Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for tenofovir disoproxil fumarate

Proprietary Product Name: Viread

Sponsor: Gilead Sciences, Australia & New Zealand

Date of first round CER: 7 November 2012
Date of second round CER: 11 January 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AACTG	Adult AIDS Clinical Trials Group
ALT	Alanine transaminase
AUC	Area under the plasma concentration versus time curve from zero to infinity after single (first) dose
BMD	Bone Mineral Density
CHB	Chronic hepatitis B
CI	Confidence interval
Cmax	Maximum drug concentration in plasma after single dose administration
CSR	Clinical Study Report
DBEE	Double-Blind Efficacy Evaluation
DEXA	Dual-Energy X-Ray Absorptiometry
EU	European Union
e.g.	Exempli gratia; for example
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	Estimated Glomerular Filtration Rate
HBeAb	Antibody to Hepatitis B early antigen
HBeAg	Hepatitis B early antigen
HBsAb	Antibody to hepatitis B surface antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
i.e.	Id est; that is
L	Litre

Abbreviation	Meaning
LLoQ	Lower limit of quantitation
mg	Milligram
mL	Millilitre
NNRTI	Non-nucleoside reverse transcriptase inhibitor
N(t)RTIs	Nucleoside/tide analogue reverse transcriptase inhibitors
PCR	Polymerase Chain Reaction
PLB	Placebo
SD	Standard Deviation
SOC	System Organ Class
$t_{1/2}$	Half-life associated with the terminal slope
TDF	Tenofovir disoproxil fumarate (VIREAD)
TFV	Tenofovir
TGA	Therapeutic Goods Administration
tmax	Time to reach maximum drug concentration in plasma after single (first) dose; time of maximum effect
ULN	Upper limit normal
US	United States
³	At or greater than
£	At or lesser than
>	Greater than
<	Less than
vs.	versus

1. Introduction

Tenofovir disoproxil fumarate (TDF) is the fumarate salt of tenofovir disoproxil, which is an oral prodrug of tenofovir (TFV). TFV is a nucleotide reverse transcriptase inhibitor (NtRTI) and a hepatitis B virus (HBV) polymerase inhibitor.

The currently approved indications as stated in the Australian Product Information (PI) for TDF are:

"VIREAD in combination with other antiretroviral agents is indicated for the treatment of HIV infected adults and paediatric patients 12 years of age and older.

VIREAD is indicated for the treatment of chronic hepatitis B in adults."

This submission is an application to extend the current chronic hepatitis B (CHB) indication of TDF to include paediatric patients 12 years of age and older, with the following proposed indications:

"VIREAD in combination with other antiretroviral agents is indicated for the treatment of HIV infected adults and paediatric patients 12 years of age and older.

VIREAD is indicated for the treatment of chronic hepatitis B in adults and in paediatric patients 12 years of age and older."[1]

In addition to proposed changes to the indications of TDF, changes to the Pharmacokinetics, Clinical Trials, Precautions, and Adverse Reactions sections of the Product Information are also proposed.[2]

2. Clinical rationale

The sponsor had stated that worldwide, approximately 350 to 400 million people have CHB, and that following acute HBV infection, the risk of progression to chronic HBV infection is inversely proportional to the age at which the infection was acquired. The sponsor had stated that 90% of children infected with HBV in the first year of life and 30% to 50% of children infected between ages of 1 and 4 years develop CHB, leading to large number of adolescents with CHB, which is in turn a major cause of chronic hepatic insufficiency, cirrhosis, and hepatocellular carcinoma (HCC).

The sponsor had stated that there was an unmet treatment need in adolescents with CHB, and that although there are 5 drugs that are currently approved by the Food and Drug Administration (FDA) for treatment of CHB in children and adolescents <18 years old in the United States (US) (lamivudine [age 2 to 17 years], adefovir [age 12 years and older], entecavir [age 16 years and older], telbivudine [age 16 years and older], and interferon-alpha [age 5 to 18 years]), there are limitations to these agents. The sponsor cited the development of viral resistance with long-term use of lamivudine, the limited safety and efficacy data of entecavir and telbivudine in patients < 16 years of age, cross-resistance between entecavir and lamivudine necessitating a higher dose of entecavir in patients with lamivudine-refractory HBV infection, side effects such as growth impairment with interferon-alpha, and inconvenient injectable dosage form of interferon alpha.

The sponsor had stated that TDF had demonstrated efficacy and safety in the treatment of CHB infection in adults in 2 previous studies (GS-US-174-0102 and GS-US-174-0103). Extrapolating from these results, the sponsor had hypothesised that TDF would be effective as a treatment for CHB in adolescents, and hence Study GS-US-174-0115 (i.e. the study submitted in this application) was initiated in adolescents with CHB to test the hypothesis.

Comments: The clinical rationale is sound and logical. In Australia, there are 7 drugs that are currently approved for the treatment of CHB in adults: 2 are cytokines (interferon alpha, pegylated interferon), 3 are nucleoside analogues (lamivudine, entecavir, telbuvidine) and 2 are nucleotide analogues (adefovir, tenofovir). Out of these, 4 are currently approved for use in children and adolescents <18 years old:

[1] Proposed Australian PI for TDF

[2] The sections on changes to the PI, other than to the *Indications*, are not included in this Extract from the Clinical Evaluation Report.

lamivudine (age 2 years and older), adefovir (age 12 years and older), entecavir (age 16 years and older), and telbivudine (age 16 years and older).

2.1. Orphan drug designation

TDF has received the Australian Orphan Drug Designation related to the sought indication.

The sponsor had stated in the application letter that:

"The orphan drug designation for VIREAD was accepted by TGA on 22 March 2012 for the following indication (Application No: PM-2012-00572-3-2):

> *VIREAD in combination with other antiretroviral agents is indicated for the treatment of HIV-infected adults and paediatric patients 12 years of age and older.*
>
> *VIREAD is indicated for the treatment of chronic hepatitis B in adults and* ***paediatric patients 12 years of age and older*** *(see CLINICAL TRIALS)."*

However, in the letter of approval of orphan drug designation by the TGA, submitted in [the sponsor's] Module 1.5.2, it is stated that

> "I have decided, pursuant to subregulation 16J(2) of the Therapeutic Goods Regulations 1990 to designate tenofovir disproxil fumarate (VIREAD) as an orphan drug. The indication is for the treatment of chronic hepatitis B and paediatric patients 12 years of age and older."

The orphan drug list available on the TGA website[3] listed only TDF's designation as an orphan drug on 13 October 2009, for the indication of "in combination with other antiretroviral agents for the treatment of HIV-infected patients 2 to 17 years of age".

It is assumed by the evaluator that the letter of approval of orphan drug designation by the TGA had contained a typographical error, but it is unclear if the sentence was intended to read "The indication is for the treatment of chronic hepatitis B **in adults** and paediatric patients 12 years of age and older", or "The indication is for the treatment of chronic hepatitis B **in** paediatric patients 12 years of age and older". If it is the latter, the indication sought in the submission is the same as the designated orphan indication. This will be brought up as a clinical question [see Section 11] in this report.

2.2. Related submissions

TDF had been previously approved by the TGA in 2002 as a once-daily, film-coated 300 mg tablet for use in combination with other antiretrovirals for the treatment of HIV infection in adults. It was later also approved for the treatment of CHB in adults in 2008 and for the treatment of HIV-infected paediatric patients aged 12 to 17 years (inclusive) in 2011.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - 1 pivotal efficacy/safety study, Study GS-US-174-0115

[3] <http://www.tga.gov.au/industry/pm-orphan-drugs.htm#t> (accessed 1st October 2012)

- 1 Week-72 virology study report of study GS-US-174-0115 (results of this virology report have been incorporated into the main study report of Study GS-US-174-0115)
- Module 1
- Application letter, application form, draft Australian PI and CMI, FDA-approved product label, European Summary of Product Characteristics

· Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety

3.2. Paediatric data

The submission included paediatric efficacy/safety data, as this application is for the extension of indication for the treatment of CHB in paediatric patients aged 12 years and older.

3.3. Good clinical practice

The clinical study reviewed in this evaluation was in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

4. Pharmacokinetics

Not applicable.

5. Pharmacodynamics

Not applicable.

6. Dosage selection for the pivotal studies

The basis for the selection of the dose regimen for the pivotal study (Study GS-US-174-0115) will be described and evaluated in Section 7.1.1.1.3

7. Clinical efficacy

7.1. For the proposed indication of treatment of chronic hepatitis B in paediatric patients 12 years of age and older

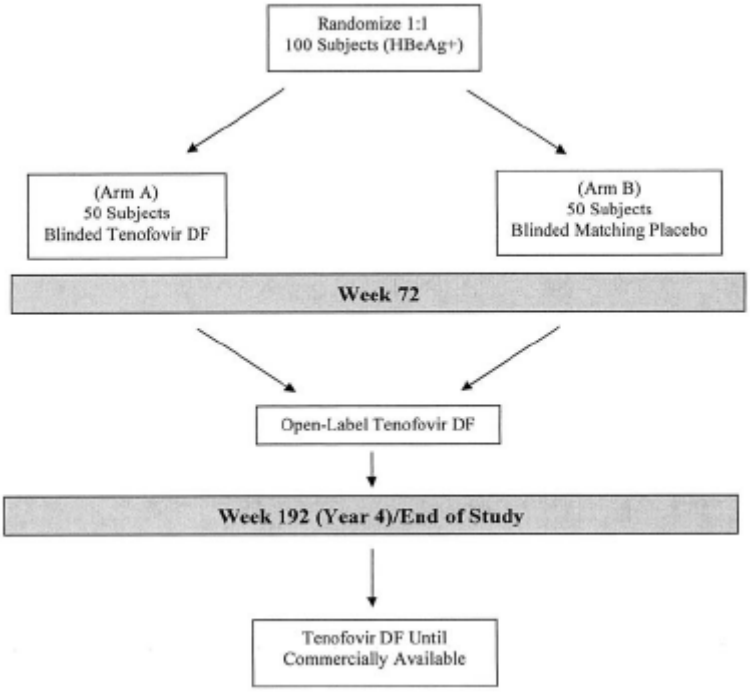
7.1.1. Pivotal efficacy studies

7.1.1.1. Study GS-US-174-0115

7.1.1.1.1. Study design, objectives, locations and dates

Study GS-US-174-0115 was a randomised, double-blind, placebo-controlled, multi-centre study evaluating the efficacy, safety and tolerability of TDF versus placebo in TDF-naive adolescents (12 to 17 years of age, inclusive) with CHB. Subjects were randomised in a 1:1 ratio to 1 of 2 treatment groups: TDF 300 mg orally (PO) once daily or matching placebo PO once daily. After 72 weeks of blinded randomised treatment, subjects could switch to open-label TDF treatment for an additional 2.5 years (i.e. additional 120 weeks). A schema of the study design is presented in Figure 1

Figure 1. GS-US-174-0115 Study Schema



The clinical study report (CSR) submitted for this application presents only the results for the 72-week double-blind phase.

The primary objective of the study was to compare the antiviral efficacy, safety and tolerability of TDF 300 mg once daily versus placebo once daily in adolescents (aged 12 to 17 years, inclusive) with CHB infection. The secondary objectives of the study were to evaluate the biochemical and serological responses to TDF versus placebo in adolescents with CHB infection, and to evaluate the incidence of drug resistance mutations.

This was a multi-centre study where subjects were enrolled in a total of 21 study sites: 8 in Poland, 3 in Romania, 3 in the US, 2 in Bulgaria, 2 in France, 2 in Spain, and 1 in Turkey. The study start date (first subject screened) was 03 December 2008. The date of last subject observation for this CSR was 01 March 2011.

7.1.1.1.2. Inclusion and exclusion criteria

Subjects enrolled in this study were adolescent subjects (12 to 17 years of age, inclusive) with HBeAg-positive or HBeAg-negative[4] chronic HBV infection (chronic HBV infection was defined as having hepatitis B surface antigen [HBsAg] positive for at least 6 months)[5], weighing ≥ 35 kg, with HBV DNA ≥ 100000 copies/mL, with creatinine clearance ≥ 80 mL/min/1.73 m^2, and either alanine transaminase (ALT) ≥ 2 × upper limit normal (ULN) at screening or any history of ALT ≥ 2 × ULN over the past 24 months.

Subjects had to be naive to TDF, but could have received interferon or any other non-TDF containing oral anti-HBV nucleoside or nucleotide therapy. Subjects receiving interferon had to have discontinued interferon therapy ≥ 6 months prior to screening, while subjects on anti-HBV

[4] there was a pre-specified enrolment cap of 50% HBeAg-negative CHB

[5] Subjects in Poland also had to have a history of prior HBV treatment (i.e. previously treated with interferon or other drugs intended to treat this indication) or a contraindication for treatment of HBV with existing drugs for this indication. This was due to a protocol amendment that was written at the request of the Polish Ethics Committee, who had considered that investigational paediatric HBV treatment for adolescents with CHB in the context of this study would be best suited for those with a previous HBV treatment history or contraindication to existing treatment options.

nucleoside or nucleotide therapy had to have discontinued therapy ≥ 16 weeks prior to screening, in order to avoid hepatitis flare if they were randomised to the placebo group. Subjects had to have been without serological evidence of co-infection with HIV, hepatitis C virus, or hepatitis D virus. Subjects with a history of significant bone or renal disease, decompensated liver disease, or evidence of hepatocellular carcinoma (or α-fetoprotein > 50 ng/mL), and pregnant or breast-feeding females were not eligible for the study.

A full list of inclusion and exclusion criteria is presented in the dossier.

Comments: The inclusion and exclusion criteria were in line with recommendations on the study population in TGA-adopted EMA *Guideline on the clinical evaluation of medicinal products intended for treatment of hepatitis B* (CHMP/EWP/6172/03, February 2006), and aimed to recruit TDF-naive adolescent subjects with CHB (serum HBsAg positive for at least 6 months) with signs of significant disease activity (serum HBV DNA ≥ 100 000 copies/mL and elevation of ALT ≥ 2 x ULN).

7.1.1.1.3. Study treatments

The study treatments were TDF 300 mg PO once daily or matching placebo PO once daily. The study drugs were taken without regard to food. Subjects were also instructed to take a daily multivitamin containing 100% of the country-specific recommended daily allowance (RDA) of vitamin D throughout the study. Subjects were treated with blinded randomised therapy for 72 weeks, followed by an optional 2.5 additional years of open-label TDF therapy.

With regards to the dose selection for TDF, the sponsor had stated that previous studies had shown that the inhibition constant (Ki) of tenofovir against HIV-1 reverse transcriptase (0.02-1.6 μM) was similar to the Ki against HBV polymerase (0.18 μM), and that the currently approved dose for treatment of both HIV infection and CHB in adults is 300mg of TDF once daily. Previous studies in HIV-infected children (studies GS-01-926, GS-01-927 and GS-02-983) had indicated that an 8 mg/kg dose in a paediatric population would result in a systemic exposure of TDF similar to that in HIV-infected adults receiving TDF 300 mg dose, and the recommended oral dose of TDF in children is 8 mg/kg of actual body weight, to a maximum of 300 mg/day (for body weight ≥ 35 kg). The currently approved dose of TDF for treatment of HIV in adolescents ≥ 12 years of age and weighing ≥ 35 kg is 300 mg once daily.

Comments: The study dose selection is appropriate, and the study drug dose is the currently approved dose of TDF for treatment of HIV in adolescents ≥ 12 years of age and weighing ≥ 35 kg. However, no rationale was given for the administration of TDF in this study without regard to food, when the currently approved Australian PI for TDF stated that "In order to optimise the absorption of tenofovir, it is recommended that VIREAD be taken with food", and that "Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in Cmax of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour". This will be raised as a clinical question in Section 11 of this report.

With regards to the use of vitamin D supplements, it is noted by the evaluator that the use of vitamin D supplementation with TDF is not part of the content of the currently approved Australian PI for TDF. The sponsor had stated in the protocol that osteomalacia in association with proximal renal tubulopathy had been identified during postmarketing surveillance of TDF, and that although the effect of supplementation with vitamin D had not been studied by the sponsor, it was considered by the sponsor that such supplementation might be beneficial.

The study design involving a placebo control is appropriate and consistent with the recommendation of the TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of chronic hepatitis B, which stated

that for studies involving paediatric subjects with CHB, who have a higher rate of spontaneous remission compared to adult CHB subjects, an active versus placebo study design should be pursued if possible.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was HBV DNA < 400 copies/mL at Week 72.

