20 September 2012
EMA/797672/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VIREAD

International non-proprietary name: TENOFOVIR DISOPROXIL FUMARATE

Procedure No. EMEA/H/C/000419/II/0115

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
BL	baseline
BMD	bone mineral density
BMI	body mass index
CCDS	Company Core Data Sheet
CFR	Code of Federal Regulations
CHB	chronic hepatitis B
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
DB	double-blind
DBEE	double-blind efficacy evaluation
DEXA	dual-energy x-ray absorptiometry
DNA	deoxyribonucleic acid
EMEA	European Medicines Evaluation Agency
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GSI	Gilead Sciences, Inc.
HBeAg	hepatitis B early antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
LLoQ	lower limits of quantitation
MAH	Marketing Authorisation Holder
NtRTI	nucleotide reverse transcriptase inhibitor
OL	open-label
PDCO	Paediatric Committee
PIP	paediatric investigation plan
PK	pharmacokinetics
PLB	placebo
pol	polymerase
PRT	proximal renal tubulopathy

RAT	randomized and treated
RDA	recommended daily allowance
RT	reverse transcriptase
RSI	Request for supplementary information
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
ULN	upper limit of the normal range
US	United States

Table of content

1. Scientific discussion

1.1. Introduction

About the product

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

Viread tablets (containing 245 mg of TDF as fumarate, equivalent to 300 mg TDF or 136 mg of TFV) once daily were approved on 5 February 2002 for use in combination with other antiretroviral (ARV) agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. Viread was subsequently approved for the treatment of chronic hepatitis B on 23 April 2008.

Viread tablets are approved in the US, Canada, Australia, and New Zealand for use in HIV-1-infected adolescents (12 to < 18 years of age and weighing ≥ 35 kg). In Europe, the Committee for Medicinal Products for Human Use (CHMP) concluded that available clinical data in HIV-1 infected, ARV treatment-experienced adolescents were inadequate to support the use of TDF in this population (Viread variation EMEA/H/C/00419/II/0098). Furthermore, the application for Viread line extension EMEA/H/C/00419/X/105/G in the treatment of HIV infection in children aged 2 to <12 years is under evaluation.

Cumulative patient exposure to TDF (for both the HIV-1 and HBV indications combined) since first marketing approval in the US in 2001 until 31 August 2011 is estimated to be more than 4.4 million patient-years of treatment.

1.2. Non-clinical aspects

No non-clinical data have been presented with this variation.

1.2.1. Ecotoxicity / environmental risk assessment

An ERA has been submitted in accordance with Article 8(3) of Directive 2001/83 requirements.

Table 1. Summary of main study results

Substance (INN / Invented Name): tenofovir disoproxil fumarate			
CAS-number (if available):			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.992 at pH 4 1.18 at pH 7 could not be determined at pH 10 due to the instability of TDF in the buffer phase	Potential PBT: no
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.5	µg/L	> 0.01 threshold

Phase II Physical-chemical properties and fate				
Study type	**Test protocol**	**Results**		
Adsorption-Desorption	OECD 121	K_{oc} = 18 L/kg		
Ready Biodegradability Test	OECD 301	Not readily biodegradable		
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	TDF rapidly underwent primary degradation converting to several degradation products		
Phase IIa Effect studies				
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**
Algae, Growth Inhibition *Pseudokirchneriella subcapitata*	OECD 201	NOEC EC_{50}	14 47	mg/L mg/L
Daphnia, acute immobilisation test / Daphna magnia	OECD 202	NOEC EC_{50}	98 ≥ 98	mg/L mg/L
Fish Acute Toxicity Test Rainbow trout, *Oncorhynchus mykiss*	OECD 203	NOEC LC_{50}	92 >92	mg/L mg/L
Daphnia sp. Reproduction Test *Water fleas*	OECD 211	NOEC EC_{50}	13 21	mg/L mg/L
Fish, Early Life Stage Toxicity Test/ Fathead Minnow, *Pimephales promelas*	OECD 210	NOEC LOEC	1.9 >1.9	mg/L mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{50}	600 940	mg/L* mg/L*
Phase IIb Studies				
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	100	mg/kg

* active ingredient

It is considered that Viread is unlikely to represent a risk to the aquatic environment, to micro-organisms, or to sediment dwelling organisms.

1.3. Clinical aspects

1.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2. Tabular overview of clinical studies

Study (Module 5 Reference)	Design	Geographic Location (No. of sites)	Study Population	Treatment	Subjects Treated	Duration (Status)
GS-US-174-0115 (m5.3.5.1)	Randomized, DB, placebo-controlled, multicenter, Phase 3 study in HBV-infected adolescent subjects	Poland (8), Romania (3), United States (3), Bulgaria (2), France (2), Spain (2), Turkey (1)	TDF-naïve adolescent subjects (12 to < 18 years of age) with chronic HBeAg-positive or HBeAg negative HBV infection	TDF 300-mg tablets once daily or PLB tablets once daily	Week 72: 106 subjects: 52 TDF and 54 PLB	192 weeks (ongoing); 72-week randomized period completed

1.3.2. Pharmacokinetics

Initial clinical studies were undertaken using an oral suspension formulation (GS-02-983 in HIV-1 infected subjects 2 to 8 years of age) and 75-mg tablets of tenofovir DF (GS-01-926 and GS-01-927 in HIV-1 infected subjects 6 to 16 years of age). Each of these studies included pharmacokinetic assessments for all subjects. Based on data from these studies, the dose of tenofovir DF selected for investigation in subsequent studies was 8 mg/kg of actual body weight to a maximum of 300 mg/day (≥ 35 kg).

Table 3. Pharmacokinetic Evaluations in HIV-1 Infected Pediatric Subjects

Study	Study Design	Age Group (years)	Number of Subjects Evaluated
GS-US-104-0321	Multidose, Phase 3	12 – < 18	8
GS-01-926	Multidose, Phase 1	6 – 16 inclusive	18
GS-01-927	Multidose, Phase 1/2	9 – 16 inclusive	7
GS-02-983	Single-dose, Phase 1	2 – 8 inclusive	12

In adolescents, the efficacy and safety of TDF is being evaluated in an ongoing Phase 3 study (GS-US-104-0321) of HIV-1 infected, treatment-experienced adolescents (12 to 18 years of age and with a body weight ≥ 35 kg) who were failing to achieve virologic suppression on their existing antiretroviral regimen. In this pivotal study, TFV pharmacokinetics were examined in 8 HIV-1 infected adolescent subjects receiving the TDF 300-mg tablet once daily plus a background antiretroviral regimen for at least 4 weeks. Steady-state TFV exposures achieved in these subjects (AUCtau 3390.6 ng•h/mL, Cmax 377.5 ng/mL, and Tmax 1.98 hours) were similar to those observed in HIV-1 infected adults receiving TDF 300 mg/day.

Pharmacokinetic data are also available from 7 HIV-1 infected subjects 12 to < 18 years of age who received multiple doses of TDF 300 mg once daily (4 × 75 mg tablets) in earlier Phase 1/2 Studies GS-01-926 and GS-01-927 (combined data). Tenofovir was rapidly absorbed with a median Tmax of 2.08 hours and mean Cmax of 268.3 ng/mL. A mean AUCtau of 3007.8 ng•h/mL and a median T½ of 13.99 hours were achieved.

Overall in adults, the same dose is recommended for treating HIV and HBV chronic infections. As for HIV infected adolescents a 8 mg/kg weight based dose has been selected as mimicking the adults exposure to predict similar efficacy/safety. For HIV and HBV clinical development adolescents were receiving the adult dose (i.e. maximal dose).

PK data in HBV-infected adolescents in study GS-US-174-0115

Pharmacokinetics of TDF was assessed in 52 adolescent aged 12 to 17 years who took part in the pivotal trial (Study GS-US-174-0115).

Results

Mean and median TDF pharmacokinetic parameters from exploratory analyses are shown in the table 3 below overall in adolescent patients and in the subset of patients 12 to 14 years or 15 to 17 years of age. Due to the lack of data over a wide range of sampling interval, AUC and half-life determinations were not performed in adolescents in the 12-to-14 years of age subset.

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

Source: Section 15.1, Table 34.2; Appendix 16.2, Listing 52

Discussion

TFV exposures in the adolescent population with CHB in Study GS-US-174-0115 were generally comparable with historical data from HIV-1 infected adult and adolescent subjects, as well as from adult healthy subjects (see historical data in the table 4 below).

Table 5. TFV Pharmacokinetic Parameters Following Multiple Doses of Tenofovir DF 300 mg/day in HBV Infected Adolescents, and Comparative Data in HIV-1 Infected Adolescents and Adults

TFV Steady-state PK Parameter	GS-US-174-0115 300 mg/day (N=52)[a]	Historical Data in HIV-1 Infected Adolescents		Historical Adult Data in HIV-1 Infected Adults					
		GS-US-104-0321 300 mg/day (N=8)[b]	GS-01-926 and GS-01-927 300 mg/day (N=7)[b]	GS-97-901 300 mg/day		GS-99-907 300 mg/day			
				8th Dose (N=8)	28th Dose (N=8)	12 Weeks (N=12)	24 Weeks (N=12)	36 Weeks (N=7)	48 Weeks (N=7)
AUC_{tau} (ng•h/mL)[c] Mean (%CV)	3015.2	3390.6 (36.0)	3007.8 (27.8)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	352.7	377.5 (35.6)	268.3 (27.2)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{tau} (ng/mL)[c] Mean (%CV)	—	64.4 (52.6)	63.0 (36.4)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.5	1.98 (1.46, 2.99)	2.08 (1.00, 4.00)	3.0	2.3	2.3	2.3	1.5	2.5
$T_{½}$ (h)[c] Median (Q1, Q3)	19.9	10.54 (9.02, 15.30)	13.99 (7.97, 17.30)	13.7	14.4	14.0	14.9	12.4	14.5

a Since only 1 randomly-timed plasma sample was collected from each subject at each visit, pooled TFV plasma concentrations by age group at study BL (12 to 14 years, 15 to 17 years) were used in the pharmacokinetic analysis. Tenofovir DF was to be administered once daily, and therefore, only samples collected within 24 hours after a DB dose were included in the analysis.

b Measured after a minimum of 4 weeks of treatment with tenofovir DF; pharmacokinetic samples collected up to 12 hours postdose (10 hours in Study GS-01-927).

c For studies GS-US-104-0321, GS-01-926, GS-01-927, GS-97-901, and GS-99-907, parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour time point.

