions in Pediatric Subjects with Chronic Hepatitis B

- The section was updated to include the Trial 1092 protocol "Subjects were then eligible to roll over to receive open-label VEMLIDY. Safety data are available through Week 96"

Bone Mineral Density Effects

- Data from the OL phase including Week 96 data from the 6 to <12-year-old and 12 to <18-year-old age groups led to the addition of the following statement: "In the open-label phase, mean percentage change in lumbar spine and whole body BMD and BMD Z-scores from baseline to Week 96 was similar in subjects who remained on VEMLIDY compared to those who switched from placebo to VEMLIDY."

Section 8.4 Pediatric Use

This section was also revised to include the younger 6 to <12 years old cohort and the ≥25kg. 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 6 to less than 18 years and weighing at least 25 kg (N=59) in Trial 1092 for up to 96 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 6 years of age or weigh less than 25 kg."

Section 12.3 Pharmacokinetics

Specific Populations: *Pediatric Patients*

- The following statement was added: "Steady-state pharmacokinetics of tenofovir alafenamide and its metabolite tenofovir were evaluated in HBV-infected pediatric subjects aged 6 to less than 18 years (Table 7)." The referenced table summarizes PK data for patients 6 to < 18 years of age weighing at least 25kg.

Section 12.4 Microbiology

Resistance in Clinical Trials

- This section was revised to include updated information from Week 96 data 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, 17/70 subjects in Cohort 1 (aged 12 to less than 18 years) and 7/18 subjects in Cohort 2, Group 1 (aged 6 to less than 12 years) receiving VEMLIDY qualified for resistance analysis at Week 96. Results were obtained from 19/24 qualified subjects. No HBV amino acid substitutions known to be associated with resistance to tenofovir alafenamide were detected through 96 weeks of treatment [see Clinical Studies (14.5)]."

Section 14.5

- Relabeled: Clinical Trial in Pediatric Subjects 6 Years of Age and Older with Chronic Hepatitis B Virus Infection
- This section was revised to include the efficacy results through Week 96 for the 6 to <12-year-old cohort and updated efficacy results through Week 96 for the 12 to <18-year-old cohort. This section includes information from Week 24, Week 48 and Week 96 to highlight the progressive decline in viral load seen with prolonged TAF therapy seen in both Cohorts.

13. 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.

14. 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. 2023.

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 1 – Financial Disclosure

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes **X**	No __ (Request list from Applicant)
Total number of investigators identified: **59 Principal Investigators and 147 Sub-Investigators**		
Number of investigators who are Sponsor 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 Sponsor of covered study: **0**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes **X**	No __ (Request explanation from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes **X**	No __ (Request explanation from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason:	Yes **X**	No __ (Request explanation from Applicant)

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/s/

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