Secondary endpoints were evaluated for Weeks 48 and 72 and included[6]:

- For all subjects: normal ALT; composite endpoint of HBV DNA < 400 copies/mL and normal ALT; HBV DNA < 169 copies/mL (i.e. the lower limit of quantitation [LLoQ] of the PCR assay); HBsAg loss; HBsAg seroconversion
- For HBeAg-positive subjects: HBeAg loss; HBeAg seroconversion; composite endpoint of HBV DNA < 400 copies/mL, normal ALT and HBeAg loss; composite endpoint of HBV DNA < 400 copies/mL, normal ALT, and HBeAg seroconversion.
- For subjects with abnormal ALT at baseline: normalised ALT; composite endpoint of HBV DNA < 400 copies/mL and normalised ALT
- For HBeAg-positive subjects with abnormal ALT at baseline: composite endpoint of HBV DNA < 400 copies/mL, normalised ALT and HBeAg loss; composite endpoint of HBV DNA < 400 copies/mL, normalised ALT and HBeAg seroconversion.

Normal ALT was defined as ALT value within the normal range (i.e. the central laboratory reference range; 6 to 34 U/L and 6 to 43 U/L for female and male adolescents aged 12-17 years, respectively) at the given post-study-baseline visit, regardless of whether the ALT value was within the normal range at study baseline. Normalised ALT was defined as ALT value within the normal range at the given post-study-baseline visit, only if the ALT value was not within the normal range at study baseline. HBeAg loss was defined as when HBeAg test changed to negative (HBeAg-) at post-study-baseline visit from HBeAg positive test (HBeAg+) at study baseline. HBeAg seroconversion was defined as when antibody to HBeAg (HBeAb) tested positive (HBeAb+) at post-study baseline visit after HBeAg loss had been achieved. HBsAg loss was defined as when HBsAg test changed to negative (HBsAg-) at post-study- baseline visit from HBsAg positive test (HBsAg+) at study baseline. HBsAg seroconversion was defined as when antibody to HBsAg (HBsAb) tested positive (HBsAb+) at post-study baseline visit after HBsAg loss had been achieved.

Other endpoints included:

- Genotypic changes from baseline within the HBV polymerase were analysed at Week 48 and Week 72 for subjects with HBV DNA ≥ 400 copies/mL, subjects who experienced virologic breakthrough (confirmed [defined as two consecutive] HBV DNA ≥ 400 copies mL after a value of < 400 copies/mL, or confirmed 1.0-$\log_{10}$ or greater [i.e. at least tenfold] increase in HBV DNA from nadir), and subjects who discontinued early (after Week 24, with HBV DNA ≥ 400 copies/mL). Phenotypic analyses were conducted for subjects in the TDF arm of the study who experienced confirmed virologic breakthrough, or who developed an emerging amino acid substitution at conserved sites (vs. polymorphic sites) of the HBV polymerase, regardless of breakthrough in HBV DNA. In addition, phenotypic analyses were done for changes observed at polymorphic residues in HBV polymerase if the changes were observed in more than one subject
- Pharmacokinetics (PK) parameters: Plasma samples from all subjects were collected at each study visit for PK analyses and assessment of adherence to therapy.

[6] Week 48 endpoints were not analysed prior to the primary efficacy analysis i.e. there was no interim analysis in this study

Comments: Overall, the primary and secondary endpoints of this study are appropriate. The TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of chronic hepatitis B recommended that the primary efficacy endpoint in confirmatory trials of antiviral non-interferon therapy of CHB be a combined endpoint including virological, histological and biochemical responses. It is noted that the study originally had as primary endpoint a composite endpoint of HBV DNA < 400 copies/mL and normal ALT at Week 72. This was subsequently changed (protocol amendment 2) to a single endpoint of HBV DNA < 400 copies/mL at Week 72, with the composite endpoint of HBV DNA < 400 copies/mL and normal ALT becoming a secondary endpoint. The sponsor had stated that the change was made because the protocol inclusion criteria allowed subjects with a history of ALT ≥ 2x ULN to be recruited (rather than only including subjects who had ALT ≥ 2 x ULN at screening), and that the enrolment of some subjects who had intermittent ALT elevations but a normal ALT at baseline meant that the original composite endpoint would not be fully evaluable. The sponsor had also stated that the utility of composite endpoints that included HBV DNA levels was judged to be limited in Study GS-US-174-0115 as the suppression of HBV DNA in the TDF arm was expected to be far greater than that seen in the placebo arm, and this effect was expected to dominate the outcome of any composite end point that included HBV DNA levels. The sponsor had also stated that the use of a placebo group in this double-blind study precluded obtaining histological parameters in this study due to the desire to limit unnecessary procedures in placebo-treated paediatric subjects.

The rationale for the primary and secondary endpoints of this study is sound. Overall, the primary and secondary endpoints allowed evaluation of virological response (HBV DNA < 400 copies/mL and HBV DNA < LLoQ of the assay [169 copies/mL]), biochemical response (normal ALT and normalised ALT), serological response (HbsAg loss and seroconversion, and HBeAg loss and seroconversion) as well as composite or combined responses of virological, biochemical and serological responses. These are consistent with current clinical practice guidelines recommendations that treatment objectives of CHB be HBV DNA suppression (desired outcome: HBV DNA <2000 IU/mL [approximately 10000 copies/ml]; optimal outcome: undetectable by PCR [HBV DNA <60 IU/mL; approximately 350 copies/ml]), HBsAg loss and seroconversion, HBeAg loss and seroconversion, and/or biochemical and histological improvement[7,8].

No rationale was given for the use of virological endpoint of HBV DNA < 400 copies/mL in the CSR and protocol submitted. However, it is noted by the evaluator that this virological endpoint had been used in prior TDF studies. The threshold used is also consistent with that stated in the TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of chronic hepatitis B, which recommended a level of HBV DNA <500-20 copies/mL as a definition of virological response to treatment, as well as with treatment objective guidelines described in the preceding paragraph.

7.1.1.1.5. Randomisation and blinding methods

Subjects were randomised in a 1:1 ratio to receive blinded TDF 300 mg PO once daily or blinded matching placebo PO once daily. Randomisation was stratified by age (12 to 14 years, 15 to 17 years) and geographical location of study site (North America, Europe). The sponsor had stated

[7] Gastroenterological Society of Australia, Australian and New Zealand Chronic Hepatitis B (CHB) Recommendations. *Digestive Health Foundation*, 2009/10

[8] European Association for The Study Of The Liver, EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatology*, 50 (2):227-42, 2009

that stratification for age was performed to ensure adequate safety exposure by age group to meet regulatory requirements, while stratification for geographical location of study site was performed for logistical purposes for study drug supply.

Subjects were assigned a screening number at the time of consent. Once eligibility had been confirmed, subjects were assigned a subject number and treatment group at the time of randomisation. A centralised randomisation procedure was used, where numbered bottles of TDF or placebo were assigned to subjects via an interactive voice response system (IVRS) according to the randomisation code. For the first 72 weeks of the study (double-blind phase), study drugs were dispensed to the subject in a blinded fashion in numbered bottles. After Week 72 (open-label part of the study), open-label TDF 300 mg were provided to the study site in unnumbered bottles.

During the double-blind phase of the study, HBV DNA results were not distributed to investigators, subjects, or clinical research personnel involved in the clinical conduct of the study except if a subject had Grade 4 ALT abnormalities[9] maintained for 16 weeks or an ALT flare[10], in which case serial HBV DNA values from screening through the time of the event would be made available to the investigator, and the subject could be offered open-label TDF after discussion with the Gilead medical monitor. The sponsor had stated that as there was no unblinding of treatment assignment in such cases, this procedure protected the blind of the study but permitted the investigator to use HBV DNA to make a medical management decision regarding these subjects with persistent Grade 4 ALT abnormalities.

7.1.1.1.6. Analysis populations

Efficacy analyses were performed on the Full Analysis Set (FAS), which included all randomised subjects who had received at least 1 dose of study drug (i.e. TDF 300 mg or matching placebo). No per-protocol analysis set was defined for this study. Safety analyses in the Week 72 analysis were performed on the safety analysis set, which included all subjects who had received at least 1 dose of study drug. The pharmacokinetic analysis set included all subjects who were treated with TDF and had evaluable drug concentrations at the timepoints of interest. The assignment of subjects to analysis sets was done before the study blind was broken for the primary analysis at the Week 72 end-of-double blind treatment analysis.

Comments: The definitions of the analysis populations are in keeping with the TGA-adopted ICH E 9 Statistical Principles for Clinical Trials. Although the FAS excluded subject who took no study drug, the intent-to-treat principle would be preserved as the study was double-blind, and the initial decision of whether or not to begin treatment would not be influenced by knowledge of the assigned treatment, and hence the exclusion of these subjects is not deemed to have introduced any potential bias.

7.1.1.1.7. Sample size

The sponsor had estimated that, with respect to the primary efficacy endpoint, a sample size of 50 subjects in each of the 2 treatment groups would provide at least 80% power to detect a difference of 30% between the groups, based on a 2-sided Fisher exact test with a significance level of 0.05. This calculation was based on assuming a response rate of 21% in the placebo group.

[9] The severity of laboratory abnormalities n the study was graded on a 4-point scale: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and possibly life threatening (Grade 4).
[10] Study definition of ALT or hepatic flare is described in Section 8.4.1.1

7.1.1.1.8. Statistical methods

For efficacy analyses, hepatitis B serology and plasma HBV DNA (PCR method) were collected at the scheduled visit timepoints. The Week 72 analysis was conducted at the end of double-blind treatment phase, after the last randomised subject reached Week 72.

The primary efficacy analysis evaluated the difference in the proportion of subjects achieving the primary efficacy endpoint between the TDF and placebo treatment groups using a Mantel-Haenszel test, controlling for randomisation age group (12 to 14 years, 15 to 17 years). Continuous secondary efficacy endpoints were summarised using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by treatment group, and a stratified Wilcoxon test, controlling for randomisation age group, was used to compare treatment groups. Categorical secondary efficacy endpoints were summarised by number and percentage of subjects who met the endpoint, and a Mantel-Haenszel test, controlling for randomisation age group, was used to compare treatment groups.

In the analyses of the primary endpoint and the categorical secondary efficacy endpoints, subjects who discontinued randomised treatment prior to Week 72 were handled using a Double-Blind Efficacy Evaluation (DBEE) algorithm. In this intent-to-treat algorithm, subjects with missing responses were treated as failures (missing = failure). In addition to the DBEE analysis, an on-treatment observed data (missing = excluded) analysis was performed for the primary endpoint and categorical secondary efficacy endpoints, as a sensitivity analysis.

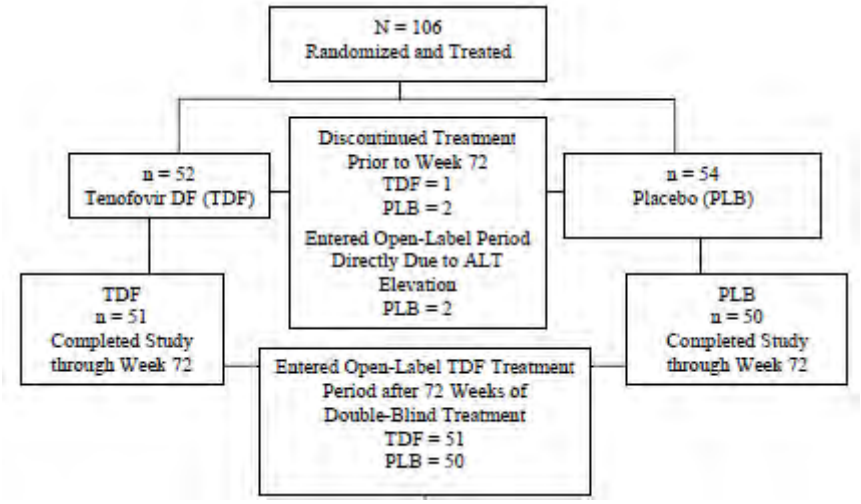
Subgroup analyses for the efficacy endpoints of HBV DNA < 400 copies/mL, HBV DNA < 169 copies/mL, ALT normalisation (in subjects with abnormal ALT at study baseline), and HBsAg loss and seroconversion were performed for subject subgroups for age (subjects aged 12 to 14 years versus 15 to 17 years), HBeAg at study baseline (HBeAg-positive versus HBeAg-negative subjects at study baseline), ALT at study baseline (subjects with abnormal versus normal ALT at study baseline; not applicable for endpoint of ALT normalisation), and prior oral anti-HBV treatment (subjects with versus without prior oral anti-HBV treatment).

7.1.1.1.9. Participant flow

Out of 149 subjects screened, 106 subjects were randomised and treated (52 and 54 subjects in the TDF and placebo groups, respectively). A total of 101 subjects (51 in the TDF group and 50 in the placebo group) completed the double-blind period through Week 72 (see flow chart in Figure 2, below). The single subject in the TDF group who did not complete the double-blind period was discontinued on study drug at Study Week 24 at the investigator's discretion, due to an SAE of Grade 4 syncope which was not considered related to study drug. Of the 4 subjects in the placebo group who did not complete the double-blind period, 2 entered the open-label period due to elevated ALT (per protocol[11]), and the other 2 had AEs (one had severe ALT elevation which was considered an SAE, and the other had AEs of mild back and neck pain and moderate weight loss).

[11] As per study protocol, in the event that any subject had sustained Grade 4 ALT abnormalities for ≥ 16 weeks, the serial HBV DNA values on study were to be provided to the investigator, and the subject could be offered open-label TDF after discussion with the Gilead medical monitor.

Figure 2. Study GS-US-174-0115. Participant flow.



A summary of the analysis population datasets is presented in Table 1.

Table 1. GS-US-174-0115: Analysis Sets for Week 72 Analysis.

	Treatment Group (Age in Years[a])						
	TDF (12–14)	TDF (15–17)	Total TDF (12–17)	PLB (12–14)	PLB (15–17)	Total PLB (12–17)	Overall Total (12–17)
Analysis Set	N=10	N=42	N=52	N=13	N=41	N=54	N=106
All Randomized[b] Analysis Set	10 (100.0%)	42 (100%)	52 (100%)	13 (100%)	41 (100%)	54 (100%)	106 (100%)
Full Analysis Set (FAS)[c]							
Safety Analysis Set[d]							
Pharmacokinetic Analysis Set[e]	10 (100.0%)	42 (100%)	52 (100%)	0	0	0	52 (49.1%)

a Age group is based on the randomization stratification (12–14 or 15–17 years of age).
b Includes all subjects who were randomized into the study, regardless of whether they received study drug.
c Includes all subjects who were randomized into the study and received at least one dose of study drug (ie, TDF 300 mg or matching PLB).
d Includes all subjects who received at least one dose of DB study medication.
e Includes all subjects who were treated with TDF during the DB period and had evaluable concentrations at the time points of interest.

7.1.1.1.10. Major protocol violations/deviations

The sponsor had presented a summary of important protocol deviations occurring during the double-blind period through Week 72 in Table 8-3 in the CSR. It is noted by the evaluator, on going through the listing of major protocol deviations in appendix 16.2.2 of the CSR that there are errors in Table 8-3. A revised table is presented as Table 2 [sourced from Appendix 16.2.2 of the Week 72 CSR] and this will be raised as a clinical question in Section 11 of this evaluation report.

Table 2. GS-US-174-0115: Important Protocol Deviations Occurring Through Week 72 (Full Analysis Set).

Protocol Deviation Category	TDF (N=52)	PLACEBO (N=54)
Number of Subjects with any Important Protocol Deviation, n (%)	**13(25%)**	**7(13%)**

Protocol Deviation Category	TDF (N=52)	PLACEBO (N=54)
Not Managed According to Protocol Criteria [Number of deviations (%)]	**14(27%)**	**8(15%)**
Informed Consent Form Issues	2 (3.8%)	2 (3.7%)
Failure to Meet One or More Inclusion/Exclusion Criteria	9 (17.3%)	4 (7.4%)
Assessment Not Performed Per Protocol	1 (1.9%)	2 (3.7%)
Incorrect Dispensing of Study Drug	2 (3.8%)	0 (0.0%)

The errors did not affect the overall conclusion that protocol deviations occurred at a higher rate in the TDF group than in the placebo group through Week 72, with 27%(per CSR; 25% per revised calculation) and 13.0% of the subjects in the TDF and placebo groups, respectively, identified as having at least one important deviation. The most commonly reported protocol deviation in either treatment groups was failure to meet 1 or more inclusion or exclusion criteria, and these occurred more frequently in the TDF group (17.3%, 9/52) than in the placebo group (7.4%; 4/54). The majority of these protocol deviations involving inclusion or exclusion criteria in the TDF group was for failure to meet the inclusion criterion regarding ALT ≥ 2 × ULN at study screening or any history of ALT ≥ 2 × ULN within 24 months prior to screening (6 subjects [11.5%] in the TDF group versus1 subject [1.8%] in the placebo group). The protocol deviation log in appendix 16.2.2 of the CSR indicated that the waiver type for all these subjects were "allowed waiver". However, the text giving details for the reasons for the waiver of these deviations were truncated (see examples below), and the degree of deviation from the pre-specified ALT criteria were unclear. This will be raised as a clinical question (Section 11).