For the overall population (adolescents from 12 to 17 years) data show that peak plasma concentrations of TDF were more rapidly achieved (Tmax 1.5 h) than in HIV-infected patients (Tmax around 2-3 h). Given that the recommended dose for adults infected with HIV and HBV is the same, the comparison seems acceptable.

PK data were also provided for the subset of patients 12 to 14 and 15 to 17 years of age. Data showed that Cmax is higher for younger children while Tmax is similar for both subsets of adolescents. Data on AUC and half-life are lacking for children of 12 to 14 years of age.

In adults, the same dose is recommended for treating HIV and HBV chronic infections.

As for HIV infected adolescents a 8 mg/kg weight based dose has been selected as mimicking the adults exposure to predict similar efficacy/safety. For HIV and HBV clinical development adolescents were in fact receiving the adult dose (i.e. maximal dose).

1.4. Clinical efficacy

1.4.1. Main study: GS-US-174-0115

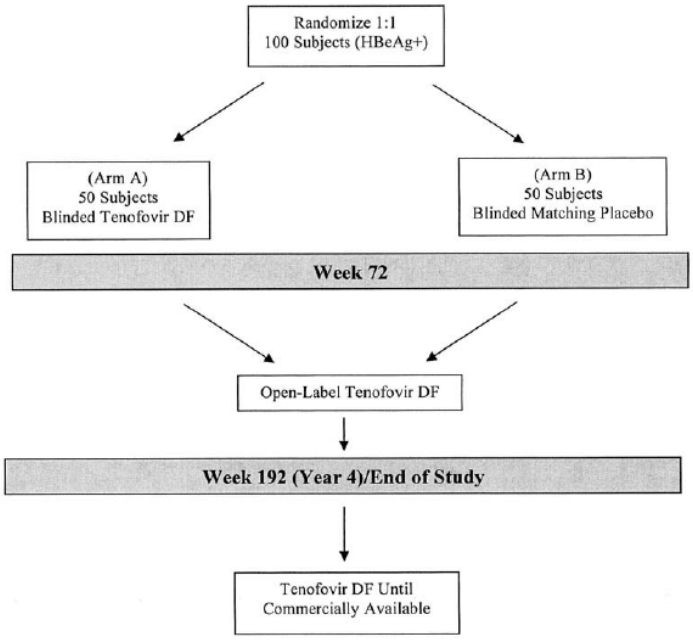
The proposed indication is supported by study GS-US-174-0115, a long-term, phase 3, randomized, double-blind controlled trial that is currently ongoing as a TDF open-label study. Clinical data coming from Studies GS-US-174-0102 and GS-US-174-0103 in adults also support these results.

Methods

- **Study Design**

Study GS-US-174-0115 was a randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection. Subjects were treated with blinded randomized therapy for 72 weeks. After blinded randomized treatment, each subject was allowed to switch to open-label TDF treatment which they could be on for 2.5 additional years.

Figure 1.



Subjects were enrolled at a total of 21 study sites: Poland (8), Romania (3), the United States (3), Bulgaria (2), France (2), Spain (2), and Turkey (1).

Randomization was stratified by age (12 to 14 and 15 to 17 years) and geographical location of study site (North America, Europe).

Use of Placebo (PLB)

GS-US-174-0115 is a randomized placebo-controlled study. A placebo comparator was used for the following main reasons:

• No agent is currently registered for the treatment of adolescents in both the EU and US.

• Use of the placebo comparator allowed a more robust evaluation of TDF safety and tolerability (eg, bone metabolism, renal safety), and did not expose subjects randomized to the placebo group to the risk of resistance development during the blinded portion of the study. Specifically, the placebo comparator allows quantification of adverse events (AEs) that are the result of the natural history of the disease, thus controlling for AEs that are unrelated to therapy.

• For the efficacy endpoints, a randomized placebo-controlled design allows measurement of the absolute effect of therapy, rather than the relative effect of therapy, as when using an active comparator treatment.

Study Participants

Adolescent subjects aged 12 to 17 years old with chronic hepatitis B infection:

- HBeAg-positive or HBeAg-negative HBV infection (hepatitis B surface antigen [HBsAg] positive for at least 6 months)
- weighing ≥ 35 kg
- with HBV DNA ≥ 10^5 copies/mL and
- either ALT ≥ 2 × ULN at screening OR any history of ALT ≥ 2 × ULN over the past ≤ 24 months, and
- creatinine clearance ≥ 80 mL/min/1.73 m2.

Subjects must have been naive to TDF, but could have received interferon or any other non-TDF containing oral anti-HBV nucleosides/nucleotide therapy. Subjects in Poland must have had a history of prior HBV treatment (previously treated with interferon or other drug intended to treat this indication) or a contraindication for treatment of HBV with existing drugs for this indication.

Subjects previously treated on oral anti-HBV nucleoside/nucleotide therapy must have discontinued therapy ≥ 16 weeks prior to screening. Subjects must have discontinued interferon ≥ 6 months prior to screening.

Subjects must have been without serological evidence of co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV), with a history of significant bone disease, decompensated liver disease, evidence of hepatocellular carcinoma (ie, α-fetoprotein > 50 ng/mL), and pregnant or breast-feeding females were not eligible for the study.

Treatments

Subjects were randomly assigned (1:1) to receive 1 of the following treatments in a blinded fashion:

Treatment A: blinded TDF 300 mg PO once daily, which could be taken without regard to food.

Treatment B: blinded matching placebo PO once daily

Subjects were required to take a daily multivitamin containing 100% of the recommended daily allowance (RDA) for vitamin D (provided by the study).

Objectives

The **primary objective** of this study was as follows:

- To compare the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate (TDF) 300 mg once daily versus placebo once daily in adolescents (aged 12 to 17 years) with chronic hepatitis B infection.

The **secondary objectives** of this study were as follows:

- To evaluate the biochemical and serological responses to TDF versus placebo in adolescents with chronic hepatitis B infection.
- To evaluate the incidence of drug resistance mutations.

Outcomes/endpoints

Efficacy: The primary efficacy endpoint was the proportion of patients with HBV DNA < 400 copies/mL at Week 72.

For Weeks 48 and 72, the following secondary endpoints were evaluated (Week 48 endpoints were not analyzed prior to the primary efficacy analysis)

- For all subjects, secondary endpoints included ALT normal; composite endpoint of HBV DNA < 400 copies/mL and ALT normal; HBV DNA < 169 copies/mL; HBsAg loss and seroconversion.

- For HBeAg-positive subjects, secondary endpoints included HBeAg loss and seroconversion; composite endpoint of HBV DNA < 400 copies/mL, ALT normal and HBeAg loss; and composite endpoint of HBV DNA < 400 copies/mL, ALT normal, and HBeAg seroconversion.

- For subjects with abnormal ALT at baseline, secondary endpoints included ALT normalized; and composite endpoint of HBV DNA < 400 copies/mL and ALT normalized.

- For HBeAg-positive subjects with abnormal ALT at baseline, secondary endpoints included composite endpoint of HBV DNA < 400 copies/mL, ALT normalized and HBeAg loss; and composite endpoint of HBV DNA < 400 copies/mL, ALT normalized, and HBeAg seroconversion.

Resistance surveillance was conducted at Baseline for all subjects. Genotypic changes from baseline within the HBV polymerase were analyzed for subjects with HBV DNA ≥ 400 copies/mL at Weeks 48 and/or 72, subjects who experienced virologic breakthrough (confirmed [defined as two consecutive] value ≥ 400 copies mL after a value < 400 copies/mL or confirmed 1.0-log10 or greater [at least tenfold] increases in HBV DNA from nadir), or subjects who discontinued early (after Week 24 with HBV DNA ≥ 400 copies/mL).

Pharmacokinetics: Plasma samples from all subjects collected at each study visit were utilized for TDF pharmacokinetic analysis and assessment of adherence to therapy (see PK section).

Safety: The primary safety endpoint was cumulative incidence of at least a 6% decrease from baseline in bone mineral density of the spine through Week 72. Cumulative incidence of at least a 6% decrease from baseline in bone mineral density (BMD) of whole body through Week 72 was a secondary endpoint. Both of these proportions through Week 48 were also secondary safety endpoints, as were corresponding changes in Z-scores. Other safety endpoints included percent change from baseline in lumbar spine BMD; percent change from baseline in bone mineral density of whole body; and development of drug resistance mutations.

Sample size

With respect to the primary efficacy endpoint (HBV DNA < 400 copies/mL at Week 72), sample sizes 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 assumed a response rate of 21% in the PLB group. Note that this was an intentionally conservative approach, resulting in an implicit assumed response rate of 51% in the TDF group, thus spanning 50% with the 2 assumed proportions and thereby maximizing the sample size given the assumed difference of 30% between the groups.

Randomisation

Approximately 100 TDF-naive subjects were randomized in a 1:1 ratio to receive blinded TDF 300 mg PO once daily (50 subjects), or blinded matching placebo PO once daily (50 subjects). Randomization was stratified by age (12 to 14 years, 15 to 17 years) and geographical location of study site (North America, Europe). A centralized randomization procedure was used, whereby numbered bottles of TDF or placebo were assigned to subjects via an interactive voice response system (IVRS) according to the randomization code. For the first 72 weeks of the study (blinded phase), study drugs were dispensed to the subject in a blinded fashion in numbered bottles from supplies stored at the study site.

Randomization could not occur until after the Baseline (pre-treatment) DEXA scan had been performed.

Blinding (masking)

During the blinded portion of the study, HBV DNA results were not distributed to investigators, subjects, or clinical research personnel involved in the clinical conduct of the study. The only exception was if a subject had Grade 4 ALT maintained for 16 weeks or an ALT flare, in which case serial HBV DNA values from Screen through the time of the event would have been made available to the investigator.

Statistical methods

Analyses of efficacy

The primary efficacy analysis was conducted at the end of DB treatment, after the last randomized subject reached Week 72, using the FAS. The analysis evaluated the difference between treatment groups in the proportion of subjects achieving the primary endpoint, using a Mantel-Haenszel test, controlling for randomization age group (12 to 14 years, 15 to 17 years), with a DBEE algorithm.