Example 1: 'Inc/Exc: Pt did not meet inclusion criterion #8 (ALT ≥ 2 x ULN at screening, or any history of ALT ≥ 2 x ULN over the past ≤ 24 months. Within in' [sic]

Example 2: 'Inc/Exc: Pt did not meet inclusion criterion #8 (ALT ≥ 2 x ULN at screening, or any history of ALT ≥ 2 x ULN over the past ≤ 24 months. Within in 10%' [sic]

Comments: The higher proportion of subjects in the TDF group with protocol deviations involving failure to meet the inclusion criterion regarding ALT ≥ 2 × ULN at study screening or any history of ALT ≥ 2 × ULN within 24 months prior to screening, initially raises concerns regarding potential bias in the study population and hence study results. It raises concerns that the subjects in the TDF group could have started off at baseline with less abnormal ALT and hence lower levels of disease activity in terms of hepatic inflammation, compared to those in the placebo group, thus potentially introducing a bias towards a more favourable efficacy result for the TDF group. This is reflected in the baseline disease characteristics (described later in Section 7.1.1.1.11) which showed that there was a numerically higher percentage of subjects with normal ALT in the TDF group (32.7%; 17/52) compared to the placebo group (22.2%; 12/54). However, this difference was not found to be statistically significant (p=0.22) during the analyses of the secondary efficacy endpoints (described in Section 7.1.1.1.13.2. In addition, the mean baseline ALT were similar between the 2 treatment groups (101 [SD 107.5] U/L and 101 [SD 90.0] U/L in the TDF and placebo groups, respectively), as were the

baseline viral load (mean [SD] baseline HBV DNA of 8.01 [1.418] log_{10} copies/mL in the TDF group, and 8.24 [1.393] log_{10} copies/mL in the placebo group).

7.1.1.1.11. Baseline data

The baseline demographic characteristics were comparable between treatment groups. The majority of subjects in each treatment group were male (73.1% [38/52] and 64.8% [35/54] in the TDF and placebo groups, respectively) and White (94.2% [49/52] and 90.7% [49/54], respectively). The mean (Standard Deviation [SD]) age was 15.5 (1.34) and 15.3 (1.43) years in the TDF and placebo groups, respectively. The median age was 16.0 and 15.0 years, respectively. Baseline BMI were similar between treatment groups (mean [SD] BMI of 21.1 [3.80] and 20.3 [3.03] in the TDF and placebo groups, respectively). The majority of subjects were enrolled at sites in Europe (96.2% [50/52] and 94.4% [51/54] in the TDF and placebo groups, respectively).

The baseline disease characteristics were also comparable between treatment groups. Baseline viral load was similar between treatment groups (mean [SD] baseline HBV DNA of 8.01 [1.418] log_{10} copies/mL in the TDF group, and 8.24 [1.393] log_{10} copies/mL in the placebo group). Baseline mean ALT was comparable between treatment groups (101 [SD 107.5] U/L and 101 [SD 90.0] U/L in the TDF and placebo groups, respectively). The majority of subjects in each treatment group were positive for HBeAg (92.3% [48/52] and 88.9% [48/54] in the TDF and placebo groups, respectively). The mean (SD) number of years of being HBV positive was 10.21 (4.798) years in the TDF group and 10.83 (4.696) years in the placebo group. Baseline bone biomarkers, whole-body bone mineral density (BMD) and lumbar spine BMD were similar between treatment groups. The proportion of subjects with prior exposure to at least 1 anti-HBV medication was comparable between treatment groups (82.7% [43/52] and 87.0% [47/54] in the TDF and placebo groups, respectively). Of these, 71.2% (37/52) of subjects in the TDF group and 81.5% (44/54) of subjects in the placebo group had been previously treated with interferon, and 59.6% (31/52) of subjects in the TDF group and 57.4% (31/54) of subjects in the placebo group had been previously treated with lamivudine.

Comments: Overall, the baseline demographic and disease characteristics were comparable between treatment groups. The majority of subjects in each treatment group were positive for HBeAg at baseline, with only 9.4% (10/106) of subjects with HBeAg-negative CHB. The worldwide prevalence of HBeAg-negative CHB varies geographically and has been found to be more common in Asia and the Mediterranean region, but the prevalence in adolescents was not well documented. It is hence difficult to comment on whether the relative proportion of HBeAg-positive and HBeA- negative CHB subjects in the study is reflective of the target patient population.

HBeAg-negative CHB is caused by HBV strains with mutations in the core promoter or precore regions that prevent HBeAg expression. HBeAg-negative CHB is considered to have a different disease profile from HBeAg-positive CHB, and is associated with a fluctuating course and progressive fibrosis. Spontaneous recovery of HBeAg-negative CHB is unusual and few patients achieve lasting remission[12]. The TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of chronic hepatitis B states that "The HBeAg negative chronic hepatitis B is established as a distinct disease entity separated from HBeAg positive hepatitis that requires separate analyses although a combined study with pre-planned analyses could be considered acceptable." As only a small number of subjects in this study had HBeAg-negative CHB, and the sponsor is not proposing to specify an indication for HBeAg-negative CHB

[12] Hadziyannis S.J., Vassilopoulos D. Hepatitis B e Antigen–Negative Chronic Hepatitis B. *Hepatology*, Vol. 34, No. 4, October 2001

separately from HBeAg-positive CHB, it is deemed appropriate that there were no separate analyses on the HBeAg-negative CHB subjects, as the small sample size would limit any meaningful statistical analysis or interpretation.

7.1.1.1.12. Results for the primary efficacy outcome

The primary efficacy outcome is the proportion of subjects with HBV DNA < 400 copies/mL at the end of double-blind treatment (Week 72). At Week 72, 88.5% (46/52) of TDF-treated subjects had HBV DNA < 400 copies/mL compared with 0.0% (0/54) of patients on placebo (p<0.001, DBEE analysis) (Table 3). From baseline through Week 48, the percentages of TDF-treated subjects who had HBV DNA < 400 copies/mL increased to about 85% and then were maintained through to Week 72 (Figure 3).

Table 3. GS-US-174-0115: Number and Percentage of Subjects with HBV DNA below 400 copies/mL (69 IU/mL) and Below 169 copies/mL (29 IU/mL) at Week 72 (Full Analysis Set)

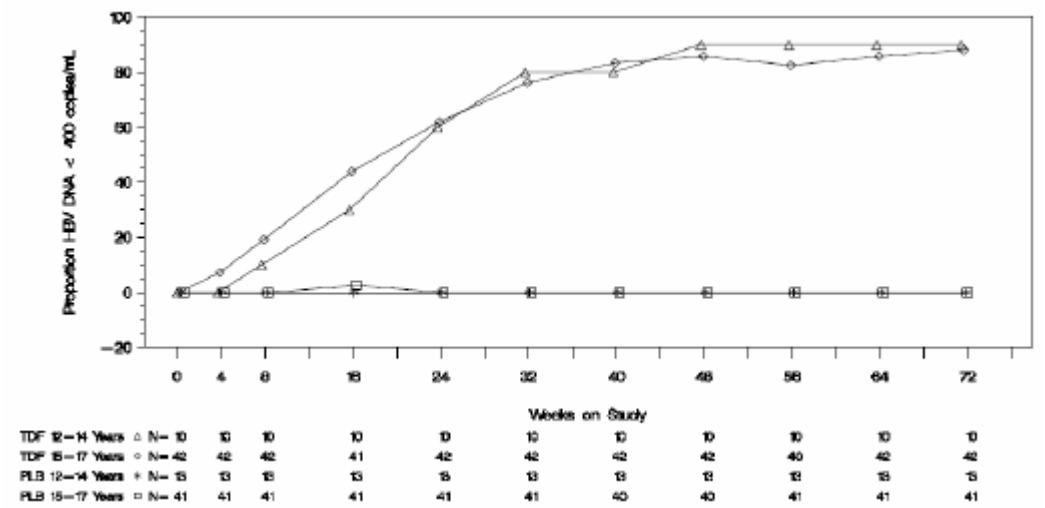
HBV DNA Category and Study Week[a]	Treatment Group (Age in Years[b])						
	TDF (12–14)	TDF (15–17)	PLB (12–14)	PLB (15–17)	Total TDF (12–17)	Total PLB (12–17)	P-value[c]
	N=10	N=42	N=13	N=41	N=52	N=54	
HBV DNA < 400 copies/mL							
DBEE Analysis (Missing=Failure)							
Baseline	0/10 (0.0%)	0/42 (0.0%)	0/13 (0.0%)	0/41 (0.0%)	0/52 (0.0%)	0/54 (0.0%)	–
Week 24	6/10 (60%)	26/42 (61.9%)	0/13 (0.0%)	0/41 (0.0%)	32/52 (61.5%)	0/54 (0.0%)	< 0.001
Week 48	9/10 (90.0%)	36/42 (85.7%)	0/13 (0.0%)	0/40 (0.0%)	45/52 (86.5%)	0/53 (0.0%)	< 0.001
Week 72	9/10 (90.0%)	37/42 (88.1%)	0/13 (0.0%)	0/41 (0.0%)	46/52 (88.5%)	0/54 (0.0%)	< 0.001
Observed (Missing=Excluded) Analysis							
Baseline	0/10 (0.0%)	0/42 (0.0%)	0/13 (0.0%)	0/41 (0.0%)	0/52 (0.0%)	0/54 (0.0%)	–
Week 24	6/10 (60%)	26/42 (61.9%)	0/13 (0.0%)	0/41 (0.0%)	32/52 (61.5%)	0/54 (0.0%)	< 0.001
Week 48	9/10 (90.0%)	36/41 (87.8%)	0/13 (0.0%)	0/38 (0.0%)	45/51 (88.2%)	0/51 (0.0%)	< 0.001
Week 72	9/10 (90.0%)	37/41 (90.2%)	0/13 (0.0%)	0/37 (0.0%)	46/51 (90.2%)	0/50 (0.0%)	< 0.001
HBV DNA < 169 copies/mL							
DBEE Analysis (Missing=Failure)							
Baseline	0/10 (0.0%)	0/42 (0.0%)	0/13 (0.0%)	0/41 (0.0%)	0/52 (0.0%)	0/54 (0.0%)	–
Week 24	4/10 (40%)	21/42 (50%)	0/13 (0.0%)	0/41 (0.0%)	25/52 (48.1%)	0/54 (0.0%)	< 0.001
Week 48	8/10 (80%)	34/42 (81.0%)	0/13 (0.0%)	0/40 (0.0%)	42/52 (80.8%)	0/53 (0.0%)	< 0.001
Week 72	9/10 (90%)	35/42 (83.3%)	0/13 (0.0%)	0/41 (0.0%)	44/52 (84.6%)	0/54 (0.0%)	< 0.001
Observed (Missing=Excluded) Analysis							
Baseline	0/10 (0.0%)	0/42 (0.0%)	0/13 (0.0%)	0/41 (0.0%)	0/52 (0.0%)	0/54 (0.0%)	–
Week 24	4/10 (40%)	21/42 (50%)	0/13 (0.0%)	0/41 (0.0%)	25/52 (48.1%)	0/54 (0.0%)	< 0.001
Week 48	8/10 (80%)	34/41 (82.9%)	0/13 (0.0%)	0/38 (0.0%)	42/51 (82.4%)	0/51 (0.0%)	< 0.001
Week 72	9/10 (90%)	35/41 (85.4%)	0/13 (0.0%)	0/37 (0.0%)	44/51 (86.3%)	0/50 (0.0%)	< 0.001

a Study baseline is defined as the first dose date of DB study drug. Study week is windowed week relative to study baseline.

b Age group is based on the randomization stratification (12–14 or 15–17 years of age).

c P-values for categorical data from a two-sided Cochran-Mantel-Haenszel test, controlling for strata (12–14 years or 15–17 years at the time of randomization).

Figure 3. GS-US-174-0115: Proportion of Subjects with HBV DNA below 400 copies/mL (69 IU/mL) at Week 72 using DBEE Analysis (Missing=Failure) (Full Analysis Set)



7.1.1.1.13. Results for other efficacy outcomes

7.1.1.1.13.1. Sensitivity analysis on the primary efficacy endpoint

A sensitivity analysis for the primary efficacy endpoint using observed data (missing = excluded) analysis yielded similar results to the primary efficacy outcome, showing that at Week 72, 90.2% (46/51) of TDF-treated subjects had HBV DNA < 400 copies/mL compared with 0.0% (0/50) of patients on placebo (p<0.001).

7.1.1.1.13.2. Secondary efficacy outcomes

The percentage of subjects with HBV DNA <169 copies/mL (LLoQ for the PCR assay) at Week 72 was 84.6% (44/52) in the TDF group and 0.0% (0/54) in the placebo group (p<0.001; DBEE analysis). From baseline through Week 48, the percentages of TDF-treated subjects who had HBV DNA <169 copies/mL rose to about 80% and then were maintained through to Week 72. Sensitivity analysis for this endpoint using the observed data (missing = excluded) analysis yielded similar results.

Mean changes from baseline in HBV DNA levels are presented in the CSR. Mean (SD) baseline HBV DNA values were similar in the TDF and placebo treatment groups (8.01 [1.418] and 8.24 [1.393] $\log_{10}$ copies/mL, respectively). Mean changes from baseline in HBV DNA levels were greater in the TDF group than in the placebo group at Weeks 24, 48 and 72 (Week 24: -5.20 $\log_{10}$ copies/mL and -0.38 $\log_{10}$ copies/mL in the TDF and placebo groups, respectively; Week 48: -5.63 and -0.60 $\log_{10}$ copies/mL, respectively; Week 72: -5.36 and -0.92 $\log_{10}$ copies/mL, respectively). No statistical testing had been applied in these analyses.

At baseline, the percentage of subjects with normal ALT was higher in the TDF group than in the placebo group (32.7% [17/52] versus 22.2% [12/54], respectively; DBEE analysis), but this difference was not found to be statistically significant (p=0.22). In the TDF group the percentage of subjects with normal ALT increased from 32.7% (17/52) at baseline to 76.9% (40/52) at Week 72 (DBEE analysis). In the placebo group, the percentage of subjects with normal ALT increased from 22.2% (12/54) at baseline to 38.9% (21/54) at Week 72 (DBEE analysis). The differences between the TDF group and the placebo group were statistically significant from Week 16 onwards. When missing values were excluded, results were similar.

Baseline mean ALT was comparable between treatment groups (101 [SD 107.5] U/L and 101 [SD 90.0] U/L in the TDF and placebo groups, respectively). Mean (SD) ALT change from baseline at Week 72 was –58 U/L (121.1) in the TDF group, compared with –13 U/L (143.8) in the placebo group. No statistical testing had been applied in these analyses.

In the TDF group, mean ALT drop from baseline increased over time through to Week 16, and was then maintained through to Week 72.

Analysis on the endpoint of normalised ALT showed that the percentage of subjects with baseline ALT above the ULN who achieved ALT within the normal range by Week 72 was statistically significantly higher in the TDF group (74.3%; 26/35) versus the placebo group (31.0%; 13/42) ($p < 0.001$, DBEE analysis). The difference between the TDF group and the placebo groups was statistically significant from Week 16 onwards. When missing values were excluded, results were similar.

Analyses of HBV serology in terms of HBsAg loss and HBsAg seroconversion showed that all subjects were HBsAg positive at study baseline, as required by the study protocol. Two subjects (both in the TDF group) experienced HBsAg loss (DBEE and Missing=Excluded analyses). One of the 2 subjects experienced both HBsAg loss and seroconversion to anti-HBs at Weeks 64 and 72. The other subject had unconfirmed HBsAg loss at Week 32, without seroconversion, and was then HBsAg-positive at subsequent visits though Week 72. No subjects in the placebo group had HBsAg loss or seroconversion through Week 72.

Analyses of HBV serology in terms of HBeAg loss and HBeAg seroconversion showed that among those who were HBeAg positive at study baseline, the difference between treatment groups in the percentages of subjects who experienced HBeAg loss by Week 72 was not statistically significant (20.8% [10/48] and 14.6% [7/48] in the TDF and placebo groups, respectively; $p = 0.41$; DBEE analysis). Analysis of the percentages of subjects who experienced seroconversion to anti-HBe by Week 72 yielded the same results (20.8% [10/48] and 14.6% [7/48] in the TDF and placebo groups, respectively; $p = 0.41$; DBEE analysis). Across time, the difference between treatment groups in the proportion of subjects with HBeAg loss or HBeAg seroconversion was not statistically significant at each 16-weekly evaluations from Week 16 (first serological evaluation timepoint) through to Week 72. When missing values were excluded, results were similar.

Analyses on the composite endpoint of HBV DNA < 400 copies/mL and normal ALT showed that 71.2% (37/52) of subjects in the TDF group had HBV DNA below 400 copies/mL and ALT within the normal range at Week 72 , compared with 0 subject (0/54) in the placebo group ($p < 0.001$; DBEE analysis). The percentages of subjects in the TDF group with this composite endpoint increased from baseline through Week 72, from 0.0% at baseline to 47.1%, 69.2% and 71.2% at Weeks 24, 48 and 72, respectively. No subjects in the placebo group met this composite endpoint from baseline through to Week 72. When subjects with missing values were excluded, results were similar.

Analyses on the composite endpoint of HBV DNA below 400 copies/mL and normal ALT and HBeAg loss among those who were HBeAg positive at study baseline showed that at Week 72, 14.6% (7/48) of subjects in the TDF group had achieved this composite endpoint, compared with 0 subject (0/48) in the placebo group ($p < 0.007$; DBEE analysis). The difference between TDF and placebo groups was statistically significant in favour of TDF from Week 32 onwards ($p < 0.05$; DBEE analysis). Analyses on the composite endpoint of HBV DNA below 400 copies/mL and normal ALT and HBeAg seroconversion yielded similar results. When subjects with missing values were excluded, results were similar for both composite endpoints.

Analyses on the composite endpoint of HBV DNA below 400 copies/mL and normalised ALT among subjects with abnormal ALT at baseline showed that at Week 72, 74.3% (26/35) of subjects in the TDF group had achieved this composite endpoint , compared with 0 subject (0/42) in the placebo group ($p < 0.001$; DBEE analysis). The difference between TDF and placebo groups was statistically significant in favour of TDF from Week 16 onwards ($p < 0.05$; DBEE analysis).

Analyses on the composite endpoint of HBV DNA below 400 copies/mL and normalised ALT and HBeAg loss among those who were HBeAg positive with abnormal ALT at study baseline

showed that at Week 72, 21.2% (7/33) of subjects in the TDF group had achieved this composite endpoint, compared with 0 subject (0/42) in the placebo group (p=0.002; DBEE analysis). The difference between TDF and placebo groups was statistically significantly in favour of TDF from Week 16 onwards (p < 0.05; DBEE analysis). Analyses on the composite endpoint of HBV DNA below 400 copies/mL and normal ALT and HBeAg seroconversion yielded similar results.

7.1.1.1.13.3. Subgroup analyses

Subgroup analyses of the endpoints of HBV DNA < 400 copies/mL, HBV DNA < 169 copies/mL, normalised ALT (in subjects with abnormal ALT at study baseline), and HBsAg loss and seroconversion were to be performed on subpopulations of interest (age group of 12 to 14 years versus 15 to 17 years, normal versus abnormal baseline ALT, baseline HBeAg status positive versus negative, and use of prior oral HBV medications versus treatment-naive). However, the event rates of the efficacy endpoint of HBsAg loss and seroconversion were too small for any subgroup analyses to be meaningful. In addition, the subgroup of subjects with baseline HBeAg status negative was too small (n=4 in TDF group, n=6 in placebo group) for meaningful interpretation.

Analyses of the specified endpoints in the age subgroups showed that the proportions of subjects with HBV DNA < 400 copies/mL, and HBV DNA < 169 copies/mL were similar between the 2 age subgroups within the TDF group in both the DBEE and observed analyses. At Week 72 the proportions of subjects with HBV DNA < 400 copies/mL were 90.0% (9/10) in the age range of 12 to 14 years and 88.1% (37/42) in the age range of 15 to 17 years (DBEE analysis), while the proportions of subjects with HBV DNA < 169 copies/mL were 90.0% (9/10) and 83.3% (35/42), respectively. At Week 72 the proportions of subjects with normalised ALT were numerically higher in the age range of 12 to 14 years (85.7%; 6/7) than in the age range of 15 to 17 years (71.4%; 20/28) (DBEE analysis). No statistical analyses were applied to these results. Interpretation of these results is limited by the small number of subjects in these analyses, with only 10 subjects in the age subgroup of 12 to 14 years.

Subgroup analyses of the endpoints of HBV DNA < 400 copies/mL and of HBV DNA < 169 copies/mL in the other subpopulations of interest are presented in the CSR. The percentages of TDF-treated subjects with HBV DNA < 400 copies/mL and with HBV DNA < 169 copies/mL at Week 72 were greater in subjects with baseline abnormal ALT compared to those with baseline normal ALT (HBV DNA < 400 copies/mL: 97.1% versus 70.6%, DBEE analysis; HBV DNA < 169 copies/mL: 94.3% versus 64.7%, DBEE analysis). The percentages of TDF-treated subjects with HBV DNA < 400 copies/mL and with HBV DNA < 169 copies/mL at Week 72 were also greater in subjects without prior oral HBV medications compared to those with prior oral HBV medications (HBV DNA < 400 copies/mL: 95.0% versus 84.4%, DBEE analysis; HBV DNA < 169 copies/mL: 95.0% versus 78.2%, DBEE analysis).

7.1.1.1.13.4. Resistance Surveillance and Genotypic/Phenotypic Analysis

Baseline HBV viral genotyping was conducted on serum samples for all subjects and showed that the distribution of genotypes was similar across both treatment groups, and that genotypes A and D were the most commonly observed genotypes in each treatment group (TDF group: 67.3% with genotype A and 28.8% with genotype D; placebo group: 63.0% and 33.3%, respectively). Sequence analysis of the nucleotide fragment encoding the reverse transcriptase/polymerase (pol/RT) domain of HBV polymerase for all baseline samples revealed that 10 subjects (7 in the TDF group and 3 in the placebo group) had conserved-site changes at baseline. The majority of these conserved-site changes observed at baseline (6 out of the 7 subjects in the TDF group and 2 out of the 3 subjects in the placebo group) were lamivudine (LAM) resistance–associated mutations.

The treatment virologic responses of the 6 TDF-treated subjects with LAM resistance-associated mutations at baseline are summarised in the CSR. Of the 6 subjects in the TDF group with LAM

resistance-associated mutations, 4 had HBV DNA < 400 copies/mL at Week 48, and all 4 subjects maintained their HBV DNA < 400 copies/mL through to Week 72. One of the other 2 remaining subjects had HBV DNA > 400 copies/mL during the Week 48 genotypic analysis but then achieved HBV DNA < 400 copies/mL at Week 72. The last remaining subject had HBV DNA > 400 copies/mL at both Week 48 and Week 72. The virologic response of these 6 subjects was comparable to the remaining 46 subjects in the TDF arm through 72 weeks.

As part of resistance surveillance, HBV DNA HBV pol/RT region sequencing was done for all subjects with HBV DNA > 400 copies/mL at Weeks 48 and/or at Week 72. At Week 48, 6 subjects in the TDF group met this HBV DNA threshold criterion. One subject experienced confirmed virologic breakthrough with 2 consecutive > 1- $\log_{10}$ increases in HBV DNA from the nadir time point. The other 5 subjects had HBV DNA > 400 copies/mL in the absence of confirmed virologic breakthrough. Sequencing demonstrated that out of the 6 subjects, 2 subjects had no change from baseline, 1 subject had unique polymorphic-site changes, 1 subject had reversion at a conserved site of a mixture back to wild-type (this is the subject with confirmed virologic breakthrough), and 2 subjects had conserved-site changes. All subjects were found to be adherent to study medication for the first 48 weeks of the study, as measured by tenofovir plasma levels, with the exception of the subject with polymorphic-site changes at Week 16.

At Week 72, 5 subjects in the TDF group met the HBV DNA threshold criteria, 2 of whom had been evaluated at Week 48: one subject had a second confirmed virologic breakthrough and sequencing showed the subjects had maintained the conserved site reversion, and the other subject remained without virologic breakthrough and maintained no change from baseline. Of the remaining 3 subjects, 1 subject had an unconfirmed virologic breakthrough, and 2 subjects had confirmed virologic breakthrough. Sequencing demonstrated that the subject with unconfirmed virologic breakthrough had unique polymorphic-site changes, and out of the remaining 2 subjects, 1 subject had no change from baseline, and the other subject had unique polymorphic-site changes. Of the 4 subjects who had virologic breakthrough (confirmed and unconfirmed) at Week 72, all had plasma tenofovir levels below the limit of quantitation, suggesting that the virologic breakthrough could be due to non-adherence to study drug.

The HBV from subjects with confirmed virologic breakthrough or who developed conserved site changes in HBV pol/RT were analysed phenotypically. At Week 48, one subject qualified for phenotypic analysis with a conserved site change (rtM250M/T) without virologic breakthrough and at Week 72, 3 subjects qualified for phenotypic analysis with confirmed virologic breakthrough. All HBV isolates tested showed full susceptibility to tenofovir, indicating that no resistance to tenofovir had developed among these subjects.

7.1.1.1.13.5. Other analyses

Mean and median TDF pharmacokinetic parameters from exploratory analyses are presented in Table 4. The sponsor has stated that due to the lack of data over a wide range of sampling interval, AUC and half-life determinations were not performed in the subset of subjects of 12 to 14 years of age.

Table 4. GS-US-174-0115: Mean and Median TDF Pharmacokinetic Parameters from Exploratory Analyses (Pharmacokinetic Analysis Set)

Age Category	AUC_{tau} (ng·hr/ml)	C_{max} (ng/ml)	$T_{1/2}$ (hr)	T_{max} (hr)
Overall				
Mean	3015.2	352.7	19.2	1.5
Median	2884.1	341.0	19.9	1.5
15–17 years				
Mean	2904.6	306.6	15.4	1.5
Median	2813.2	370.0	19.5	0.25
12–14 years				
Mean	-	444.7	-	1.5
Median	-	480.0	-	1.5

7.1.2. Other efficacy studies

Not applicable.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.2. Evaluator's conclusions on clinical efficacy for the extension of indication of TDF for treatment of CHB in paediatric patients 12 years of age and older

Overall, the study design, study inclusion and exclusion criteria, and study endpoints were appropriate and in line with recommendations of the TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of chronic hepatitis B. The primary and secondary endpoints allowed evaluation of virological response (HBV DNA < 400 copies/mL and HBV DNA < LLoQ of the PCR assay [169 copies/mL]), biochemical response (normal ALT and normalised ALT), serological response (HbsAg loss and seroconversion, and HBeAg loss and seroconversion) as well as composite or combined responses of virological, biochemical and serological responses. These are consistent with current clinical practice guidelines recommendations on treatment objectives of CHB.

The baseline demographic and disease characteristics of the study population were comparable between treatment groups. Main efficacy results are summarised in Table 5 and Table 6.

Table 5. GS-US-174-0115: Summary of Key Efficacy Results at Week 72

	TDF 300 mg (12–17 years)[a] (N = 52)	PLB (12–17 years)[a] (N = 54)	P-value[b]
Primary Efficacy Endpoint			
HBV DNA < 400 copies/mL, n (%) (DBEE Analysis)	46/52 (88.5%)	0/54 (0.0%)	< 0.001
HBV DNA, n (%)			
HBV DNA < 169 copies/mL (DBEE Analysis)	44/52 (84.6%)	0/54 (0.0%)	< 0.001
Mean (SD) Change from Baseline in HBV DNA (Log_{10} copies/mL) (FAS)	-5.36 (1.952)	-0.92 (1.944)	–
Secondary Efficacy Endpoints			
ALT, n (%)			
Normal ALT (DBEE Analysis)	40/52 (76.9%)	21/54 (38.9%)	< 0.001
Normalized ALT[c] (DBEE Analysis)	26/35 (74.3%)	13/42 (31.0%)	< 0.001
Mean (SD) Change from Baseline[b] in ALT (U/L)	–58 (121.3)	–13 (143.8)	–
Serology, n (%)			
HBeAg Loss (DBEE Analysis)	10/48 (20.8%)	7/48 (14.6%)	0.41
Seroconversion to anti-HBe (DBEE Analysis)	10/48 (20.8%)	7/48 (14.6%)	0.41
HBsAg Loss (DBEE Analysis)	1/52 (1.9%)	0/54	0.32
Seroconversion to anti-HBs (DBEE Analysis)	1/52 (1.9%)	0/54	0.32
Genotypic Analysis, n (%)			
Changes from Baseline at Conserved Sites within the HBV Polymerase/Subjects Evaluated	1/52 (1.9%)	5/54 (9.3%)	–

a Age group is based on the randomization stratification (12–14 or 15–17 years of age).
b P-values for categorical data from a two-sided Cochran-Mantel-Haenszel test, controlling for strata (12–14 years or 15–17 years at the time of randomization).
c Study baseline is defined as the first dose date of DB study drug. Study week is windowed week relative to study baseline

Table 6. Summary of composite efficacy endpoints, Study GS-US-174-0115

	TDF 300 mg (12–17 years) (N = 52)	Placebo (12–17 years) (N = 54)	P-value
composite endpoint of HBV DNA < 400 copies/mL and normal ALT, n/N (%), DBEE analysis	37/52 (71.2%)	0/54 (0.0%)	< 0.001
composite endpoint of HBV DNA < 400 copies/mL and normal ALT and HBeAg loss[a], n/N (%), DBEE analysis	7/48 (14.6%)	0/48 (0.0%)	< 0.007
composite endpoint of HBV DNA < 400 copies/mL and normal ALT and HBeAg seroconversion[a], n/N (%), DBEE analysis	7/48 (14.6%)	0/48 (0.0%)	< 0.007
composite endpoint of HBV DNA < 400 copies/mL and normalised ALT[b], n/N (%), DBEE analysis	26/35 (74.3%)	0/42 (0.0%)	< 0.05
composite endpoint of HBV DNA < 400 copies/mL and normalised ALT and HBeAg loss[c], n/N (%), DBEE analysis	7/33 (21.2%)	0/42 (0.0%)	0.002
composite endpoint of HBV DNA < 400 copies/mL and normal ALT and HBeAg seroconversion[c], n/N	7/33 (21.2%)	0/42 (0.0%)	0.002

	TDF 300 mg (12–17 years) (N = 52)	Placebo (12–17 years) (N = 54)	P-value
(%), DBEE analysis			

a: among subjects who were HBeAg positive at study baseline

b: among subjects with abnormal ALT at baseline

c: among subjects who were HBeAg positive with abnormal ALT at study baseline

Efficacy analyses showed results in favour of TDF over placebo in terms of virological response (HBV DNA suppression) and biochemical response (ALT levels). However, no statistically significant differences were found between TDF and placebo in the incidences of HBeAg loss or seroconversion, and of HBsAg loss or seroconversion.

Efficacy results in terms of HBV DNA suppression at Week 72 showed that the proportion of subjects with HBV DNA < 400 copies/mL was statistically significantly higher in the TDF group compared to the placebo group (88.5% versus 0.0%; p<0.001), as was the proportion of subjects with HBV DNA below the LLoQ for the PCR assay of 169 copies/mL at Week 72 (84.6% versus 0.0%; p<0.001). Mean change from baseline in HBV DNA levels at Week 72 was -5.36 $\log_{10}$ copies/mL in the TDF group compared with -0.92 $\log_{10}$ copies/mL in the placebo group. The proportions of TDF-treated subjects with HBV DNA < 400 copies/mL and < 169 copies/mL increased from baseline to Week 48 and then was maintained through to Week 72. The mean change from baseline in HBV DNA levels in the TDF group also showed the same trend over time from baseline to Week 72.

The sponsor had provided a comparison of the virological response rates in this study with those of adult subjects with CHB treated with TDF in two Phase 3 studies (studies GS-US-174-0102 and GS-US-174-0103). The virological response rates in this study through Week 48 were generally comparable with those of the adult CHB subjects.

Subgroup analyses by age range subgroups (12 to 14 years versus 15 to 17 years) showed that the results were consistent across the age subgroups. The proportions of subjects with HBV DNA < 400 copies/mL, and HBV DNA < 169 copies/mL at Week 72 were similar between the 2 age subgroups within the TDF group (HBV DNA < 400 copies/mL: 90.0% in the age subgroup of 12 to 14 years versus 88.1% in the age subgroup of 15 to 17 years; HBV DNA < 169 copies/mL: 90.0% vs. 83.3%). Other subgroup analyses showed that the percentages of TDF-treated subjects with HBV DNA < 400 copies/mL and with HBV DNA < 169 copies/mL at Week 72 were greater in subjects with baseline abnormal ALT compared to those with baseline normal ALT (HBV DNA < 400 copies/mL: 97.1% versus 70.6%, DBEE analysis; HBV DNA < 169 copies/mL: 94.3% versus 64.7%, DBEE analysis), and also greater in subjects without prior oral HBV medications compared to those with prior oral HBV medications (HBV DNA < 400 copies/mL: 95.0% versus 84.4%, DBEE analysis; HBV DNA < 169 copies/mL: 95.0% versus 78.2%, DBEE analysis). No statistical test of significance was performed on these results. However, results showed that within the subgroup of subjects who had prior oral HBV medications, a much higher proportion of TDF-treated subjects than placebo-treated subjects achieved HBV DNA < 400 copies/mL (84.4% vs. 0.0%) and HBV DNA < 169 copies/mL (78.2% vs. 0.0%).