All subjects who were randomized into the study and received at least 1 dose of study drug (ie, TDF 300 mg or matching PLB) were included in the FAS used for analysis of primary and secondary efficacy endpoints. Of note, in the study protocol, this analysis set was referred to as the randomized and treated (RAT) analysis set.

Subjects discontinuing randomized therapy prior to Week 72 were handled using a DB efficacy evaluation (DBEE) algorithm for the purpose of the primary efficacy analysis and all analyses of categorical secondary efficacy endpoints. Subjects with missing responses were treated as failures in this intent-to-treat algorithm. The DBEE algorithm used all available data for the DB period, and excluded any data for the OL period. Logistic regression analyses were conducted to examine assumptions made in the algorithm regarding data-missing-completely-at-random at Week 72. None of the covariates tested were statistically significant, suggesting that any data missing at Week 72 were missing completely-at-random.

Subgroup analyses of efficacy endpoints included analyses for age (12 to 14 years vs. 15 to < 18 years), for HBeAg-positive vs. HBeAg-negative subjects at study baseline, for subjects with abnormal vs. normal ALT at study baseline (not applicable for ALT normalization), and for subjects with vs. without prior oral anti-HBV treatment.

Analysis sets

Data were evaluated using the following analysis sets:

All Randomized: The randomized analysis set included all subjects who were randomized into the study, regardless of whether they received study drug.

Full Analysis Set: The FAS included all subjects who were randomized into the study and received at least 1 dose of study drug (ie, TDF 300 mg or matching PLB). Of note, in the protocol, this analysis set was referred to as the randomized and treated (RAT) analysis set. The FAS was the primary analysis set for all efficacy analyses in the Week 72 end of DB treatment analysis.

Subjects discontinuing randomized therapy prior to Week 72 were handled using a double-blind efficacy evaluation (DBEE) algorithm (all FAS subjects included), for the purpose of the primary efficacy analysis and all analyses of categorical secondary efficacy endpoints.

Safety Analysis Set: The safety analysis set included all subjects who received at least 1 dose of DB study medication. The safety analysis set was the primary analysis set for all safety analyses in the Week 72 end of DB treatment analysis.

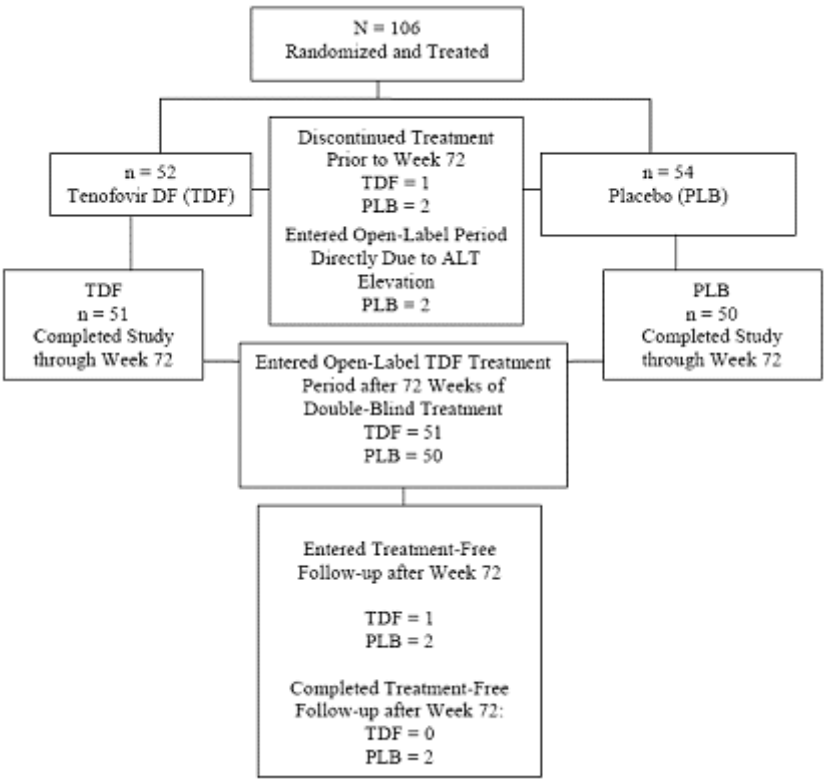
Pharmacokinetics analysis set: The pharmacokinetic (PK) analysis set included all subjects who were treated with TDF (during DB or OL period) and had evaluable concentrations at the time points of interest.

Open-Label analysis set: The OL analysis set will include all subjects who received at least 1 dose of OL TDF. This analysis set will be subdivided based on DB drug, as OL TDF (DB TDF) or OL TDF (DB PLB). This is the primary analysis set to be used for tabular summaries in the analyses at Weeks 144 and 192.

Strata and Covariates: Subjects were randomized according to stratified age (12 to 14 or 15 to 17 years) and geographical location of study site (North America, Europe). *Results*

Participant flow

Figure 2. GS-US-174-0115: Disposition of Study Subjects



A total of 106 of the 149 subjects screened (71%) were randomized and treated. A total of 101 subjects (51 in the TDF group and 50 in the PLB group; 95.3%) completed the double-blind period through Week 72. A total of 103 subjects (51 in the TDF group and 52 in the PLB group; 97.2%) entered the open-label period of the study.

One subject in the TDF group did not complete the double-blind period at the investigator's discretion. Of the 4 subjects in the PLB group who did not complete the double-blind period, 2 entered the open-label period due to elevated ALT (per protocol) and 2 entered treatment-free follow-up after Week 72 without entering open-label period of the study, with the reason recorded as investigator's discretion.

Recruitment

The first subject was screened on 3 December 2008. The last subject observed for this report was on the 1 March 2011.

Conduct of the study

The original study protocol was amended 4 times; the first amendment occurred prior to the start of the study. Second amendment was implemented during the double-blind treatment phase and applied only to investigative sites within Poland. Upon request of Poland authorities, all subjects enrolled in this study in Poland must have had a history of prior HBV treatment (previously treated with interferon or other drug intended to treat this indication) or a contraindication for treatment of HBV with existing drugs for this indication.

During the double-blind treatment phase a third change to the protocol was done: The primary endpoint was changed from a composite of HBV DNA < 400 copies/mL and ALT normal at Week 72 to the single endpoint of HBV DNA < 400 copies/mL. The protocol permitted entry based upon historical ALT in the event that ALT was not > 2 x the upper limit of normal at screening. Thus, some subjects may have been enrolled who had intermittent ALT elevations but a normal ALT at the time of baseline such that the composite endpoint would not be fully evaluable. Additionally, the inclusion criteria were modified to permit up to 50% of subjects enrolled to be HBeAg-negative considering that initial screening indicated that approximately 50% of potential subjects have HBeAg-negative disease.
The fourth amendment applied only to investigative sites within Poland, and made the same changes to the protocol described above.

Baseline data

Demographics and baseline characteristics

Overall, demographics and baseline characteristics were similar between the TDF and PLB treatment groups and were also generally similar in the 2 age categories (12 to 14 years and 15 to 17 years) within each treatment group. Subjects were predominantly white (92.5%), male (68.9%) and between the ages of 15 and 17 years (78.3%) (mean age of 15 years overall). The majority of subjects (95.3%) were enrolled at sites in Europe, and had HBV genotype A (65.1%) or D (31.1%). Baseline height, weight, and BMI were similar between treatment groups.

Baseline disease characteristics

Most of the subjects were positive for both HBeAg and HBsAg at baseline (90.6% and 100%, respectively). The mean number of years HBV positive was 10.5 years. Ninety of 106 subjects (84.9%) had prior exposure to at least 1 anti-HBV medication. Of these, 44/106 (41.5%) had previously been treated with interferon and lamivudine, either concurrently or serially, and 25/106 (23.6%) had

previously been treated with interferon alone. Baseline viral load was similar between treatment groups and age categories within the treatment groups; mean baseline HBV DNA was 8.01 log10 copies/mL (SD 1.418) in the TDF group and 8.24 log10 copies/mL (SD 1.393) in the PLB group (Table 5). Ten subjects (9.4%) overall had seroconverted to anti-HBe at baseline**.** Baseline ALT was abnormally high in the majority of subjects (72.6%); consistent with the inclusion criteria. The mean baseline ALT was 101 U/L in both treatment groups, indicating that this was a largely immune-active population.

Table 6. GS-US-174-0115: Study Baseline Disease Characteristics (Safety Analysis Set)

	TDF 12-14 Years[a] (N=10)	TDF 15-17 Years[a] (N=42)	PLB 12-14 Years[a] (N=13)	PLB 15-17 Years[a] (N=41)	Total TDF (N=52)	Total PLB (N=54)	Total (N=106)
Baseline[b] HBV DNA (Log_{10} copies/mL)[c]							
N	10	42	13	41	52	54	106
Mean (SD)	8.26 (1.455)	7.95 (1.421)	8.61 (1.166)	8.12 (1.451)	8.01 (1.418)	8.24 (1.393)	8.13 (1.403)
Median	8.53	8.43	8.82	8.48	8.43	8.50	8.49
Q1, Q3	7.52, 9.28	6.94, 9.07	8.38, 9.29	7.79, 9.16	7.13, 9.17	7.87, 9.26	7.48, 9.22
Min, Max	5.54, 10.11	4.91, 9.81	6.22, 10.08	4.79, 10.04	4.91, 10.11	4.79, 10.08	4.79, 10.11
Baseline[b] ALT (U/L)							
N	10	42	13	41	52	54	106
Mean (SD)	77 (54.8)	106 (116.4)	101 (95.4)	101 (89.5)	101 (107.5)	101 (90.0)	101 (98.5)
Median	68	58	64	80	62	75	68
Q1, Q3	42, 89	35, 140	30, 125	45, 122	35, 125	44, 125	40, 125
Min, Max	21, 207	19, 563	16, 359	20, 501	19, 563	16, 501	16, 563
Baseline[b] ALT Normal/Abnormal							
Normal	3 (30.0%)	14 (33.3%)	4 (30.8%)	8 (19.5%)	17 (32.7%)	12 (22.2%)	29 (27.4%)
Abnormal	7 (70.0%)	28 (66.7%)	9 (69.2%)	33 (80.5%)	35 (67.3%)	42 (77.8%)	77 (72.6%)
Baseline[b] AST (U/L)							
N	10	42	13	41	52	54	106
Mean (SD)	53 (33.1)	66 (73.6)	82 (108.6)	62 (46.6)	64 (67.7)	67 (66.2)	66 (66.6)
Median	44	38	49	49	40	49	46
Q1, Q3	30, 63	30, 78	35, 68	34, 71	30, 71	34, 71	32, 71
Min, Max	23, 134	18, 432	20, 432	18, 261	18, 432	18, 432	18, 432