Efficacy results in terms of ALT levels showed that the proportion of subjects with normal ALT at Week 72 was statistically significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p<0.001). Mean ALT

change from baseline at Week 72 was -58 U/L in the TDF group, compared with -13 U/L in the placebo group. The proportion of TDF-treated subjects with normal ALT and with normalised ALT increased from baseline to Week 16 and then was maintained through to Week 72. The mean change from baseline in ALT levels in the TDF group also showed the same trend over time from baseline to Week 72. Results for the proportion of subjects with normal ALT at Week 72 were consistent across the age subgroups (80.0% in the age subgroup of 12 to 14 years versus 76.2% in the age subgroup of 15 to 17 years). However, the proportion of subjects with normalised ALT at Week 72 was numerically higher in the age subgroup of 12 to 14 years (85.7%; 6/7) than in the age subgroup of 15 to 17 years (71.4%; 20/28).

The sponsor had provided a comparison of the biochemical response rates in this study with those of adult subjects with CHB treated with TDF in two Phase 3 studies (studies GS-US-174-0102 and GS-US-174-0103). The biochemical response rates in this study through Week 48 were generally comparable with those of the adult CHB subjects.

Efficacy results in terms of serological responses (HBeAg loss or seroconversion; HBsAg loss or seroconversion) showed that the difference between the TDF and placebo groups in the proportion of subjects who were HBeAg positive at study baseline and who then experienced HBeAg loss or seroconversion to anti-HBe by Week 72 was not statistically significant. All subjects were HBsAg positive at study baseline, but overall, only two subjects (both in the TDF group) experienced HBsAg loss, one of whom experienced both HBsAg loss and seroconversion to anti-HBs at Weeks 64 and 72.

Various composite endpoints of HBV DNA < 400 copies/mL and normal or normalised ALT with/without HBeAg loss or HBeAg seroconversion all yielded statistically significant difference between TDF and placebo, in favour of TDF. The results of the composite endpoints were largely driven by that of the component of HBV DNA < 400 copies/mL.

Genotypic analysis showed that virologic response to TDF of the 6 subjects in the TDF group who had lamivudine (LAM) resistance–associated mutations at baseline was comparable to that of the remaining 46 subjects in the TDF group without these mutations. In addition, the majority (4 out of the 6) of these TDF-treated subjects with baseline LAM resistance-associated mutations achieved HBV DNA < 400 copies/mL at Week 48 and maintained this through Week 72, while an additional 1 subject achieved HBV DNA < 400 copies/mL at Week 72.

The majority of subjects (5 out of 6 subjects) that qualified for genotypic analysis at Week 48 (i.e. had HBV DNA > 400 copies/mL) had not experienced virologic breakthrough. At Week 72, 3 out of the 5 subjects that qualified for genotypic analysis had confirmed virologic breakthrough and 1 subject had unconfirmed virologic breakthrough However, all 4 instances of viral breakthrough were associated with probable non-adherence to study drug (i.e. TDF) as determined by tenofovir plasma levels below the limit of quantification. Phenotypic analyses of 1 subject that qualified for phenotypic testing at Week 48 and 3 subjects that qualified for phenotypic testing at Week 72 showed that no resistance to tenofovir had developed among these subjects.

Pharmacokinetics evaluations showed that PK parameters of tenofovir in the adolescent CHB subjects in this study receiving TDF 300 mg daily were generally comparable with historical PK data from HIV-infected adolescents and adults, as summarised by the sponsor in the Summary of Clinical Pharmacology.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy study (Study GS-US-174-0115)

In the pivotal efficacy study, the following safety data were collected:

· General adverse events (AEs)

The occurrence of AEs was checked at every visit throughout the study. All AEs that occurred after the subject consented to participate in the study and throughout the duration of the study, including the follow-up off-study medication period, were to be recorded as AEs. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) for the double-blind period were defined as AEs that began on or after the first dose date of blinded study drug and on or before the date of the last double-blind treatment period visit (for all subjects; i.e., whether they completed 72 weeks of treatment or discontinued the study prior to Week 72) or AEs that had no recorded start date.

· AEs of particular interest

The primary safety endpoint was cumulative incidence of at least a 6% decrease from baseline in bone mineral density (BMD) of the lumbar spine[13] through Week 72. Secondary safety endpoint included the cumulative incidence of at least a 6% decrease from baseline in BMD of whole body through Week 72. Other safety endpoints were both of these proportions through Week 48 and the corresponding changes in Z-scores, percent change from baseline in lumbar spine BMD, and percent change from baseline in whole body BMD. The sponsor had stated that a 6% decrease was selected in order to clearly detect a signal above the least significant change, the value of which was based on research literature[14]. Other AEs of interest included renal AEs, hepatic AEs, and bone events or fractures.

· Laboratory tests, as listed below, were performed according to the schedule.
  – Haematology (complete blood count with differential counts and platelet count)
  – Serum chemistry and liver function tests (including albumin, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [direct bilirubin if total bilirubin > 1.5 × ULN], bicarbonate, blood urea nitrogen [BUN], calcium, chloride, creatinine phosphokinase [CPK], creatinine and calculated creatinine clearance[15], glucose, lactate dehydrogenase [LDH], magnesium, phosphorus, potassium, sodium, uric acid, and amylase [lipase testing if total amylase was ≥ 1.5 × ULN])
  – Prothrombin time (PT), international normalised ratio (INR)
  – Bone biochemical markers: bone reabsorption markers (N- and C-telopeptides), bone formation markers (serum osteocalcin and bone specific alkaline phosphatase), serum parathyroid hormone (PTH) and vitamin D levels
  – Urinalysis for protein, glucose, and blood

The severity of laboratory abnormalities was graded on a 4-point scale: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and possibly life threatening (Grade 4). In addition, the protocol defined "marked laboratory abnormalities" as at least a 3-grade worsening from baseline (i.e. normal to Grade 3 or 4, or Grade 1 to Grade 4). Values with study baseline that were missing and with a toxicity Grade of 3 or more at any on-treatment post-study baseline

[13] A baseline dual energy x-ray absorptiometry (DEXA) scan of spine and whole body was performed between the screening and baseline visits (baseline DEXA scan had to have been performed prior to randomisation and receipt of study drugs), and then at Weeks 24, 48 and 72.
[14] Lenora J, Akesson K, Gerdhem P. Effect of precision on longitudinal follow-up of bone mineral density measurements in elderly women and men. *J Clin Densitom*, 13 (4):407-12, 2010.
[15] Creatinine clearance was estimated by the Schwartz formula (12 to 17 years old) or the Cockcroft-Gault equation (> 18 years old; i.e. as the adolescent subjects reached adulthood [age ≥ 18 years] during the study, the Cockcroft-Gault equation was applied).

visit up to and including the date of last double-blind treatment period visit were also considered marked laboratory abnormalities.

Hepatic or ALT flare was defined as serum ALT > 2 × baseline and > 10 × ULN with or without associated symptoms, or confirmed ALT elevation (defined as 1-grade shift or 2 times the previous value) associated with confirmed changes outside of the normal range in other laboratory parameters suggestive of worsening hepatic function (total bilirubin ≥ 2 mg/dL above baseline, abnormal prothrombin time ≥ 2 seconds or INR ≥ 0.5 over baseline, abnormal serum albumin ≥ 1 g/dL below baseline, or elevated serum lactate levels [defined as 2 × ULN per the Adult AIDS Clinical Trials Group guidelines]). All events of hepatic flares were to be reported as a serious adverse event (SAE).

Comments: Overall, the safety endpoints and laboratory tests, evaluating effects of TDF on the kidneys, liver and bones, were appropriate. The currently approved Australian PI for TDF states that postmarketing safety data showed that TDF may cause renal adverse reactions (including renal failure, Fanconi syndrome, and other proximal tubulopathies). Animal toxicology studies had shown bone toxicities including a reduction in BMD. In addition, osteomalacia associated with TDF proximal renal tubulopathy had been identified as an adverse reaction through postmarketing surveillance. Postmarketing surveillance has also identified hepatic events of hepatic steatosis, increased liver enzymes and hepatitis. Recurrent ALT flares may also occur as part of the natural history of CHB.

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable

8.1.3. Dose-response and non-pivotal efficacy studies

Not applicable

8.1.4. Other studies evaluable for safety only

Not applicable

8.2. Patient exposure

All subjects completed at least 24 weeks of treatment (Table 7). The mean duration of treatment was 497.3 days in the TDF group and 489.7 days in the placebo group. The percentage of subjects with 72 weeks of study drug exposure was 98.1% in the TDF group and 92.6% in the placebo group.

Comments: Overall, the study drug exposure is adequate to assess if the safety profile is consistent with that reported in the Product Information.

Table 7. GS-US-174-0115: Exposure to Double-Blind Study Drug (Safety Analysis Set[a])

	TDF 12-14 Years[b] (N=10)	TDF 15-17 Years[b] (N=42)	PLB 12-14 Years[b] (N=13)	PLB 15-17 Years[b] (N=41)	Total TDF (N=52)	Total PLB (N=54)
Days on Study Drug[c]						
N	10	42	13	41	52	54
Mean (SD)	503.6 (1.90)	495.8 (52.65)	503.9 (1.55)	485.1 (59.79)	497.3 (47.32)	489.7 (52.58)
Median	503.5	504.0	504.0	504.0	504.0	504.0
Q1, Q3	502.0, 504.0	503.0, 504.0	503.0, 504.0	503.0, 505.0	502.0, 504.0	503.0, 505.0
Min, Max	502, 508	163, 513	502, 508	260, 509	163, 513	260, 509
Cumulative duration of exposure						
Baseline [Study Day 1]	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)
Week 4 [Study Day 2 - 42]	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)
Week 8 [Study Day 43 - 84]	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)
Week 16 [Study Day 85 - 140]	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)
Week 24 [Study Day 141 - 196]	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)
Week 32 [Study Day 197 - 252]	10 (100.0%)	41 (97.6%)	13 (100.0%)	41 (100.0%)	51 (98.1%)	54 (100.0%)
Week 40 [Study Day 253 - 308]	10 (100.0%)	41 (97.6%)	13 (100.0%)	41 (100.0%)	51 (98.1%)	54 (100.0%)
Week 48 [Study Day 309 - 364]	10 (100.0%)	41 (97.6%)	13 (100.0%)	39 (95.1%)	51 (98.1%)	52 (96.3%)
Week 56 [Study Day 365 - 420]	10 (100.0%)	41 (97.6%)	13 (100.0%)	38 (92.7%)	51 (98.1%)	51 (94.4%)
Week 64 [Study Day 421 - 476]	10 (100.0%)	41 (97.6%)	13 (100.0%)	37 (90.2%)	51 (98.1%)	50 (92.6%)
Week 72 [Study Day 477 - 532]	10 (100.0%)	41 (97.6%)	13 (100.0%)	37 (90.2%)	51 (98.1%)	50 (92.6%)
Adherence (%)						
N	10	42	13	41	52	54
Mean (SD)	99.3 (0.35)	98.6 (2.27)	97.9 (4.03)	97.9 (3.77)	98.7 (2.06)	97.9 (3.80)
Median	99.4	99.5	99.6	99.2	99.4	99.2
Q1, Q3	99.2, 99.4	98.0, 100.0	98.8, 99.8	97.8, 99.8	98.7, 99.8	98.2, 99.8
Min, Max	98.8, 100.0	88.7, 100.0	86.3, 100.0	82.1, 100.0	88.7, 100.0	82.1, 100.0
Adherence Categories						
< 90%	0	1 (2.4%)	1 (7.7%)	2 (4.9%)	1 (1.9%)	3 (5.6%)
≥ 90%	10 (100.0%)	41 (97.6%)	12 (92.3%)	39 (95.1%)	51 (98.1%)	51 (94.4%)
Adherence (%) (North America)						
N	0	2	1	2	2	3
Mean (SD)		98.5 (0.62)	86.3	95.3 (3.24)	98.5 (0.62)	92.3 (5.71)
Median		98.5	86.3	95.3	98.5	93.0
Q1, Q3		98.0, 98.9	86.3, 86.3	93.0, 97.6	98.0, 98.9	86.3, 97.6
Min, Max		98.0, 98.9	86.3, 86.3	93.0, 97.6	98.0, 98.9	86.3, 97.6
Adherence Categories (North America)						
< 90%	0	0	1 (100.0%)	0	0	1 (33.3%)
≥ 90%	0	2 (100.0%)	0	2 (100.0%)	2 (100.0%)	2 (66.7%)
Adherence (%) (Europe)						
N	10	40	12	39	50	51
Mean (SD)	99.3 (0.35)	98.6 (2.32)	98.9 (2.09)	98.0 (3.78)	98.7 (2.10)	98.2 (3.46)
Median	99.4	99.6	99.7	99.2	99.4	99.4
Q1, Q3	99.2, 99.4	98.0, 100.0	98.8, 99.9	98.2, 99.8	98.8, 99.8	98.2, 99.8
Min, Max	98.8, 100.0	88.7, 100.0	92.5, 100.0	82.1, 100.0	88.7, 100.0	82.1, 100.0
Adherence Categories (Europe)						
< 90%	0	1 (2.5%)	0	2 (5.1%)	1 (2.0%)	2 (3.9%)
≥ 90%	10 (100.0%)	39 (97.5%)	12 (100.0%)	37 (94.9%)	49 (98.0%)	49 (96.1%)

a. The safety analysis set included subjects who received at least 1 dose of DB study medication

b. Age group is based on the randomization stratification (12-14 or 15-17 years of age)

c. Duration of exposure is calculated from (last double-blind dose date – first double-blind dose date +1)

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal study

An overview of the number and percentage of subjects with TEAEs in each treatment group is presented in Table 8. The percentages of subjects with any TEAEs were comparable between treatment groups (84.6% [44/52] and 88.9% [48/54] in the TDF and placebo groups, respectively).

TEAEs that occurred in ≥5% of subjects in either treatment group are presented in the CSR. The most commonly reported TEAEs in the TDF group were pharyngitis (28.8% vs. 20.4% in the placebo group), nasopharyngitis (9.6% vs. 22.2%), upper respiratory tract infection (9.6% vs. 13.0%), and rhinitis (9.6% vs. 5.6%). Among TEAEs occurring with ≥ 5% incidence in either treatment group, statistically significant differences were noted only for increased ALT (p = 0.024), acne (p = 0.029) and lymphadenopathy (p = 0.027), all of which had higher incidence in the placebo group than in the TDF group.

Table 8. GS-US-174-0115: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set[a])

Adverse Event Category, n (%)[b]	TDF 12-14 Years[c] (N=10)	TDF 15-17 Years[c] (N=42)	PLB 12-14 Years[c] (N=13)	PLB 15-17 Years[c] (N=41)	Total TDF (N=52)	Total PLB (N=54)
Number of Subjects with Treatment-Emergent AEs[d]	9 (90.0%)	35 (83.3%)	8 (61.5%)	40 (97.6%)	44 (84.6%)	48 (88.9%)
Number of Subjects with Grade 3 or 4 Treatment-Emergent AEs[d]	1 (10.0%)	4 (9.5%)	4 (30.8%)	9 (22.0%)	5 (9.6%)	13 (24.1%)
Number of Subjects with Grade 2, 3, or 4 Treatment-Emergent AEs[d]	6 (60.0%)	19 (45.2%)	5 (38.5%)	31 (75.6%)	25 (48.1%)	36 (66.7%)
Number of Subjects with Study Drug-Related Treatment-Emergent AEs[d]	1 (10.0%)	7 (16.7%)	3 (23.1%)	6 (14.6%)	8 (15.4%)	9 (16.7%)
Number of Subjects with Grade 3 or 4 Study Drug-Related Treatment-Emergent AEs[d]	0	1 (2.4%)	2 (15.4%)	2 (4.9%)	1 (1.9%)	4 (7.4%)
Number of Subjects with Grade 2, 3, or 4 Study Drug-Related Treatment-Emergent AEs[d]	1 (10.0%)	2 (4.8%)	2 (15.4%)	3 (7.3%)	3 (5.8%)	5 (9.3%)
Number of Subjects with Treatment-Emergent AEs[d] that Caused Dose Change or Interruption of Study Drug	0	0	1 (7.7%)	0	0	1 (1.9%)
Number of Subjects with Treatment-Emergent SAEs[d]	3 (30.0%)	3 (7.1%)	4 (30.8%)	8 (19.5%)	6 (11.5%)	12 (22.2%)
Number of Subjects with Study Drug-Related Treatment-Emergent SAEs	0	1 (2.4%)	2 (15.4%)	1 (2.4%)	1 (1.9%)	3 (5.6%)
Number of Subjects with Permanent Study Drug Discontinuation due to Treatment-Emergent AEs[d]	0	1 (2.4%)	0	0	1 (1.9%)	0
Number of Subjects with Non-Treatment-Emergent AEs[d]	1 (10.0%)	6 (14.3%)	2 (15.4%)	9 (22.0%)	7 (13.5%)	11 (20.4%)
Number of Subjects with Permanent Study Drug Discontinuation due to Non-Treatment-Emergent AEs[d]	0	0	0	0	0	0
Number of Subjects Who Died during Study	0	0	0	0	0	0

a The safety analysis set included subjects who received at least 1 dose of DB study medication.

b Subjects are counted once only for each category.

c Age group is based on the randomization stratification (12-14 or 15-17 years of age).

d Treatment-emergent AEs for the double-blind period were defined as events that met 1 of the following criteria: Began on or after the first dose date of blinded study drug and on or before the date of the last double-blind treatment period visit (for all subjects; ie, whether they completed 72 weeks of treatment or discontinued the study prior to Week 72) or had no recorded start date.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal study

The incidences of any treatment-related TEAEs were comparable between treatment groups (15.4% [8/52] and 16.7% [9/54] in the TDF and placebo groups, respectively). Treatment-related TEAEs are presented in Table 9.