	TDF 12-14 Years[a] (N=10)	TDF 15-17 Years[a] (N=42)	PLB 12-14 Years[a] (N=13)	PLB 15-17 Years[a] (N=41)	Total TDF (N=52)	Total PLB (N=54)	Total (N=106)
Baseline[b] HBeAg							
Negative	1 (10.0%)	3 (7.1%)	0	6 (14.6%)	4 (7.7%)	6 (11.1%)	10 (9.4%)
Positive	9 (90.0%)	39 (92.9%)	13 (100.0%)	35 (85.4%)	48 (92.3%)	48 (88.9%)	96 (90.6%)
Baseline[b] HBsAg							
Positive	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)	106 (100.0%)
Baseline[b] Anti-HBe							
- Missing -	9 (90.0%)	39 (92.9%)	13 (100.0%)	35 (85.4%)	48 (92.3%)	48 (88.9%)	96 (90.6%)
Positive	1 (10.0%)	3 (7.1%)	0	6 (14.6%)	4 (7.7%)	6 (11.1%)	10 (9.4%)
Baseline[b] Anti-HBs							
- Missing -	10 (100.0%)	42 (100.0%)	13 (100.0%)	41 (100.0%)	52 (100.0%)	54 (100.0%)	106 (100.0%)

Bone markers

Bone biomarkers were similar between treatment groups, as was whole-body and spine BMD. Overall mean baseline whole-body BMD was 1.08 g/cm2 (SD 0.105), and spine BMD was 1.00 g/cm2 (SD 0.160). Mean baseline vitamin D levels were 19.9 ng/mL (SD 7.59), above the lower limit of normal for adolescents (25[OH]D levels ≤ 15 ng/mL or 37.5 nmol/L).

Adherence to the Study Drug Regimen

Overall subject adherence to the study drug regimen, as determined by pill counts, was high and similar in both treatment groups (98.7% [SD 2.06] in the TDF group and 97.9% [SD 3.80] in the PLB group) and across all age groups within and across treatment groups.

Table 7. Exposure and Adherence to Double-Blind Study Drug Safety Analysis set.

	TDF 12-14 Years (N=10)	TDF 15-17 Years (N=42)	PLB 12-14 Years (N=13)	PLB 15-17 Years (N=41)	Total TDF (N=52)	Total PLB (N=54)
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%)

Prior HBV medication

Ninety of 106 subjects (84.9%) had prior exposure to at least 1 anti-HBV medication. Of these, 44/106 (41.5%) had previously been treated with interferon and LAM, either concurrently or serially, and 25/106 (23.6%) had previously been treated with interferon alone.

Numbers analysed

All 3 analysis sets comprised the same number and percentage of subjects within each treatment/age group and overall. The primary efficacy analysis was conducted at the end of DB treatment, after the last randomized subject reached Week 72, using the FAS. The FAS included all subjects who were randomized into the study and received at least 1 dose of study drug (ie, TDF 300 mg or matching PLB).

Table 8. 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.

Source: Section 15.1, Table 3; Appendix 16.2, Listing 3

Outcomes and estimation

Primary Efficacy Endpoint

The primary efficacy endpoint in this study is the proportion of subjects with HBV DNA < 400 copies/mL (69 IU/mL) at the end of DB treatment (Week 72).

Of equal interest is the proportion of subjects with HBV DNA below the lower limits of quantitation (LLoQ) of the assay, 169 copies/mL (29 IU/mL), at Week 72.

Table 9. GS-US-174-0125: Number and percentage of subjects with HBV DNA below 400 copies/ml and below 169 copies/ml at week 72 (end of DB treatment) (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).

At Week 72, the proportion of subjects with HBV DNA < 400 copies/mL (69 IU/mL) (end of DB period) in the TDF group was 88.5% (46/52) vs 0 % (0/54) subject in the placebo group (1 subject with HBV DNA < 400 copies/mL at Week 16 only).

The proportion of subjects with HBV DNA below the lower limits of quantitation (LLoQ) of the assay, 169 copies/mL (29 IU/mL), at Week 72 in the TDF group was 84.6%.

In the placebo group, 1 subject had HBV DNA below 400 copies/mL or below 169 copies/mL at Week 16 only.

HBV DNA Change Over Time Through Week 72:
Mean changes were greater in the TDF group through Week 48 and held steady thereafter. At Week 72, mean change from baseline in HBV DNA was −5.36 SD 1.952) log10 copies/mL in the TDF group versus −0.92 (SD 1.944) log10 copies/mL in the PLB group. Given that measurements below the LLoQ were set to a value of 168 copies/ml, the maximum log decline that it was possible to detect was bounded by this value (eg log[168]=2.2=lowest possible HBV log DNA level).

Secondary Efficacy endpoints
Secondary efficacy endpoints evaluated in this study through Week 72 included the percentage of subjects with normal and normalized ALT at each visit, serological status (HBeAg/anti-HBe and HBsAg/anti-HBs), and composite endpoints of HBV DNA < 400 copies/mL and < 169 copies/mL with normal ALT, with HBsAg loss, and with seroconversion.

Normal and Normalized ALT Through Week 72
The percentage of subjects with normal ALT at week 72 increased from 32.7% at baseline to 76.9% at Week 72 (DBEE analysis). When missing values were excluded, results were similar. Results were also similar between the two age ranges within the TDF group. In the PLB group among subjects aged 12 to 14 years, there was no change in the percentage of subjects with normal ALT through Week 72 (30.8% at both baseline and Week 72, DBEE and M=E analyses). In the PLB group among subjects aged 15 to 17 years, however, the percentage of subjects with normal ALT increased from 19.5% at baseline to 41.5% at Week 72 (DBEE analysis).

The percentage of subjects with baseline ALT above the ULN who achieved ALT within the normal range by Week 72 was significantly larger in the TDF group (74.3%) versus the PLB group (31.0%) ($p < 0.001$, DBEE analysis) and was consistent across age groups. After Week 8, the difference between the TDF and PLB groups in the percentage of subjects with normal and normalized ALT was statistically significant ($p \leq 0.002$, DBEE and M=E analyses).

Table 10.

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	
Normal ALT							
DBEE Analysis (Missing=Failure)							
Week 72	8/10 (80.0%)	32/42 (76.2)	4/13 (30.8%)	17/41 (41.5%)	40/52 (76.9%)	21/54 (38.9%)	< 0.001
Normalized ALT[d]							
DBEE Analysis (Missing=Failure)							
Week 72	6/7 (85.7%)	20/28 (71.4%)	2/9 (22.2%)	11/33 (33.3%)	26/35 (74.3%)	13/42 (31.0%)	< 0.001

HBeAg Loss and Seroconversion to anti-HBe by Week 72

Only 1 subject (in the TDF group) experienced confirmed HBeAg loss and seroconversion.

Table 11.

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	
HBeAg Loss[d]							
DBEE Analysis (Missing=Failure)							
Week 72	1/9 (11.1%)	9/39 (23.1%)	3/13 (23.1%)	4/35 (11.4%)	10/48 (20.8%)	7/48 (14.6%)	0.41
Seroconversion to Anti-HBe[d]							
DBEE Analysis (Missing=Failure)							
Week 72	1/9 (11.1%)	9/39 (23.1%)	3/13 (23.1%)	4/35 (11.4%)	10/48 (20.8%)	7/48 (14.6%)	0.41

HBsAg Loss and Seroconversion to anti-HBs by Week 72

Two subjects (both in the TDF group) experienced HBsAg loss (DBEE analysis). One of the 2 subjects who experienced HBsAg loss also had seroconversion to anti-HBs at Weeks 64 and 72. The other subject had unconfirmed HBsAg loss at Week 32, with no seroconversion. However, this subject was HBsAg-positive at subsequent visits though Week 72.

Composite endpoints

Percentage of Subjects with HBV DNA below 400 Copies/mL and Normal ALT

A total of 71.2% of subjects in the TDF group had HBV DNA below 400 copies/mL and ALT within the normal range at Week 72 (versus 0 subjects in the PLB group; $p < 0.001$; DBEE analysis). When subjects with missing values were excluded, results were similar (72.5% in the TDF group and 0 subjects in the PLB group). Percentages were higher in subjects treated with TDF who were between the ages of 12 and 14 years (80.0%) compared to those between the ages of 15 and 17 years (69.0%) in the DBEE analysis. When subjects with missing values were excluded, results were similar.

Percentage of Subjects with HBV DNA below 400 Copies/mL and Normalized ALT

A total of 74.35 (26/35) of subjects that had baseline ALT above the ULN in the TDF group had HBV DNA below 400 copies/mL and ALT within the normal range at Week 72 (versus 0 subjects in the PLB group; $p < 0.001$; DBEE analysis).

Percentage of Subjects with HBV DNA Below 400 copies/mL, Normal ALT, and HBeAg Loss or Seroconversion

At Week 72, 7/48 (14.6%) subjects in the TDF group had achieved the composite endpoint with HBeAg loss, while no subjects in the PLB group had done so (DBEE analysis). The same was true for the composite endpoint with HBeAg seroconversion; at Week 72, 7/48 (14.6%) subjects in the TDF group had achieved this composite endpoint, while no subjects in the PLB group had done so (DBEE analysis).

Percentage of Subjects with HBV DNA Below 400 copies/mL, Normalized ALT, and HBeAg Loss or

Seroconversion

At Week 72, 7/33 (21.2%) subjects in the TDF group had achieved the composite endpoint with HBeAg loss, while no subjects in the PLB group had done so (DBEE analysis). The same was true for the composite endpoint with HBeAg seroconversion; at Week 72, 7/33(21.2%) subjects in the TDF group had achieved this composite endpoint, while no subjects in the PLB group had done so (DBEE analysis).

Composite Endpoint of HBV DNA < 400 copies/mL + HBeAg loss in HBeAg-Positive Subjects

An ad-hoc analysis for the composite endpoint of HBV DNA < 400 copies/ mL + HBeAg loss in HBeAg-positive subjects showed a statistically significant difference between the number of subjects achieving the endpoint in the TDF versus PLB treatment groups at Week 72.

Ten of 48 subjects (20.8%) in the TDF group and 0 subjects in the PLB group had HBV DNA < 400 copies/mL and HBeAg loss at Week 72 ($p = 0.001$) (DBEE analysis).

Subgroup analyses

Table 12. GS-US-174-0115: Analysis of HBV DNA Below Thresholds of Interest within Relevant Subgroups (Full Analysis Set; DBEE)

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)
	N=10	N=42	N=13	N=41	N=52	N=54
HBV DNA < 400 copies/mL (69 IU/mL), n (%) **HBV DNA < 169 copies/mL (29 IU/mL), n (%)**						
Normal Baseline ALT						
Week 24	2/3 (66.7%) 2/3 (66.7%)	8/14 (57.1) 8/14 (57.1)	0/4 (0.0%) 0/4 (0.0%)	0/8 (0.0%) 0/8 (0.0%)	10/17 (58.8%) 10/17 (58.8%)	0/12 (0.0%) 0/12 (0.0%)
Week 48	2/3 (66.7%) 2/3 (66.7%)	10/14 (71.4%) 9/14 (64.3%)	0/4 (0.0%) 0/4 (0.0%)	0/8 (0.0%) 0/8 (0.0%)	12/17 (70.6%) 11/17 (64.7%)	0/12 (0.0%) 0/12 (0.0%)
Week 72	2/3 (66.7%) 2/3 (66.7%)	10/14 (71.4%) 9/14 (64.3%)	0/4 (0.0%) 0/4 (0.0%)	0/8 (0.0%) 0/8 (0.0%)	12/17 (70.6%) 11/17 (64.7%)	0/12 (0.0%) 0/12 (0.0%)
Abnormal Baseline ALT						
Week 24	4/7 (57.1%) 2/7 (28.6%)	18/28 (64.3%) 13/28 (46.4%)	0/9 (0.0%) 0/9 (0.0%)	0/33 (0.0%) 0/33 (0.0%)	22/35 (62.9%) 15/35 (42.9%)	0/42 (0.0%) 0/42 (0.0%)
Week 48	7/7 (100%) 6/7 (85.7%)	26/28 (92.9%) 25/28 (89.3%)	0/9 (0.0%) 0/9 (0.0%)	0/32 (0.0%) 0/32 (0.0%)	33/35 (94.3%) 31/35 (88.6%)	0/41 (0.0%) 0/41 (0.0%)
Week 72	7/7 (100%) 7/7 (100%)	27/28 (96.4%) 26/28 (92.9%)	0/9 (0.0%) 0/9 (0.0%)	0/33 (0.0%) 0/33 (0.0%)	34/35 (97.1%) 33/35 (94.3%)	0/42 (0.0%) 0/42 (0.0%)
HBeAg Negative at Baseline						
Week 24	1/1 (100.0%) 0/1 (0.0%)	3/3 (100.0%) 3/3 (100.0%)	0/0 (0.0%) 0/0 (0.0%)	0/6 (0.0%) 0/6 (0.0%)	4/4 (100.0%) 3/4 (75.0%)	0/6 (0.0%) 0/6 (0.0%)
Week 48	1/1 (100.0%) 1/1 (100.0%)	3/3 (100.0%) 3/3 (100.0%)	0/0 (0.0%) 0/0 (0.0%)	0/6 (0.0%) 0/6 (0.0%)	4/4 (100.0%) 4/4 (100.0%)	0/6 (0.0%) 0/6 (0.0%)
Week 72	1/1 (100.0%) 1/1 (100.0%)	3/3 (100.0%) 3/3 (100.0%)	0/0 (0.0%) 0/0 (0.0%)	0/6 (0.0%) 0/6 (0.0%)	4/4 (100.0%) 4/4 (100.0%)	0/6 (0.0%) 0/6 (0.0%)
HBeAg Positive at Baseline						
Week 24	5/9 (55.6%) 4/9 (44.4%)	23/39 (59.0) 18/39 (46.2)	0/13 (0.0%) 0/13 (0.0%)	0/35 (0.0%) 0/35 (0.0%)	28/48 (58.3%) 22/48 (45.8%)	0/48 (0.0%) 0/48 (0.0%)
Week 48	8/9 (88.9%) 7/9 (77.8%)	33/39 (84.6%) 31/39 (79.5%)	0/13 (0.0%) 0/13 (0.0%)	0/34 (0.0%) 0/34 (0.0%)	41/48 (85.4%) 38/48 (79.2%)	0/47 (0.0%) 0/47 (0.0%)
Week 72	8/9 (88.9%) 8/9 (88.9%)	34/39 (87.2%) 32/39 (82.1%)	0/13 (0.0%) 0/13 (0.0%)	0/35 (0.0%) 0/35 (0.0%)	42/48 (87.5%) 40/48 (83.3)	0/48 (0.0%) 0/48 (0.0%)

Analyses based on the immune status

The CHMP raised doubts on the population included in this study since, neither liver biopsies were performed nor historical data were provided in adolescents in this study to better evaluate this issue. The MAH has addressed this concern and provided further analyses as described below.

The protocol required subjects to have alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal (ULN) at the time of screening or at any time over the previous ≤ 24 months. Thus, all subjects were required to have evidence of elevated ALT, but some were included with normal baseline values.

Overall, 29/106 (27.4%) subjects had ALT values within the normal range (32.7% TDF and 22.2% PLB) at baseline.

An ad hoc analysis based on ALT level at baseline was conducted in which two subpopulations were identified – an IA subgroup (baseline ALT > 1.5 × ULN), and an IT subgroup (baseline ALT ≤ 1.5 × ULN). In the TDF subgroups (both IA and IT), high viral suppression was demonstrated at Week 72 in comparison to PLB in both subgroups and higher in the IA subgroup (96.4% TDF IA vs 0% in PLB IA, and 79.2% TDF IT vs 0% in PLB IT group, $p < 0.001$).

IA subjects treated with TDF had a significantly greater biochemical (75% with normal ALT) response in comparison to PLB at Week 72. In the IT subgroups, there was a suggestion of a treatment effect on ALT levels.

The effect of TDF on HBeAg loss and seroconversion was evaluated in these subgroups. At Week 72, 10/48 (20.8%) subjects treated with TDF experienced HBeAg loss compared with 7/48 (14.6%) PLB subjects ($p = 0.41$; double-blind efficacy evaluation [DBEE] analysis). When evaluated by IA status, differences were observed between TDF and PLB. In the TDF IA subgroup, 8/26 (30.8%) subjects experienced HBeAg loss at Week 72 compared with 4/32 (12.5%) subjects in the PLB IA subgroup ($p = 0.11$). In contrast, in the IT subgroups, 2/22 (9.1%) subjects in the TDF IT subgroup and 3/16 (18.8%) subjects in the PLB IT subgroup experienced HBeAg loss at Week 72 ($p = 0.63$). Identical results were observed when the IA and IT subgroups were evaluated for HBeAg seroconversion to anti-HBe.

Furthermore, in the TDF groups, the stringent composite endpoint of HBV DNA<400 copies/ml, Normal ALT and HBeAg loss was achieved in 23% (n=6) of patients with immune active disease versus 4.5% (n=1) in immune-tolerant patients, which further highlights that the IA population is the population that can most benefit from treatment.

Other Analyses Related to Efficacy

Genotypic Analysis at Baseline within the HBV Polymerase

Genotypes A and D were the most commonly observed genotypes in each treatment group (65% and 31% respectively). Overall, 3 subjects were identified with genotype B virus (3%), and 1 subject had genotype C virus (1%). The distribution of genotypes was similar across both treatment groups.

Sequence analysis of HBV pol/RT for all baseline samples revealed that 10 subjects, 7 in the TDF group and 3 in the PLB group, had conserved site changes at baseline. The majority of the conserved site changes observed at baseline (6/7 subjects in the TDF group and 2/3 subjects in the PLB group) were lamivudine (LAM) resistance-associated mutations (rtL180M ± rtM204V/I).

Genotypic Change from Baseline within the HBV Polymerase at week 72

In the TDF group, 5 subjects qualified for resistance surveillance at Week 72. One Subject qualified for genotypic analysis at Week 72 because the subject had HBV DNA > 400 copies/mL in the absence of virologic breakthrough. Despite the subject's HBV DNA never having been < 400 copies/mL by Week 72, this subject experienced a 6.86-log10 decline in HBV DNA from baseline. Genotypic analysis of the Week 72 sample revealed no sequence changes compared to baseline, identical to what was observed at Week 48.

One subject qualified for genotypic analysis due to unconfirmed virologic breakthrough. This subject had HBV DNA < 400 copies/mL by Week 8, which was maintained until Week 72 when the subject's HBV DNA increased to 5.72 log10 copies per mL. This increase in HBV DNA was associated with study drug nonadherence, as determined by tenofovir plasma levels below the limit of quantitation at Week 72. The increase in HBV DNA was transient, as HBV DNA returned to < 400 copies/ mL at the following visit. Genotypic analysis revealed unique polymorphic site changes compared to baseline.