Table 9. GS-US-174-0115: Treatment-Emergent Adverse Events Related to Study Drug (Safety Analysis Set[a])

Number of Subjects with Treatment-Emergent Adverse Events, Per SOC, HLT, and PT [b,c,d]	TDF 12-14 Years[e] (N=10)	TDF 15-< 18 Years[e] (N=42)	PLB 12-14 Years[e] (N=13)	PLB 15-< 18 Years[e] (N=41)	Total TDF (N=52)	Total PLB (N=54)
Number of Subjects with Any Event	1 (10.0%)	7 (16.7%)	3 (23.1%)	6 (14.6%)	8 (15.4%)	9 (16.7%)
Gastrointestinal Disorders	0	4 (9.5%)	1 (7.7%)	0	4 (7.7%)	1 (1.9%)
Dental and Periodontal Infections and Inflammations	0	1 (2.4%)	0	0	1 (1.9%)	0
Dental Caries	0	1 (2.4%)	0	0	1 (1.9%)	0
Flatulence, Bloating, and Distension	0	1 (2.4%)	0	0	1 (1.9%)	0
Flatulence	0	1 (2.4%)	0	0	1 (1.9%)	0
Gastrointestinal and Abdominal Pains (Excl Oral and Throat)	0	1 (2.4%)	1 (7.7%)	0	1 (1.9%)	1 (1.9%)
Abdominal Pain	0	1 (2.4%)	1 (7.7%)	0	1 (1.9%)	1 (1.9%)
Nausea and Vomiting Symptoms	0	2 (4.8%)	1 (7.7%)	0	2 (3.8%)	1 (1.9%)
Nausea	0	2 (4.8%)	0	0	2 (3.8%)	0
Vomiting	0	0	1 (7.7%)	0	0	1 (1.9%)
Oral Soft Tissue Swelling and Edema	0	1 (2.4%)	0	0	1 (1.9%)	0
Gingival Swelling	0	1 (2.4%)	0	0	1 (1.9%)	0
General Disorders and Administration Site Conditions	0	0	0	1 (2.4%)	0	1 (1.9%)
Asthenic Conditions	0	0	0	1 (2.4%)	0	1 (1.9%)
Malaise	0	0	0	1 (2.4%)	0	1 (1.9%)
Hepatobiliary Disorders	0	1 (2.4%)	0	0	1 (1.9%)	0
Hepatocellular Damage and Hepatitis NEC	0	1 (2.4%)	0	0	1 (1.9%)	0
Hepatitis	0	1 (2.4%)	0	0	1 (1.9%)	0
Investigations	0	1 (2.4%)	2 (15.4%)	3 (7.3%)	1 (1.9%)	5 (9.3%)
Digestive Enzymes	0	0	0	1 (2.4%)	0	1 (1.9%)
Lipase Increased	0	0	0	1 (2.4%)	0	1 (1.9%)
Liver Function Analyses	0	1 (2.4%)	2 (15.4%)	2 (4.9%)	1 (1.9%)	4 (7.4%)
Alanine Aminotransferase Increased	0	1 (2.4%)	2 (15.4%)	2 (4.9%)	1 (1.9%)	4 (7.4%)
Metabolism and Nutrition Disorders	0	0	1 (7.7%)	0	0	1 (1.9%)
Appetite Disorders	0	0	1 (7.7%)	0	0	1 (1.9%)
Anorexia	0	0	1 (7.7%)	0	0	1 (1.9%)
Musculoskeletal and Connective Tissue Disorders	1 (10.0%)	0	0	1 (2.4%)	1 (1.9%)	1 (1.9%)
Bone Disorders NEC	1 (10.0%)	0	0	0	1 (1.9%)	0
Exostosis	1 (10.0%)	0	0	0	1 (1.9%)	0
Bone Related Signs and Symptoms	0	0	0	1 (2.4%)	0	1 (1.9%)
Bone Pain	0	0	0	1 (2.4%)	0	1 (1.9%)
Skin and Subcutaneous Tissue Disorders	0	2 (4.8%)	0	1 (2.4%)	2 (3.8%)	1 (1.9%)
Alopecias	0	1 (2.4%)	0	1 (2.4%)	1 (1.9%)	1 (1.9%)
Alopecia	0	1 (2.4%)	0	1 (2.4%)	1 (1.9%)	1 (1.9%)
Nail and Nail Bed Conditions (Excl Infections and Infestations)	0	1 (2.4%)	0	0	1 (1.9%)	0
Nail Disorder	0	1 (2.4%)	0	0	1 (1.9%)	0

a The safety analysis set included subjects who received at least 1 dose of DB study medication.

b Events coded using MedDRA version 11

c Subjects are counted once only for each category.

d Treatment-emergent AEs for the double-blind period were defined as events that met 1 of the following criteria: Began on or after the first dose date of blinded study drug and on or before the date of the last double-blind treatment period visit (for all subjects; ie, whether they completed 72 weeks of treatment or discontinued the study prior to Week 72) or had no recorded start date.

e Age group is based on the randomization stratification (12 to 14 or 15 to < 18 years of age).

HLT: High level term; SOC: system organ class; PT: preferred term

The most commonly reported treatment-related TEAE by preferred term in the TDF group was nausea (3.8% [2/52] vs. 1.9% [1/54] in the placebo group). All other treatment-related TEAEs in the TDF group were reported by only 1 subject each.

The majority of treatment-related TEAEs in the TDF group were assessed as being of grade 1 or 2 in severity, and only 1 subject (1.9%) in the TDF group had a Grade 3 or 4 treatment-related TEAE (hepatitis), compared with 4 subjects (7.4%) in the placebo group.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal study

There were no deaths during Study GS-US-174-0115.

Overall, 11.5% of subjects (6/52) in the TDF group and 22.2% of subjects (12/54) in the placebo group reported any SAEs. The most frequently reported SAE by preferred term in the TDF group was hepatitis (3.8% [2/52] vs. 13.0% [7/54] in the placebo group). All other SAEs in the TDF group were reported by only 1 subject each.

Overall, 1.9% of subjects (1/52) in the TDF group and 5.6% of subjects (3/54) in the placebo group reported any treatment-related SAEs. The single report of treatment-related SAE in the TDF group was that of hepatitis (1.9% [1 subject] vs. 0.0% [0/54] in the placebo group).

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal study

The incidence rate of any TEAEs resulting in permanent discontinuation of study drug was 1.9% (1/52) in the TDF group and 0.0% (0/54) in the placebo group. The single subject in the TDF group who was withdrawn from study drug had experienced Grade 4 syncope on Day 145. This was considered a SAE but was not considered to be related to study drug.

8.4. Laboratory tests

Treatment-emergent marked laboratory abnormalities are summarised. The incidence rate of any treatment-emergent marked laboratory abnormalities was 13.5% (7/52) in the TDF group and 20.4% (11/54) in the placebo group. The most frequently reported marked laboratory abnormalities in the TDF group were urine blood (7.7% [4/52] vs. 9.3% [5/54] in the placebo group) and serum lipase (3.8% [2/52] vs. 1.9% [1/54] in the placebo group).

Treatment-emergent Grade 3 or 4 laboratory abnormalities are summarised. The incidence rate of any treatment-emergent Grade 3 or 4 laboratory abnormalities was 26.9% (14/52) in the TDF group and 50.0% (27/54) in the placebo group. The most frequently reported grade 3 or 4 laboratory abnormalities in the TDF group were in ALT (11.5% [6/52] vs. 40.7% [22/54] in the placebo group) and urine blood (7.7% [4/52] vs. 11.1% [6/54] in the placebo group).

8.4.1. Liver function

8.4.1.1. Pivotal study

Liver laboratory tests were summarised as on-treatment or off-treatment hepatic flare, which definition has been presented in Section 8.1. Overall, 2 subjects (3.8%) in TDF group and 10 subjects (18.5%) in placebo group had on-treatment hepatic flares. One additional subject in the placebo group experienced an off-treatment hepatic flare during the treatment-free follow-up period.

8.4.2. Kidney function

8.4.2.1. Pivotal study

No study subjects had a Grade 3 or 4 increase in serum creatinine or decrease in serum phosphorus. The mean (SD) serum creatinine levels at baseline were comparable between treatment groups (0.7 [0.12] mg/dL and 0.7 [0.13] mg/dL in the TDF and placebo groups, respectively). The mean changes in creatinine from baseline to Week 72 were similar between

the TDF and placebo groups (0.1 [SD 0.10] mg/dL in the TDF group and 0.1 [SD 0.09] mg/dL in the placebo group).

No subject had a confirmed increase from baseline in serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance rate of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. Six subjects (11.5%) in the TDF group and 2 subjects (3.7%) in the placebo group had a confirmed increase from baseline in serum creatinine of at least 0.3 mg/dL. All of these elevations were transient or within the normal range. Three subjects (5.8%) in the TDF group and 5 subjects (9.3%) in the placebo group had a confirmed creatinine clearance rate of < 80 mL/min.

8.4.3. Prothrombin time

8.4.3.1. Pivotal study

No subject in the TDF group had prothrombin time > ULN, compared with 2 subjects (3.8%) in the placebo group who did.

8.4.4. Bone-specific laboratory parameters

8.4.4.1. Pivotal study

Bone biochemical markers for bone formation (serum osteocalcin and bone specific ALP) and bone reabsorption (N- and C-telopeptides), serum PTH and vitamin D levels were evaluated.

At Week 72, mean decreases from baseline in serum osteocalcin and in bone-specific ALP were comparable between both treatment groups (mean [SD] change from baseline in serum osteocalcin: -23.9 [35.48] ng/mL and -29.7 [41.16] ng/mL in the TDF and placebo groups, respectively; serum bone-specific ALP: -25.62 [28.045] µg/L and -24.90 [31.666] µg/L, respectively). Analyses of biochemical markers of bone resorption showed that at Week 72, mean decreases from baseline in serum N-telopeptides and in serum C-telopeptides were also comparable between both treatment groups (mean [SD] change from baseline in serum N-telopeptides: -9.7 [17.92] nmol BCE/L and -12.0 [18.55] nmol BCE/L in the TDF and placebo groups, respectively; serum C-telopeptides: -0.224 [0.6443) ng/mL and -0.347 [0.5289] ng/mL, respectively). At Week 72, mean change from baseline in serum PTH was small in both treatment groups (2 [SD 22.8] pg/mL in the TDF group and -4 [SD 21.8] pg/mL in the placebo group). At Week 72, the mean change from baseline in 25-hydroxy vitamin D levels were comparable between treatment groups (6.3 [SD 9.84] ng/mL in the TDF group and 5.1 [SD 9.91] ng/mL in the placebo group).

8.5. Bone mineral density (BMD)

8.5.1. Pivotal study

8.5.1.1. Lumbar spine BMD

The primary safety endpoint was the cumulative incidence of at least a 6% decrease from baseline in BMD of the lumbar spine through Week 72. Results showed that no subjects in either treatment group met this primary safety endpoint. Five subjects (3 in the TDF group and 2 in the placebo group), had a decrease from baseline of > 4% in lumbar spine BMD. None of these subjects were reported as having had bone AEs, including fractures. Categorical summaries of percent change from baseline in lumbar spine BMD are presented in Table 10.

Table 10. GS-US-174-0115: Percent Change from Study Baseline in Spine Bone Mineral Density by Study Week: Categorical Summaries on Number of Subjects (Safety Analysis Set[a])

Spine Bone Mineral Density (g/cm^2)	TDF 12-14 Years[b] (N=10)	TDF 15-< 18 Years[b] (N=42)	PLB 12-14 Years[b] (N=13)	PLB 15-< 18 Years[b] (N=41)	Total TDF (N=52)	Total PLB (N=54)
Percent Change from Baseline[c] Category at Week 24[d]						
Percent Change ≤ -6%	0	0	0	0	0	0
-6% < Percent Change ≤ -3%	0	2 (4.8%)	1 (7.7%)	0	2 (3.8%)	1 (1.9%)
-3% < Percent Change ≤ 0%	0	12 (28.6%)	1 (7.7%)	8 (19.5%)	12 (23.1%)	9 (16.7%)
0% < Percent Change ≤ 3%	3 (30.0%)	19 (45.2%)	1 (7.7%)	17 (41.5%)	22 (42.3%)	18 (33.3%)
3% < Percent Change ≤ 6%	4 (40.0%)	5 (11.9%)	3 (23.1%)	11 (26.8%)	9 (17.3%)	14 (25.9%)
Percent Change > 6%	3 (30.0%)	4 (9.5%)	6 (46.2%)	5 (12.2%)	7 (13.5%)	11 (20.4%)
Missing	0	0	1 (7.7%)	0	0	1 (1.9%)
Percent Change from Baseline[c] Category at Week 48[d]						
Percent Change ≤ -6%	0	0	0	0	0	0
-6% < Percent Change ≤ -3%	0	2 (4.8%)	0	1 (2.4%)	2 (3.8%)	1 (1.9%)
-3% < Percent Change ≤ 0%	0	12 (28.6%)	2 (15.4%)	6 (14.6%)	12 (23.1%)	8 (14.8%)
0% < Percent Change ≤ 3%	1 (10.0%)	12 (28.6%)	0	9 (22.0%)	13 (25.0%)	9 (16.7%)
3% < Percent Change ≤ 6%	1 (10.0%)	9 (21.4%)	2 (15.4%)	10 (24.4%)	10 (19.2%)	12 (22.2%)
Percent Change > 6%	8 (80.0%)	6 (14.3%)	8 (61.5%)	11 (26.8%)	14 (26.9%)	19 (35.2%)
Missing	0	1 (2.4%)	1 (7.7%)	4 (9.8%)	1 (1.9%)	5 (9.3%)
Percent Change from Baseline[c] Category at Week 72[d]						
Percent Change ≤ -6%	0	0	0	0	0	0
-6% < Percent Change ≤ -3%	0	3 (7.1%)	0	2 (4.9%)	3 (5.8%)	2 (3.7%)
-3% < Percent Change ≤ 0%	0	5 (11.9%)	1 (7.7%)	3 (7.3%)	5 (9.6%)	4 (7.4%)
0% < Percent Change ≤ 3%	0	10 (23.8%)	2 (15.4%)	6 (14.6%)	10 (19.2%)	8 (14.8%)
3% < Percent Change ≤ 6%	1 (10.0%)	11 (26.2%)	0	9 (22.0%)	12 (23.1%)	9 (16.7%)
Percent Change > 6%	7 (70.0%)	10 (23.8%)	9 (69.2%)	16 (39.0%)	17 (32.7%)	25 (46.3%)
Missing	2 (20.0%)	3 (7.1%)	1 (7.7%)	5 (12.2%)	5 (9.6%)	6 (11.1%)

a The safety analysis set included subjects who received at least 1 dose of DB study medication.
b Age group is based on the randomization stratification (12 to 14 or 15 to < 18 years of age).
c Study baseline is defined as the first dose date of double-blind study drug.
d Study week is windowed week relative to study baseline.

At Week 72, the proportion of subjects with change from baseline in lumbar spine BMD of between -6% and -3%, and of between -3% and 0% was higher in the TDF group than in the placebo group. With regards to increases from baseline in lumbar spine BMD at Week 72, the proportion of subjects with change from baseline in lumbar spine BMD of between 0% and 3% and of between 3% and 6% was higher in the TDF group than in the placebo group. However, there was a lower proportion of TDF-treated subjects at Week 72 with increase from baseline in lumbar spine BMD of > 6%, compared to the placebo group (32.7% [17/52] in the TDF group vs. 46.3% [25/54] in the placebo group). These results were not analysed for statistical significance.

Mean baseline lumbar spine BMDs were comparable between treatment groups (1.00 [SD 0.160] g/cm^2 and 1.01 [SD 0.162] g/cm^2 in the TDF and placebo groups, respectively). Overall, both treatment groups had an increase in mean lumbar spine BMD from baseline through to Week 72, which was expected for an adolescent population. However, the percent increase from baseline in lumbar spine BMD in the TDF-treated subjects was less than that in the placebo subjects at Week 24 (1.87% in the TDF group vs. 3.42% in the placebo group, p = 0.005), at Week 48 (3.50% vs. 5.58%, p = 0.046), and at Week 72 (4.95% vs. 8.14%, p = 0.053).

Overall, there was a decrease in mean lumbar spine BMD Z-score[16] from baseline to Weeks 24, 48 and 72 in the TDF group compared to an increase in the placebo group (Week 24: -0.06 [SD 0.214] in the TDF group vs. 0.04 [SD 0.233] in the placebo group; Week 48: -0.08 [SD 0.254] vs. 0.02 [SD 0.322]; Week 72: -0.05 [SD 0.310] vs. 0.07 [SD 0.377]). These results were not analysed for statistical significance. Results showed that there was no obvious trend of decreasing mean Z-score with time from baseline to Week 72 in the TDF-treated subjects. (mean change from baseline in whole body BMD Z-scores of -0.06, -0.08 and -0.05 at Weeks 24, 48 and 72, respectively).

Categorical summaries of lumbar spine BMD Z-scores are presented in the CSR. At Week 72, the majority of subjects in both treatment groups had Z-scores in the > -1 category (65.4% [34/52] in the TDF group and 72.2% [39/54] in the placebo group). At Week 72, the proportion of subjects with Z-scores of between -1 and -2, and of less than -2 was higher in the TDF group than in the placebo group (Z-scores of -1 to -2: 21.2% [11/52] in the TDF group vs. 14.8% [8/54] in the placebo group; Z-scores of less than -2: 3.8% [2/52] vs. 1.9% [1/54]). Results showed that there was no obvious trend of increasing proportion of subjects with Z-scores less than -2 with time from baseline to Week 72 in the TDF group.

8.5.1.2. Whole body BMD

Secondary safety endpoints included the cumulative incidence of at least a 6% decrease from baseline in BMD of whole body through Week 72. Results showed that no subjects in either treatment group met this secondary safety endpoint. Categorical summaries of percent change from baseline in whole body BMD are presented in the CSR. At Week 72, the proportion of subjects with change from baseline in whole body BMD of between -6% and -3%, and of between -3% and 0% was higher in the TDF group than in the placebo group. With regards to increases from baseline in whole body BMD at Week 72, the proportion of subjects with change from baseline in whole body BMD of between 0% and 3% was higher in the TDF group than in the placebo group. However, there was a lower proportion of TDF-treated subjects at Week 72 with increases from baseline in whole body BMD of between 3% and 6% and of > 6%, compared to the placebo group (change from baseline of between 3% and 6%: 23.1% [12/52] in the TDF group vs. 33.3% [18/54] in the placebo group; change from baseline of > 6%: 13.5% [7/52] vs. 31.5% [17/54]). These results were not analysed for statistical significance.

Mean baseline whole body BMDs were comparable between treatment groups (1.09 [SD 0.115] g/cm^2 and 1.07 [SD 0.095] g/cm^2 in the TDF and placebo groups, respectively). Overall, both treatment groups had an increase in mean whole body BMD from baseline through to Week 72, which was expected for an adolescent population. However, the percent increase from baseline in whole body BMD in the TDF-treated subjects was less than that in the placebo subjects at Week 24 (1.10% in the TDF group vs. 2.52% in the placebo group, $p<0.001$), at Week 48 (2.05% vs. 3.87%, $p<0.001$), and at Week 72 (2.84% vs. 5.37%, $p = 0.013$).

Overall, there was a decrease in mean whole body BMD Z-score from baseline to Weeks 24, 48 and 72 in the TDF group compared to an increase in the placebo group (Week 24: -0.07 [SD 0.259] in the TDF group vs. 0.09 [SD 0.217] in the placebo group; Week 48: -0.12 [SD 0.318] vs. 0.03 [SD 0.316]; Week 72: -0.15 [SD 0.379] vs. 0.06 [SD 0.361]). These results were not analysed for statistical significance. Results showed that there appeared to be a trend of decreasing mean Z-scores with time from baseline through to Week 72 in the TDF-treated subjects (mean change from baseline in whole body BMD Z-scores of -0.07, -0.12 and -0.15 at Weeks 24, 48 and 72 respectively).

[16] Z-scores were used to express the deviation from a reference population for lumbar spine and whole body BMD. A Z-score of 0 indicates that a subject's BMD is typical of the population for their age and gender. A negative Z-score indicates that the subject's recorded BMD value is lower than typical for their age and gender. A positive Z-score indicates that the subject's recorded BMD value is higher than typical for their age and gender.

Categorical summaries of whole body BMD Z-scores are presented in the CSR. At Week 72, the majority of subjects in both treatment groups had Z-scores in the > -1 category (67.3% [35/52] in the TDF group and 70.4% [38/54] in the placebo group). At Week 72, the proportion of subjects with Z-scores of between -1 and -2 was lower in the TDF group than in the placebo group (15.4% [8/52] in the TDF group vs. 18.5% [10/54] in the placebo group). At Week 72, there were 2 subjects (3.8%) in the TDF group with whole body BMD Z-scores less than -2, compared to 1 subject (1.9%) in the placebo group. Results showed that there was no obvious trend of increasing proportion of subjects with Z-scores less than -2 with time from baseline through to Week 72 in the TDF group.

8.6. Height, weight and body mass index

8.6.1. Pivotal study

Mean (SD) baseline Z-scores[17] for height were similar between treatment groups (0.13 [0.844] in the TDF group and 0.17 [1.017] in the placebo group). There was no statistically significant difference between treatment groups in mean change from baseline in height Z-scores from Week 4 through to Week 72.

Mean (SD) baseline Z-score for weight was numerically higher in the TDF group compared to the placebo group (0.10 [0.908] in the TDF group and -0.02 [0.945] in the placebo group). Weight Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at all timepoints except at Weeks 40, 48, 56 and 72. Results showed that there appeared to be a trend of decreasing mean Z-scores with time from baseline through to Week 72 in the TDF-treated subjects (mean change from baseline in weight Z-scores of -0.03, -0.08, -0.12, -0.13, -0.14, -0.13, -0.12, -0.18, -0.20 and -0.20 at Weeks 4, 8, 16, 24, 32, 40, 48, 56, 64 and 72, respectively).

Mean (SD) baseline Z-scores for BMI was numerically higher in the TDF group compared to the placebo group (-0.09 [1.075] in the TDF group and -0.20 [1.019] in the placebo group). BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at all timepoints except at Week 40 and Week 48. Results showed that there appeared to be a trend of decreasing mean Z-scores with time from baseline through to Week 72 in the TDF-treated subjects (mean change from baseline in BMI Z-scores of 0.05, 0.02, 0.00, -0.04, -0.01, -0.11, -0.07, -0.08, -0.11 and -0.10 at Weeks 4, 8, 16, 24, 32, 40, 48, 56, 64 and 72, respectively).

8.7. Adverse events of interest

8.7.1. Pivotal study

8.7.1.1. Renal AEs

Overall, renal and urinary AEs were reported in 3 subjects in the study, all of whom were in the placebo group. One subject reported an AE of Grade 3 acute renal colic, which was recorded as an SAE, and was not considered to be related to study drug. Another subject reported an AE of Grade 1 pollakiuria (not considered to be related to study drug) and the third subject had Grade 1 proteinuria (not considered to be related to study drug).

Changes in creatinine and creatinine clearance have been discussed in Section 8.4.2.1.

[17] Z-scores were used to express the deviation from a reference population for height, weight, and BMI, separately. A Z-score of 0 indicates that a subject is typical of the population for their age and gender. A negative Z-score indicates that the subject's recorded value is lower than typical for their age and gender. A positive Z-score indicates that the subject's recorded value is higher than typical for their age and gender.

8.7.1.2. Hepatic AEs

Overall, 13 subjects (3 subjects [5.8%; 3/52] in the TDF group and 10 subjects [18.5%; 10/54] in the placebo group) had "Hepatobiliary Disorders" SOC events reported as an AE. Of these, "hepatitis" (preferred term) was reported in the 3 TDF-treated subjects (5.8%; 3/52) and in 7 of the 10 placebo-treated subjects (13.0%, 7/54). "Hepatomegaly" was reported in the other 2 placebo-treated subjects, and "hypertransaminasemia" was reported in the remaining placebo-treated subject. In addition, 18 subjects (4 subjects [7.7%; 4/52] in the TDF group and 14 subjects [25.9%; 14/54] in the placebo group) had "Investigations" SOC results related to liver function reported as an AE. Of these, increased ALT (preferred term) was reported as an AE by 3 subjects (5.8%; 3/52) in the TDF group, and 12 subjects (22.2%; 12/54) in the placebo group.

Hepatic flares that were reported as grade 3 or 4 AEs occurred in 14 subjects in the study (2 subjects [3.8%; 2/52] in the TDF group and12 subjects [22.2%; 12/54] in the placebo group). Among these, 8 subjects in the placebo group had grade 4 hepatic flares AEs, while no hepatic flare was reported as Grade 4 AEs in the TDF group. The proportion of subjects with hepatic flares based on clinical laboratory criteria had been presented in Section 8.4.1.1.

8.7.1.3. Bone AEs

Overall 5 subjects (3 subjects [5.8%; 3/52] in the TDF group and 2 subjects [3.7%; 2/54] in the placebo group) in the study had AEs related to bone events or fractures. One subject in the TDF group had a grade 3 hand fracture sustained in an altercation, which was considered an SAE, but not related to study drug. The remaining 2 subjects in the TDF group had exostosis and jaw pain, respectively. The 2 subjects in the placebo group reported AEs of bone pain.

8.8. Post-marketing experience

The sponsor had stated that a cumulative assessment of paediatric safety data for TDF in HBV mono-infected patients from the Gilead Drug Safety and Public Health database up to 31 December 2011 had been performed, and that after excluding reports of SAEs from Study GS-US-174-0115, no cases involving HBV mono-infected paediatric patients < 18 years old had been identified. The sponsor had stated that a search of the literature had also been performed up to 31 December 2011, and did not identify any literature articles of clinical studies conducted to evaluate TDF in the treatment of HBV mono-infected paediatric subjects. Hence, no changes to the prescribing information relating to post-marketing adverse drug reactions are being proposed as a consequence of the data included in this submission.

8.9. Evaluator's overall conclusions on clinical safety

Overall, the incidences of all-causality AEs and of treatment-related AEs were comparable between the 2 treatment groups. The incidences of grade 3 or 4 all-causality AEs, grade 3 or 4 treatment-related AEs, all-causality SAEs and treatment-related SAEs were lower in the TDF group compared to the placebo group. The safety results of the study were consistent with the known adverse effects of TDF.

The AEs elicited in this pivotal study are known adverse effects of TDF stated in the currently-approved Australian PI for TDF. The incidence rate of any treatment-emergent Grade 3 or 4 laboratory abnormalities was lower in the TDF group compared to the placebo group (26.9% vs. 50.0%). The most frequently reported grade 3 or 4 laboratory abnormality in the TDF group involved ALT. This is a known adverse effect associated with TDF as stated in the currently-approved Australian PI for TDF. In addition, the incidence of grade 3 or 4 ALT abnormalities was lower in the TDF group compared to the placebo group (11.5% vs. 40.7%).

Safety analyses with regards to potential liver, renal and bone toxicities yielded results consistent with known effects of TDF, and did not raise significant safety concerns. However,

safety evaluations with regards to effect on growth raised some concerns which were not fully addressed in the CSR. This will be described later in this section.

With regards to potential liver toxicity, study results showed that the proportion of subjects with on-treatment hepatic flares based on clinical laboratory criteria was lower in the TDF group compared to the placebo group (3.8% vs. 18.5%). The proportion of subjects with hepatic flares reported as grade 3 or 4 AEs was also lower in the TDF group compared to the placebo group (3.8% vs. 22.2%). The incidence of hepatitis reported as an AE was lower in the TDF group compared to the placebo group (5.8% vs. 13.0%), as was that of increased ALT reported as an AE (5.8% vs. 22.2%). No subjects in the TDF group had prothrombin time, a test of liver function, above the upper limit normal.

With regards to potential renal toxicity, study results showed that no TDF-treated subjects had a Grade 3 or 4 increase in serum creatinine or decrease in serum phosphorus, a confirmed increase from baseline in serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance rate of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. The mean changes in creatinine from baseline to Week 72 were similar between the TDF and placebo groups (0.1 mg/dL in both TDF and placebo groups). No subject in the TDF group had renal and urinary disorders AEs, compared with 3 subjects in the placebo group who had.

With regards to potential bone toxicity, study results showed that at Week 72, the mean changes from baseline in the bone biochemical markers for bone formation (serum osteocalcin and bone specific ALP) and for bone reabsorption (N- and C-telopeptides), serum PTH and 25-hydroxy vitamin D levels were all comparable between the TDF and placebo groups. The incidence of bone AEs was comparable between treatment groups (5.8% in the TDF group and 3.7% in the placebo group). With regards to bone fractures, one subject in the TDF group reported a fracture but this was not considered related to study drug.

No TDF-treated subjects met the safety endpoints of a 6% decrease in lumbar spine BMD or a 6% decrease in whole body BMD. There was an increase in mean lumbar spine BMD and in mean whole body BMD from baseline through to Week 72 in both treatment groups, but the percent increase from baseline in the TDF-treated subjects was statistically significantly less than that in the placebo subjects at Week 24 (lumbar spine BMD: 1.87% vs. 3.42%, p = 0.005; whole body BMD: 1.10% vs. 2.52%, p<0.001), at Week 48 (lumbar spine BMD: 3.50% vs. 5.58%, p = 0.046; whole body BMD: 2.05% vs. 3.87%, p<0.001) and at Week 72 for whole body BMD (2.84% vs. 5.37%, p = 0.013). The percent increase from baseline in lumbar spine BMD was also less in the TDF-treated subjects than that in the placebo subjects at Week 72, but this was not found to be statistically significant (4.95% vs. 8.14%, p = 0.053). At Week 72, there was a decrease of 0.05 in mean lumbar spine BMD Z-scores from baseline in the TDF group compared to an increase of 0.07 from baseline in the placebo group, and a decrease of 0.15 in mean whole body BMD Z-scores from baseline in the TDF group compared to an increase of 0.06 in the placebo group, although these differences were not analysed for statistical significance. At Week 72, only 2 subjects in the TDF group had lumbar spine BMD Z-scores of less than -2 (compared to one subject in the placebo group), and the majority of the subjects (65.4% in the TDF group and 72.2% in the placebo group) had lumbar spine BMD Z-scores of above -1 at Week 72. Similar results were obtained for whole body BMD Z-scores, where at Week 72, only 2 subjects in the TDF group had whole body BMD Z-scores of less than -2 (compared to one subject in the placebo group), and the majority of the subjects (67.3% in the TDF group and 70.4% in the placebo group) had whole body BMD Z-scores of above -1 at Week 72.

Overall, the safety analyses results with regards to potential bone toxicity were comparable with those presented in the currently approved Australian PI in TDF-treated HIV-infected adolescents.

Evaluation of effect on growth was done by analysing the Z-scores for height, weight and BMI. Results showed that the difference between treatment groups in mean change from baseline in height Z-scores from Week 4 through to Week 72 was not statistically significant across all visit timepoints. However, weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at all timepoints except at Weeks 40, 48, 56 and 72 for weight Z-scores, and Weeks 40 and 48 for BMI Z-scores. Results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. The maximum decrease from baseline in mean weight Z-score in the TDF group was 0.20 at Week 64 (versus a decrease of 0.06 in placebo group; p=0.029) and at Week 72 (versus a decrease of 0.05 in placebo group; p=0.063). The maximum decrease from baseline in mean BMI Z-score in the TDF group was 0.30 at Week 72 (versus a decrease of 0.10 in placebo group; p=0.046). It is noted that the maximum decreases from baseline in mean weight Z scores and mean BMI Z-scores in the TDF group were small. However, the proportions of subjects in the TDF and placebo groups, respectively, with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1, which would allow a better evaluation of the clinical relevance of the weight and BMI Z-scores, were not presented by the sponsor. This will be raised as a clinical question (see Section 11).

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefit of TDF in the proposed usage is the treatment of CHB in paediatric patients 12 years of age and older.

The exact prevalence of CHB in adolescents in Australia is not well-documented, but the overall prevalence of CHB in Australia was estimated in year 2000 to be between 90000 and 160000 patients, representing a prevalence rate of 0.5% to 0.8%, with about 6000-8000 new notifications to the National Notifiable Diseases Surveillance System annually[18]. In Australia between 1990 and 2002, deaths from CHB doubled from 100 to nearly 200 per annum. Australians with CHB had a 40-90% increased risk of mortality compared to a matched population, and the risks of liver disease-related mortality and of liver cancer-related mortality were estimated to be 12 and 28 times higher respectively, than those for the background population.

The risk of an acute HBV infection becoming chronic varies inversely with age: chronic HBV infection occurs in about 90% of infants infected at birth, 20%–50% of children infected at 1–5 years of age, and about 1%–10% of persons infected as older children and adults[19]. There are currently only 2 drugs approved in Australia for the treatment of CHB in adolescents aged 12 years and older: lamivudine (age 2 years and older) and adefovir (age 12 years and older). Entecavir and telbivudine are approved in Australia for use only in adolescents aged age 16 years and older. There is hence potential benefit in having an additional oral drug option for the treatment of CHB in adolescents aged 12 years and older.