The remaining 3 subjects qualified for resistance surveillance at Week 72 due to having confirmed virologic breakthrough. From these, one subject had confirmed virologic breakthrough at Week 40 which was maintained through Week 64. This subject experienced another episode of confirmed virologic breakthrough at Week 72, with a 5.37-log10 increase in HBV DNA from nadir at Week 32. Virologic breakthrough could be attributed to study drug nonadherence, as determined by tenofovir plasma levels below the limit of quantitation at Week 72. Identical to what was observed at Week 48, genotypic analysis at Week 72 revealed a reversion back to wild-type at a conserved site (rtR/W3W) along with maintenance of LAM resistance-associated mutations detected at baseline (rtL180L/M, rtM204M/V). Another subject had HBV DNA below 400 copies/mL from Week 24 through Week 56 and then had confirmed virologic breakthrough at Week 64 with low-level viremia of 3.79 log10 copies/mL. Virologic breakthrough could be attributed to study drug nonadherence, as determined by tenofovir plasma levels below the limit of quantification at Weeks 64 and 72. Genotypic analysis of the Week 72 sample demonstrated one unique polymorphic site change compared to baseline. One subject had HBV DNA below 400 copies/mL from Week 32 to Week 56 and then had confirmed virologic breakthrough at Week 64 with HBV DNA values increasing to over 8 log10. Virologic breakthrough could be attributed to study drug nonadherence, as indicated by low tenofovir plasma levels below the limit of quantification at Weeks 64 and 72. Genotypic analysis of the Week 72 sample showed no changes from baseline. Of the 4 subjects who had virologic breakthrough at Week 72, all had plasma tenofovir levels below the limit of quantitation indicating that breakthrough was due to non-adherence to study drug.

Comparison with adults data

The rates of response in this study through Week 48 were generally consistent with that of adult subjects during the first 48 weeks of the double-blind TDF treatment in two Phase 3 clinical studies of TDF in chronic HBV (GS-US-174-0102 and GS-US-174-0103):

Table 13. Comparison of HBV DNA Response in Adolescent Subjects Versus Adult Subjects Receiving TDF

Study (Population)	Week 24	Week 48
	Percentage of Subjects with HBV DNA < 169 copies/mL/ Mean Change from Baseline in HBV DNA (log_{10} copies/mL)	
GS-US 174-0102 (HBeAg-negative adult subjects receiving TDF 300 mg once daily)	75.6%[a] / –4.46 (SD 1.202)	91.2%[a] / –4.57 (SD 1.347)
GS-US-174-0103 (HBeAg-positive adult subjects receiving TDF 300 mg once daily)	37.5%[a] / –5.73 (SD 1.028)	68.8%[a] / –6.17 (SD 1.067)
GS-US-174-0115 (HBeAg-negative and positive adolescent subjects receiving TDF 300 mg once daily)	48.1% (Overall)[a] / –5.20 (SD 1.267) 75.0% (HBeAg–) 45.8% (HBeAg+)	80.8% (Overall)[a] / –5.63 (SD 1.365) 100% (HBeAg–) 79.2% (HBeAg+)

a Based on analyses in which subjects with missing HBV DNA values at the time point of interest were considered failures for the endpoint.

The rates of biochemical response in this study through Week 48 were generally consistent with that of adult subjects during the first 48 weeks of the double-blind TDF treatment in two Phase 3 clinical studies of TDF in chronic HBV (GS-US-174-0102 and GS-US-174-0103):

Table 14. Comparison of Biochemical Response in Adolescent Subjects Versus Adult Subjects Receiving TDF

Study (Population)	Week 24	Week 48
	Percentage of Subjects with Normal ALT / Mean Change from Baseline in ALT (U/mL)	
GS-US 174-0102 (HBeAg-negative adult subjects receiving TDF 300 mg once daily)	75.2%[a] / –92.2 (SD 104.43)	77.2%[a] / –95.0 (SD 102.31)
GS-US-174-0103 (HBeAg-positive adult subjects receiving TDF 300 mg once daily)	56.8%[a] / –93.5 (SD 113.22)	69.3%[a] / –107.2 (SD 109.37)
GS-US-174-0115 (HBeAg-positive and negative adolescent subjects receiving TDF 300 mg once daily)	58.8% (Overall)[a] / –60 (SD 109)	75.0% (Overall)[a] / –67 (SD 109.2)

a Based on analyses in which subjects with missing ALT values at the time point of interest were considered failures for the endpoint.

Summary of main study results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15. Summary of Efficacy for trial GS-US-174-0115

Title: A Randomised, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (TDF) Versus Placebo (PLB) in Adolescents with Chronic Hepatitis B Infection.			
Study identifier	Gilead Protocol Number: GS-US-174-0115 EudraCT number: 2007-003704-35		
Design	Phase 3, randomised, double-blind study comparing the antiviral efficacy, safety, and tolerability of TDF to PLB in adolescents with chronic hepatitis B virus (HBV) infection. One hundred six (106) TDF-naïve adolescents aged 12 to 17 years with chronic HBV infection (either hepatitis B early antigen [HBeAg]-positive or HBeAg-negative), HBV deoxyribonucleic acid (DNA) ≥ 10^5 copies/mL AND either alanine aminotransferase (ALT) ≥ 2 × upper limit of normal (ULN) at screening OR any history of ALT ≥ 2 × ULN over the past ≤ 24 months were randomised in a 1:1 ratio to treatment group A or B: - Treatment A: blinded TDF 300 mg orally (PO) once daily - Treatment B: blinded matching placebo PO once daily		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		72 weeks Not applicable 120 weeks open label TDF 300 mg (total duration: 192 weeks)
Hypothesis	Superiority		
Treatments groups	Treatment A		Blinded TDF 300 mg orally (PO) once daily for 72 weeks (n = 52)
	Treatment B		Blinded matching placebo PO once daily for 72 weeks (n = 54)
Endpoints and definitions	Primary endpoint:	HBV-DNA	HBV DNA < 400 copies/mL at Week 72.
		HBV-DNA	HBV DNA < 169 copies/mL at Week 72.
	Key Secondary endpoints:	ALT-normal	ALT levels normal at Week 72

		ALT-normalised	For all subjects with abnormal ALT at baseline, secondary endpoints included ALT levels normalised at Week 72.
		HBeAg-loss	For HBeAg-positive subjects, secondary endpoints included HBeAg loss at Week 72.
		HBeAg-sero	For HBeAg-positive subjects, secondary endpoints included HBeAg seroconversion at Week 72.
		HBsAg-loss	HBsAg loss at Week 72.
		HBsAg-sero	HBsAg seroconversion at Week 72.
Database lock	13th May 2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): The FAS included all subjects who were randomised into the study and received at least 1 dose of study drug (ie, TDF 300 mg or matching PLB).		
Descriptive statistics and estimate variability	Treatment group	Treatment A: blinded TDF 300 mg orally (PO) once daily	Treatment B: blinded matching placebo PO once daily
	Number of subjects per treatment group:	52	54
	HBV-DNA < 400 copies/mL n (%)	46/52 (88.5%)	0/54 (0.0%)
	HBV-DNA < 169 copies/mL n (%)	44/52 (84.6%)	0/54 (0.0%)
	ALT-normal n (%)	40/52 (76.9%)	21/54 (38.9%)
	ALT-normalised n (%)	26/35 (74.3%)	13/42 (31.0%)
	HBeAg-loss n (%)	10/48 (20.8%)	7/48 (14.6%)
	HBeAg-sero n (%)	10/48 (20.8%)	7/48 (14.6%)
	HBsAg-loss n (%)	1/52 (1.9%)	0/54 (0.0%)
	HBsAg-sero n (%)	1/52 (1.9%)	0/54 (0.0%)
	HBV-genotyping	1/52 (1.9%)*	5/54 (9.3%)
	* HBV from subjects on TDF with confirmed virologic breakthrough or who developed conserved site changes in HBV pol/RT were analysed phenotypically. All HBV isolates tested showed full susceptibility to tenofovir indicating that no resistance to tenofovir had developed among these subjects.		
Effect estimate per comparison	HBV-DNA < 400 copies/mL	Comparison groups	Treatment A vs Treatment B
		Difference between groups	88.5% - 0.0%
		P-value**	<0.001

	HBV-DNA < 169 copies/mL	Comparison groups	Treatment A vs Treatment B
		Difference between groups	84.6% - 0.0%
		P-value**	<0.001
	ALT-normal	Comparison groups	Treatment A vs Treatment B
		Difference between groups	76.9% - 38.9%
		P-value**	<0.001
	ALT-normalised	Comparison groups	Treatment A vs Treatment B
		Difference between groups	74.3% - 31.0%
		P-value**	<0.001
	HBeAg-loss	Comparison groups	Treatment A vs Treatment B
		Difference between groups	20.8% - 14.6%
		P-value**	0.41
	HBeAg-sero	Comparison groups	Treatment A vs Treatment B
		Difference between groups	20.8% - 14.6%
		P-value**	0.41
	HBsAg-loss	Comparison groups	Treatment A vs Treatment B
		Difference between groups	1.9% - 0.0%
		P-value**	0.32
	HBsAg-sero	Comparison groups	Treatment A vs Treatment B
		Difference between groups	1.9% - 0.0%
		P-value**	0.32
	** P-value 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 randomisation).		
Notes	-		

1.4.2. Discussion on clinical efficacy

To support the extension of the indication for Viread in adolescents chronically infected with HBV, the MAH submitted the 72 weeks results of the ongoing pivotal study, GS-US-174-0115. This study is a Phase 3, double-blind, randomized, placebo-controlled study of the Safety and Efficacy of Tenofovir DF in Adolescents with CHB infection. Long term data Studies GS-US-174-0102 and GS-US-174-0103 in adults could also be considered as support of efficacy and safety.

The study was initiated in December 2008 and was primarily conducted in Europe (mostly in Poland) and US. The study design (72 weeks comparison between TDF and placebo) allows from an efficacy

point of view to compare with spontaneous seroconversion rates and from a safety point of view to evaluate the effect on bone mineral density.

No liver biopsy was performed before inclusion in the study and ALT criterion for inclusion in the study was not stringent, allowing inclusion of patients with ALT $\geq 2 \times$ ULN at screening (not confirmed) or any history of ALT $\geq 2 \times$ ULN over the past ≤ 24 months.

The study population consists mainly of adolescents with HBeAg-positive disease (90%) and with prior exposure to lamivudine and/or interferon (only 15% were naïve to any HBV treatment). This is considered acceptable because in adults, the efficacy has been validated in both HBe Ag + and -. The same consideration applies for treatment naïve and pretreated patients. The efficacy of tenofovir in adults is established in both populations.

Study GS-US-174-0115 showed superiority of TDF over placebo on the primary endpoint (proportion of patients with HBV DNA <400 copies/ml), when the most conservative analysis was considered (missing=failures). Superiority was also demonstrated for the more stringent criterion of proportion of patients with HBV DNA <169 copies/ml (88.5% vs 0%, p<0.001). Response rate were comparable in the 12-14 (n= 23) and 15-17 (n= 83) years age groups. Patients with abnormal ALT at baseline had notably greater rate of response as compared to patients who had normal ALT at baseline.

TDF showed greater potency over placebo not only on the primary endpoint but also on all secondary endpoints.

However, the viral response is not translated into a major differential in terms of HBeAg seroconversion rate. The difference in favour of TDF (21% vs 15%), was not statistically significant.

Moreover, the 21% rate of HBeAg seroconversion in the TDF arm illustrates the need for a life long treatment for the vast majority of adolescents. These results raised several questions: 1) the benefit of introducing Viread with its bone toxicity in a population still in bone modelling process, as compared to introducing the drug in the adulthood 2) The need to delineate a population for which an immediate need could justify outweighing the bone risk (these issues are further discussed at the safety and benefit risk sections).

The MAH has addressed these concerns and provided further analyses. An ad hoc analysis based on ALT level at baseline was conducted. In the TDF subgroups (both IA and IT), viral suppression was demonstrated at Week 72 in comparison to PLB (96.4% TDF IA vs 0% in PLB IA, and 79.2% TDF IT vs 0% in PLB IT group, p < 0.001). IA subjects treated with TDF had a significantly greater biochemical (75% with normal ALT) response in comparison to PLB at Week 72. In the IT subgroups, there was a suggestion of a treatment effect on ALT levels. In the TDF IA subgroup, 8/26 (30.8%) subjects experienced HBeAg loss at Week 72 compared with 4/32 (12.5%) subjects in the PLB IA subgroup (p = 0.11). In contrast, in the IT subgroups, 2/22 (9.1%) subjects in the TDF IT subgroup and 3/16 (18.8%) subjects in the PLB IT subgroup experienced HBeAg loss at Week 72 (p = 0.63). In the TDF groups, the stringent composite endpoint of HBV DNA<400 copies/ml, Normal ALT and HBeAg loss was achieved in 23% (n=6) of patients with immune active disease versus 4.5% (n=1) in immune-tolerant patients, which further highlights that the IA population is the population that can most benefit from treatment. Overall, these results reinforce the use in patients in active status of the disease.

No patients had TDF resistance-associated mutation through week 72 in this study. TDF showed a high genetic barrier in children as it was observed for adults.

Overall, TDF appears as effective in adolescents as in adults. The study is ongoing with an open-label phase for up to a total of 4 years that will help to document longer-term efficacy and resistance of TDF in adolescents.

1.5. Clinical safety

Patient exposure

A total of 106 subjects (52 in the TDF group and 54 in the placebo group) were randomized and treated. A total of 101 subjects (51 in the TDF group and 50 in the placebo group) completed the double-blind period through Week 72.

A total of 103 subjects (51 in the TDF group and 52 in the placebo group) entered the Open-Label period of the study. One subject in the TDF group did not complete the double-blind period at the investigator's discretion. Of the 4 subjects in the PLB group who did not complete the DB period, 2 entered the Open-Label period due to elevated ALT (per protocol) and 2 entered treatment free follow-up after Week 72 without entering Open-Label period of the study, with the reason recorded as investigator's discretion.

All subjects completed at least 24 weeks of treatment. The mean duration of treatment was 497.3 days in the TDF group vs 489.7 days in the placebo group. The percentage of subjects with 72 weeks of study drug exposure was > 92% in both groups.

Subjects were predominantly white (92.5%), male (68.9%) and between the ages of 15 and < 18 years (78.3%) (mean age of 15 years overall).

In summary the safety of TDF has been studied in 52 subjects aged from 12 to 18 years old (10 subjects in group age 12-14 years and 42 subjects in group 15-<18). The mean duration of treatment was 497.3 days in the TDF group.

Adverse events

An overview of treatment emergent adverse events in study GS-US-174-0115 is provided in the table 15 below.

Table 16. GS-US-174-0115: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

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 similar proportion of subjects in the TDF group (84.6 %) and in the placebo group (88.9%) experienced a treatment emergent AEs. However when comparing by group age a higher proportion of subjects aged 12-14 years old experienced treatment emergent AEs in the TDF group compared to the placebo group (90% vs 61.5%). However the small number of subjects in the age group 12 to 14 years should be taken into account in the interpretation of the results. In the group age 15-<18 years a lower proportion of subjects experienced treatment emergent AEs in the TDF group (83.3%) compared to the placebo group (97.6%).

The number of patients who experienced treatment-emergent SAEs was lower in the TDF group (11.5%) vs placebo group (22.2%).

A similar proportion of subjects in the TDF group (15.4%) and in the placebo group (16.7%) experienced an AE that was considered study drug related.

Primary safety endpoint

The primary safety endpoint was cumulative incidence of at least a 6% decrease from study baseline in lumbar spine BMD through Week 72. No subjects met the primary safety endpoint of a 6% decrease in

lumbar spine BMD. As expected for an adolescent population, both treatment groups experienced an overall increase in mean lumbar spine BMD. However, the percent increase from baseline in lumbar spine BMD in subjects who received TDF was less than the percent increase in spine BMD attained by subjects who received placebo at Week 24 (1.87% vs 3.42%), at Week 48 (3.50% vs 5.58%), and at Week 72 (4.95% vs 8.14%). Five subjects (3 in the TDF group and 2 in the placebo group) had a decrease of > 4% in spine BMD. None of these subjects were reported as having had associated bone events, including fracture.

Table 17. GS-US-174-0115: Percent Change from Study Baseline in Spine Bone Mineral Density (g/cm^2) by Study Baseline in Spine Bone Mineral Density (g/cm^2) by Study Week: Categorical Summaries on Number of Subjects (Safety Analysis Set[2]).

	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)
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%)

Regarding the whole body BMD, in the TDF 15-17 years group, 24% patients experienced a decrease of BMD (≤0%) compared to 11% in the placebo group.

However, no patient in the TDF group (vs 2.8% subject in the placebo group) had a decrease of > 4% in spine BMD.

No decreased is observed in the 12-14 years groups. However, at week 72 only 6 patients in the TDF group had a BMD measure.

Common adverse events

In both treatment group, the highest proportion of subjects reported AEs in the following SOCs: Infections and Infestations (TDF: 59.6% vs placebo: 63.0%), Investigations (TDF: 25.0% vs placebo:

31.5%), Gastrointestinal Disorders (TDF: 21.2% vs placebo: 31.5%), and Respiratory, Thoracic, and Mediastinal Disorders (TDF: 23.1% vs placebo: 20.4%).

The most frequently reported treatment emergent AEs in the TDF group were the following: Pharyngitis (15 subjects), Nasopharyngitis (5 subjects), Upper respiratory tract infection (5 subjects), Rhinitis (5 subjects). And the most frequently reported treatment emergent AEs in the placebo group were: Nasopharyngitis (12 subjects), Alanine aminotransferase increased (12 subjects), Pharyngitis (11 subjects), Acne (10 subjects), Headache (8 subjects).

Treatment emergent AEs occurring with ≥ 5 % incidence and reported for higher proportion of subjects in the TDF group compared to placebo group were the following: Pharyngitis (28.8% vs 20.4%), Rhinitis (9.6% vs 5.6%), Blood creatine phosphokinase increased (7.7% vs 3.7%), Cough (5.8% vs 5.6%), Diarrhoea (7.7% vs 1.9%), Epistaxis (5.8% vs 3.7%), Pyrexia (5.8% vs 1.9%) and Nail disorder (5.8% vs 0%).

Serious adverse event / deaths / other significant events

Grade 3 or 4 treatment-emergent AEs were reported for 5 subjects (9.6%) in the TDF group and 13 subjects (24.1%) in the placebo group.

The most frequently reported Grade 3 or 4 treatment-emergent AEs were increased ALT (5 subjects in the placebo group) and hepatitis (2 subjects in the TDF group and 6 subjects in the placebo group).

A higher proportion of patients experienced grade 3 or 4 treatment-emergent AEs in the placebo group (24.1% vs 9.6%) is explained by the fact that more patients receiving placebo experienced severe hepatic events. Reported grade 3 or 4 AEs in TDF group consisted in Tooth Disorder (n=1), Gingivitis (n=1), Hepatitis (n=2), Hand Fracture (n=1), Muscle Spasms (n=1) and syncope (n=1).

No death was reported during the randomized treatment period.

Renal Adverse Events

No renal adverse events have been reported in the TDF group.

Hepatic Adverse Events

Thirteen subjects had “Hepatobiliary Disorders” SOC events (3 subjects in the TDF group and 10 subjects in the placebo group). Hepatitis was reported in 3 TDF-treated subjects and 7 placebo-treated subjects, hepatomegaly in 2 placebo treated subjects, and hypertransaminasemia was reported in 1 placebo-treated subject. In addition, 30 subjects including 13 subjects in the TDF group and 17 subjects in the placebo group had “Investigations” SOC results related to liver function reported as an AE. Of those, 15 subjects had increased ALT reported as an AE (3 subjects in the TDF group and 12 subjects in the placebo group).

Fourteen subjects had hepatic flares (including ALT increased, hepatitis, and transaminases increased) reported as a Grade 3 or 4 AE (2 subjects in the TDF group vs 12 subjects in the placebo group). An additional subject in the TDF group had Grade 2 ALT increased reported as an AE; however, this subject’s ALT values did not meet the Grade 3 or 4 criterion for a hepatic flare. There were no ALT flares reported as Grade 4 AEs in the TDF group, whereas there were 8 subjects with ALT flares reported as Grade 4 AEs in the placebo group.

Bone Adverse Events

One subject receiving TDF had a hand fracture. The subject had a Grade 3 fracture of the left hand forefinger sustained in an altercation on Day 406 that was considered serious, but not related to study drug. The event resolved by Day 448. The subject remained in the study with no interruptions to study drug administration.

Other potentially bone-related AEs included exostosis in 1 subject (TDF), bone pain in 2 subjects (placebo), and jaw pain in 1 subject (TDF).

Laboratory findings

A lower proportion of subjects experienced treatment-emergent Grade 3-4 laboratories abnormalities in the TDF group (26.9%) compared to the placebo group (50%).

A higher proportion of subjects in the TDF group compared to the placebo group experienced grade 3 or 4 increased serum amylase (2 subjects vs 1 subject), serum lipase (3 subjects vs 1 subject), and increased creatine kinase (1 subject vs 0 subject). Of note no pancreatitis considered as related to TDF has been reported.