The clinical goal of CHB treatment is to prevent progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma, through achieving HBV DNA suppression (desired treatment outcome: HBV DNA <2000 IU/mL [approximately 10000 copies/ml]; optimal treatment outcome: undetectable by PCR [HBV DNA <60 IU/mL; approximately

[18] Gastroenterological Society of Australia, Australian and New Zealand Chronic Hepatitis B (CHB) Recommendations. *Digestive Health Foundation,* 2009/10

[19] Australian government department of health and ageing. Vaccine Preventable Disease in Australia, 2005-2007. *Communicable Disease Intelligence*, Volume 34, supplement Dec 2010.

350 copies/ml]), ALT normalisation, HBsAg loss and seroconversion, HBeAg loss and seroconversion, and/or histological improvement[20].

Efficacy results in study GS-US-174-0115 showed statistically significant virological and biochemical responses with TDF compared to placebo. Overall, 88.5% of subjects in the TDF group achieved HBV DNA suppression to < 400 copies/mL at Week 72 (compared to 0.0% in the placebo group, p<0.001), and 84.6% of subjects in the TDF group achieved HBV DNA below the LLoQ for the PCR assay of 169 copies/mL at Week 72 (compared to 0.0% in the placebo group, p<0.001). Biochemical improvement in terms of ALT levels showed that the proportion of subjects with normal ALT at Week 72 was statistically significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p<0.001). The virological and biochemical response rates in the TDF-treated adolescent CHB subjects in this study through Week 48 were generally comparable with those of TDF-treated adult CHB subjects in previous studies. However, efficacy results of serological responses showed that the incidence rates of HBeAg loss and of seroconversion to anti-HBe at Week 72 in the TDF-treated subjects were not statistically significantly different from that of the subjects on placebo (20.8% vs. 14.6% in TDF and placebo groups, respectively; p = 0.41 for both endpoints). The incidence rates of HBsAg loss and of seroconversion to anti-HBs at Week 72 were low in both treatment groups, and there was no statistically significant difference between treatment groups (1.9%% vs. 0.0% in TDF and placebo groups, respectively; p = 0.32 for both endpoints).

Although treatment objectives of CHB include HBV DNA suppression, ALT normalisation, HBsAg loss and seroconversion, HBeAg loss and seroconversion, and/or histological improvement, evidence showed that the serum level of HBV DNA is the major clinical feature related to liver disease progression, and is predictive of the risk of disease progression[21, 22]. Prolonged ALT level elevation indicates liver injury and disease progression, and hence ALT within normal range with treatment is indicative of reduced liver inflammation and injury. The efficacy results of study GS-US-174-0115 showed that the use of TDF in the treatment of CHB in adolescents aged 12 years and above led to statistically significant results in these 2 major outcomes of HBV DNA suppression and ALT within normal range, compared to placebo.

Although loss of HBsAg and seroconversion to anti-HBs is considered a complete response, it has been found to be uncommon after therapy with currently available treatment regimen, occurring in 3-8% of patients receiving interferon and <5% of patients receiving nucleoside/nucleotide analogue therapy[21]. The low rate of HBsAg loss and of seroconversion to anti-HBs in study GS-US-174-0115 was consistent with this.

Loss of HBeAg and seroconversion to anti-HBe has been found to be associated with decreased viral replication and improved liver histology. The rate of HBeAg seroconversion has been reported in 10-30% of patients following interferon therapy[21]. The Australian Product Information for lamivudine reported an HBeAg seroconversion rate of 16% to 18% in CHB adult patients on lamivudine 100 mg daily after 52 weeks, but that in children and adolescents was not presented. The Australian Product Information for TDF reported an HBeAg seroconversion rate of 12% in HBeAg positive CHB adult patients on TDF 300 mg daily after 48 weeks (study 0103). The rate of HBeAg seroconversion found in study GS-US-174-0115 (20.8%) was generally comparable to these reported rates. The Australian Product Information for lamivudine reported an HBeAg seroconversion rate of 4% in CHB adult Asian patients on

[20] European Association for The Study Of The Liver, EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatology*, 50 (2):227-42, 2009

[21] Gastroenterological Society of Australia, Australian and New Zealand Chronic Hepatitis B (CHB) Recommendations. *Digestive Health Foundation,* 2009/10

[22] Chen C., Yang H, Iloeje U.H. Hepatitis B Virus DNA Levels and Outcomes in Chronic Hepatitis B. *Hepatology*, Vol. 49, No. 5, Suppl., 2009

placebo (study NUCB3009). This is in contrast to a higher rate of spontaneous HBeAg seroconversion found in the placebo group (14.6%) in study GS-US-174-0115. A literature search showed that the rate of spontaneous HBeAg seroconversion in children varies according to geographic region and initial mode of acquisition of HBV infection, but the TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of chronic Hepatitis B reported that the annual spontaneous HBeAg seroconversion rate in Caucasian children is up to 14-18%, that about 40% of children clear HBeAg within one year after the detection of elevated aminotransferase, and that long-term follow-up studies in Caucasian children have shown that more than 80% seroconvert from HBeAg to anti-HBe before reaching adulthood. These data suggest that there appeared to be a higher rate of spontaneous HBeAg seroconversion in children and adolescents with CHB (versus that in adult CHB patients), and that while the rate of HBeAg seroconversion in the TDF-treated adolescent CHB patients in study GS-US-174-0115 appeared to be generally comparable with that in adult CHB patients treated with TDF or lamivudine, it was not statistically significantly higher than the spontaneous HBeAg seroconversion rate in adolescents with CHB. However, overall, study evaluation of the combined response (i.e. composite endpoint) of HBV DNA < 400 copies/mL, normalised ALT and HBeAg loss or seroconversion among those who were HBeAg positive with abnormal ALT at study baseline, showed that a statistically significantly higher proportion of subjects in the TDF group (21.2%) achieved this composite endpoint at Week 72, than in the placebo group (0.0%, p=0.002).

Resistance analyses lent support to the potential benefit of TDF as an additional oral drug option for the treatment of CHB in adolescents, showing that the majority (5 out of the 6) of TDF-treated subjects with LAM resistance-associated mutations at baseline went on to have HBV DNA suppression < 400 copies/mL at Week 72. In addition, subgroup analyses showed that within the subgroup of subjects who had prior oral HBV medications, a much higher proportion of TDF-treated subjects than placebo-treated subjects achieved HBV DNA < 400 copies/mL (84.4% vs. 0.0%) and HBV DNA < 169 copies/mL (78.2% vs. 0.0%).

9.2. First round assessment of risks

The risks of TDF in the proposed usage are:

Potential liver toxicity: Study results showed that the incidence of on-treatment hepatic flares based on clinical laboratory criteria was lower in the TDF group compared to that in the placebo group (3.8% vs. 18.5%), as was the incidence of hepatic flares reported as grade 3 or 4 AEs (3.8% vs. 22.2%), the incidence of hepatitis reported as an AE (5.8% vs. 13.0%), and the incidence of increased ALT reported as an AE (5.8% vs. 22.2%). In addition, no subjects in the TDF group had prothrombin time, a test of liver function, above the upper limit normal.

Potential renal toxicity: Study results showed that no TDF-treated subjects had a Grade 3 or 4 increases in serum creatinine or decrease in serum phosphorus, a confirmed increase from baseline in serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance rate of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. The mean change in creatinine from baseline to Week 72 was small and similar between the TDF and placebo groups (0.1 mg/dL in both TDF and placebo groups), and no subject in the TDF group had renal and urinary disorders AEs (compared with 3 subjects in the placebo group who had).

Potential bone toxicity: Study results showed that there was no statistically significant difference between TDF and placebo in mean change from baseline for the biochemical markers of bone formation (serum osteocalcin and bone specific ALP) and bone reabsorption (N- and C-telopeptides), as well as for serum PTH and 25-hydroxy vitamin D levels. There was also no statistically significant difference between TDF and placebo in the incidence of bone AEs in study GS-US-174-0115. The percent increase from baseline of mean lumbar spine BMD whole

body BMD and in the TDF-treated subjects was statistically significantly less than that in the placebo subjects at Weeks 24, 48, 72 (whole body BMD only at Week 72). In addition, there was a decrease of 0.05 in mean lumbar spine BMD Z-scores from baseline in the TDF group at Week 72 compared to an increase of 0.07 from baseline in the placebo group, and a decrease of 0.15 in mean whole body BMD Z-scores from baseline in the TDF group at Week 72 compared to an increase of 0.06 in the placebo group. However, these mean decreases from baseline in the lumbar spine and whole body BMD Z-scores in the TDF group were small, and results showed that at Week 72, only 2 subjects in the TDF group had lumbar spine BMD Z-scores or whole body BMD Z-scores of < -2, and the majority of the subjects (approximately 66%) had lumbar spine BMD Z-scores or whole body BMD Z-scores of above -1 at Week 72.

Potential effects on growth (height, weight, BMI): Weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at a majority of timepoints. At Week 72, BMI Z-score was statistically significantly more decreased from baseline in the TDF group compared to the placebo group. In addition, results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. It is noted that in the TDF group, from baseline through to Week 72, the maximum decrease from baseline in mean weight Z scores (0.20) and in mean BMI Z-scores (0.30) were small and not likely to be clinically significant. However, the respective proportions of subjects in the TDF and placebo groups with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1 at Week 72 would allow a better evaluation of the clinical relevance of the weight and BMI Z-scores, and these were not presented by the sponsor. This will be raised as a clinical question (see Section 11).

Overall, the safety results of the study GS-US-174-0115 were consistent with the known adverse effects of TDF. Safety analyses with regards to potential liver, renal and bone toxicities also yielded results consistent with known effects of TDF, and did not raise significant safety concerns, although safety analyses with regards to effect on growth were not fully addressed in the CSR.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of TDF, given the proposed usage, is favourable.

The risk of an acute HBV infection becoming chronic varies inversely with age. CHB is associated with progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma. There are currently only 2 drugs approved in Australia for use in adolescents aged 12 and older with CHB.

Efficacy results in study GS-US-174-0115 showed statistically significant virological and biochemical responses with TDF compared to placebo, with 88.5% of subjects in the TDF group achieving HBV DNA suppression to < 400 copies/mL at Week 72 (compared to 0.0% in the placebo group; p<0.001), and 84.6% achieving HBV DNA below the LLoQ for the PCR assay of169 copies/mL at Week 72 (compared to 0.0% in the placebo group; p<0.001). The proportion of subjects with normal ALT at Week 72 was statistically significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p<0.001). The incidence rates of HBsAg loss and of seroconversion to anti-HBs at Week 72 were low in both treatment groups with no statistically significant difference (1.9%% vs. 0.0% in TDF and placebo groups, respectively; p = 0.32 for both endpoints), but this is comparable with the low rate of HBsAg seroconversion in CHB patients treated with interferon (3-8%) or nucleoside/ nucleotide analogue therapy (<5%). The rate of HBeAg seroconversion in the TDF-treated adolescent CHB patients in study GS-US-174-0115 appeared to be generally comparable with that in adult CHB patients treated with TDF or lamivudine, although it was not statistically significantly higher than the spontaneous HBeAg seroconversion rate in adolescents with CHB. Overall study evaluation of the combined

response (i.e. composite endpoint) of HBV DNA < 400 copies/mL, normalised ALT and HBeAg loss or seroconversion among those who were HBeAg positive with abnormal ALT at study baseline, showed that a statistically significantly higher proportion of subjects in the TDF group (21.2%) achieved this composite endpoint at Week 72, than in the placebo group (0.0%, p=0.002)

Overall, the safety results of the study GS-US-174-0115 were consistent with the known adverse effects of TDF. Safety analyses with regards to potential liver, renal and bone toxicities also yielded results consistent with known effects of TDF, and did not raise significant safety concerns.

10. First round recommendation regarding authorisation

It is recommended that the application for extension of indication of TDF for 'treatment of CHB in paediatric patients 12 years of age and older' be approved.

This is subject to a satisfactory response to the clinical questions raised in Section 11.

11. Clinical questions and second round evaluation of clinical data submitted in response to questions

11.1. Pharmacokinetics

None.

11.2. Pharmacodynamics

None

11.3. Efficacy

Question 1. Please clarify the approved indication for orphan drug designation by the TGA [remainder of question is as described in Section 2. 1, above]

Response from the sponsor

Gilead advises that there was a typographical error in the letter of approval of orphan drug designation and the orphan drug indication should read as "indication is for the treatment of chronic hepatitis B in adults and paediatric patients 12 years of age and older". VIREAD is approved for the use in the treatment of chronic hepatitis B in adults and the orphan application was to extend this indication to include paediatric patients 12 years of age and older with chronic hepatitis B.

TGA comment: Response noted and accepted.

Question 2. Please provide rationale for the administration of TDF in study GS-US-174-0115 without regard to food.

As commented in Section 7.1.1.1.3 (above), no rationale had been given in the CSR or study protocol for the administration of TDF in study GS-US-174-0115 without regard to food, when the currently approved Australian PI for TDF stated that "In order to optimise the absorption of tenofovir, it is recommended that VIREAD be taken with food", and that "Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase

in Cmax of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour".

Response from the sponsor

The recommendation in the currently approved Australia PI is for VIREAD be taken with food, however Gilead does not consider that food has an adverse effect on the safety and efficacy of tenofovir DF and this is reflected in the approved US label for VIREAD. Since the GS-US-174-115 study was conducted in both the US and Europe, the study protocol was designed with this rationale in mind. Therefore patients in this study took VIREAD without consideration of food representing worse case scenario and efficacy was still shown.

TGA comment: Response acceptable

Question 3. Please review and verify the data presented in Table 8-3 of the CSR

As described in Section 7.1.1.1.10, above, the sponsor had presented a summary of important protocol deviations occurring during the double-blind period through Week 72 in Table 8-3 in the CSR. It is noted by the evaluator, on going through the listing of major protocol deviations in appendix 16.2.2 of the CSR that there are errors in Table 8-3. A revised table is presented (Table 2 in the evaluation report, above).

Response from the sponsor:

Gilead confirms that the revised table (Table 2, above) which TGA produced is correct and apologises for the error.

TGA comment: Response noted and accepted.

Question 4. Please provide details on the degree of deviation from the pre-specified inclusion criteria involving ALT levels at screening, for the 6 subjects in the TDF group and 1 subject in the placebo group who were enrolled into the study and randomised despite failure to meet the inclusion criterion regarding ALT ≥ 2 × ULN at study screening or any history of ALT ≥ 2 × ULN within 24 months prior to screening.

As described in Section 7.1.1.1.10 above, the most commonly reported protocol deviation in either treatment groups was failure to meet 1 or more inclusion or exclusion criteria, and these occurred more frequently in the TDF group (17.3%, 9/52) than in the placebo group (7.4%; 4/54). The majority of these protocol deviations involving inclusion or exclusion criteria in the TDF group was for failure to meet the inclusion criterion regarding ALT ≥ 2 × ULN at study screening or any history of ALT ≥ 2 × ULN within 24 months prior to screening (6 subjects [11.5%] in the TDF group versus1 subject [1.8%] in the placebo group). The protocol deviation log in appendix 16.2.2 of the CSR indicated that the waiver type for all these subjects were "allowed waiver". However, the text giving details for the reasons for the waiver of these deviations were truncated (see examples in Section 7.1.1.1.10, above), and the degree of deviation from the pre-specified ALT criteria were unclear.

Response from the sponsor:

Gilead apologises for the omission of details in Section 16.2.2 of the CSR. It has been reproduced fully and is included [as an Attachment to this response].

TGA comment: Response noted and accepted. It is noted that the missing words are "…within in 10% variance"

11.4. Safety

Question 1. Please provide analysis results on the proportions of subjects in the TDF and placebo groups, respectively, with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1.

As commented in Section 8.9, above, safety results showed that weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at all timepoints except at Weeks 40, 48, 56 and 72 for weight Z-scores, and Weeks 40 and 48 for BMI Z-scores. Results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. It is noted that in the TDF group, the maximum decrease from baseline in mean weight Z scores (0.20) and mean BMI Z-scores (0.30) were small and not likely to be clinically significant. However, the proportions of subjects in the TDF and placebo groups, respectively, with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1 would allow a better evaluation of the clinical relevance of the weight and BMI Z-scores, and these were not presented by the sponsor.

Response from the sponsor:

Weight Z-scores and BMI Z-scores of <-2 between -2 and -1 and >-1 are provided in an Attachment. Please note no statistical differences in either BMI Z-score or Weight Z-score were observed between TDF and placebo groups considering the 3 categories analyzed.

TGA comment: Response noted and accepted.

12. Second round benefit-risk assessment

There is no change to the first round benefit risk assessment following the responses to the clinical questions. The benefit-risk balance of TDF for treatment of CHB in paediatric patients 12 years of age and older is considered favourable.

13. Second round recommendation regarding authorisation

The sponsor's responses to the clinical questions raised in Section 11 are considered satisfactory. Registration approval is recommended for extension of indication of TDF to include 'treatment of CHB in paediatric patients 12 years of age and older'.

14. References

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