A lower proportion of subjects in the TDF group compared to the placebo group experienced grade 3 or 4 increases in ALT (6 subjects vs 22 subjects), increases in AST (3 subjects vs 9 subjects).

Bone-Specific Evaluations - Bone mineral density

Lumbar Spine Bone Mineral Density

Percentage Change from Baseline in Lumbar Spine BMD

Statistically significant differences in mean lumbar spine BMD percent change from baseline were observed at Week 24 and Week 48 between the placebo and TDF groups. At Week 72, subjects in the TDF group had a mean lumbar spine BMD increase from baseline of 4.95%, compared to 8.14% for subjects in the Placebo group as shown in the table 17 below.

Table 18. GS-US-174-0115: Percent Change from Study Baseline in Lumbar Spine Bone Mineral Density (g/cm^2) by Study Week (Safety Analysis Set).

	TDF 12-14 Years[a] (N=10)	TDF 15-< 18 Years[a] (N=42)	PLB 12-14 Years[a] (N=13)	PLB 15-< 18 Years[a] (N=41)	Total TDF (N=52)	Total PLB (N=54)	p-value[d]
Spine BMD (g/cm^2) at Baseline[b,c]							
N	10	42	12	41	52	53	
Mean (SD)	0.81 (0.084)	1.05 (0.139)	0.89 (0.132)	1.04 (0.155)	1.00 (0.160)	1.01 (0.162)	
Median	0.83	1.07	0.90	1.03	1.02	1.00	
Q1, Q3	0.74, 0.86	0.95, 1.14	0.83, 0.97	0.89, 1.17	0.89, 1.11	0.88, 1.15	
Min, Max	0.70, 0.96	0.70, 1.27	0.59, 1.08	0.78, 1.37	0.70, 1.27	0.59, 1.37	
Percent Change in Spine BMD (g/cm^2) at Week 72							
N	8	39	12	36	47	48	
Mean (SD)	11.81 (4.015)	3.54 (4.612)	14.06 (10.060)	6.17 (6.164)	4.95 (5.467)	8.14 (7.993)	0.053
Median	12.08	3.52	16.75	4.95	4.39	6.46	
Q1, Q3	11.63, 13.50	0.44, 6.30	4.72, 22.93	1.95, 10.07	0.87, 9.46	2.41, 12.23	
Min, Max	3.05, 17.03	-5.93, 15.46	-2.67, 26.92	-4.69, 21.73	-5.93, 17.03	-4.69, 26.92	

Lumbar Spine BMD Z-Score

To further assess any effect of treatment on lumbar spine BMD, Z-scores were calculated. 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, race, and/or gender. A positive Z-score indicates that the subject's recorded value is higher than typical for their age, race, and/or gender. A negative change in Z-score indicates that a subject is falling behind his age and gender matched peers.

The mean change in lumbar spine BMD Z-score from baseline to Week 72 in the TDF group was -0.05. The mean change in lumbar spine BMD Z-score in the placebo group was 0.07.

Table 19. GS-US-174-0115: Z-Scores for Lumbar Spine Bone Mineral Density Change from Study Baseline by Study Week (Safety Analysis Set).

	TDF 12-14 Years[a] (N=10)	TDF 15-< 18 Years[a] (N=42)	PLB 12-14 Years[a] (N=13)	PLB 15-< 18 Years[a] (N=41)	Total TDF (N=52)	Total PLB (N=54)
Spine Total BMD Z-Score at Baseline[b,c]						
N	10	42	12	41	52	53
Mean (SD)	-0.78 (0.530)	-0.34 (0.793)	-0.05 (0.775)	-0.35 (0.820)	-0.43 (0.764)	-0.28 (0.813)
Median	-0.97	-0.25	0.10	-0.28	-0.50	-0.17
Q1, Q3	-1.15, -0.51	-0.90, 0.33	-0.65, 0.51	-1.01, 0.31	-1.04, 0.27	-0.92, 0.34
Min, Max	-1.39, 0.14	-2.43, 0.83	-1.69, 0.95	-2.18, 1.21	-2.43, 0.83	-2.18, 1.21
Change in Spine Total BMD Z-Score at Week 72						
N	8	39	12	36	47	48
Mean (SD)	-0.03 (0.314)	-0.05 (0.313)	0.09 (0.506)	0.07 (0.332)	-0.05 (0.310)	0.07 (0.377)
Median	-0.08	-0.05	0.17	0.05	-0.05	0.06
Q1, Q3	-0.17, 0.24	-0.28, 0.22	-0.22, 0.51	-0.16, 0.26	-0.23, 0.22	-0.17, 0.34
Min, Max	-0.57, 0.38	-0.78, 0.60	-0.80, 0.78	-0.47, 1.17	-0.78, 0.60	-0.80, 1.17

Whole Body Bone Mineral Density

Percentage Change from Baseline in Whole Body BMD

Statistically significant differences in whole body BMD percent change from baseline were observed at Weeks 24, 48, and 72 between the Placebo and TDF groups. At Week 72, subjects in the TDF group had a mean whole body BMD increase from baseline of 2.84%, compared to 5.37% for subjects in the placebo group.

Table 20. GS-US-174-0115: Percent Change from Study Baseline in Whole Body Bone Mineral Density (g/cm^2) by Study Week (Safety Analysis Set).

	TDF 12-14 Years[a] (N=10)	TDF 15-< 18 Years[a] (N=42)	PLB 12-14 Years[a] (N=13)	PLB 15-< 18 Years[a] (N=41)	Total TDF (N=52)	Total PLB (N=54)	p-value[d]
Whole Body BMD (g/cm^2) at Baseline[b,c]							
N	9	42	13	41	51	54	
Mean (SD)	0.95 (0.044)	1.12 (0.102)	1.00 (0.076)	1.09 (0.091)	1.09 (0.115)	1.07 (0.095)	
Median	0.96	1.10	0.99	1.08	1.09	1.05	
Q1, Q3	0.91, 0.98	1.07, 1.15	0.96, 1.04	1.04, 1.14	1.02, 1.14	1.01, 1.13	
Min, Max	0.88, 1.01	0.89, 1.47	0.87, 1.16	0.87, 1.29	0.88, 1.47	0.87, 1.29	
Percent Change in Whole Body BMD (g/cm^2) at Week 72							
N	6	38	13	36	44	49	
Mean (SD)	7.91 (3.740)	2.04 (2.679)	8.40 (4.464)	4.27 (3.682)	2.84 (3.456)	5.37 (4.273)	0.013
Median	7.47	2.25	7.11	3.71	2.76	4.86	
Q1, Q3	4.89, 9.69	0.04, 3.76	4.97, 11.23	2.05, 6.00	0.37, 4.76	2.31, 7.11	
Min, Max	3.90, 14.01	-3.00, 7.41	3.33, 17.47	-3.02, 15.27	-3.00, 14.01	-3.02, 17.47	

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

Whole Body BMD Z-Score

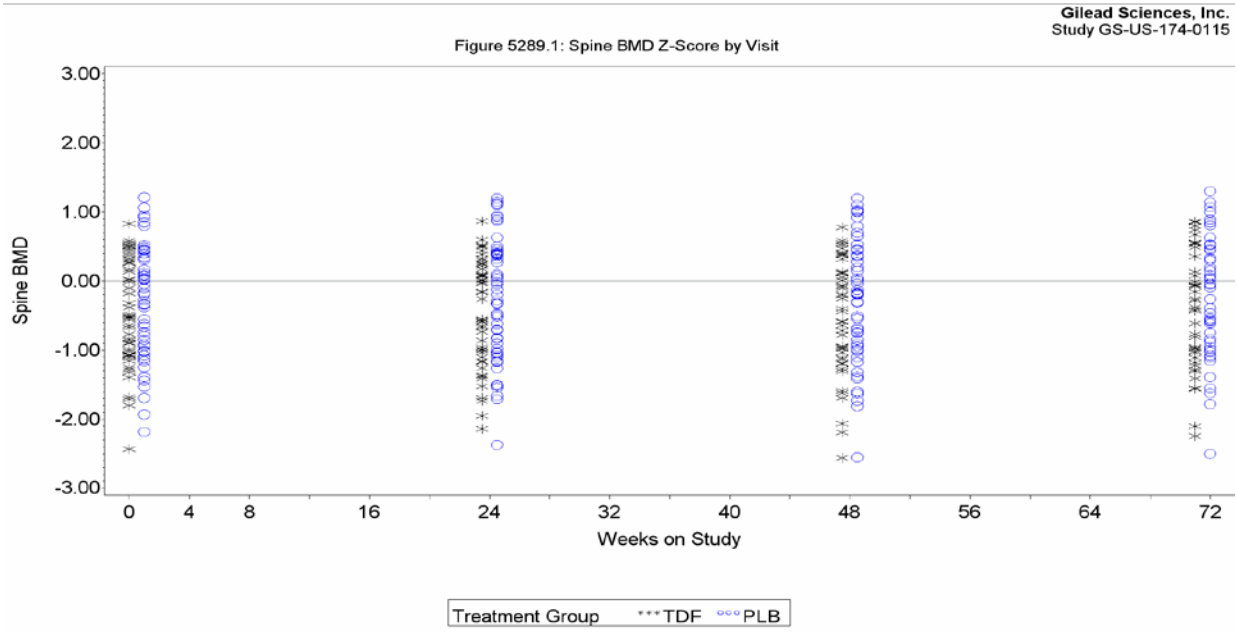
The mean change in whole body BMD Z-score from baseline to Week 72 in the TDF group was -0.15 and in the Placebo group was 0.06. According to the MAH, these small aggregate differences were unlikely to be clinically meaningful.

Further analyses provided by the MAH on BMD Z-scores following RSI

In general, a Z-score of less than or equal to -2 is considered by the ISCD to be an indication of low BMD. For purposes of data analyses, however, a conservative cut-off of -1.5 was used to identify the subjects with the lowest Z-scores to compare TDF data to placebo (PLB).

Figure 3 shows the distribution of individual subjects' lumbar spine BMD Z-scores.

Figure 3. GS-US-174-0115: Distribution of Lumbar Spine BMD Z-Scores at Baseline and Weeks 24, 48, 72



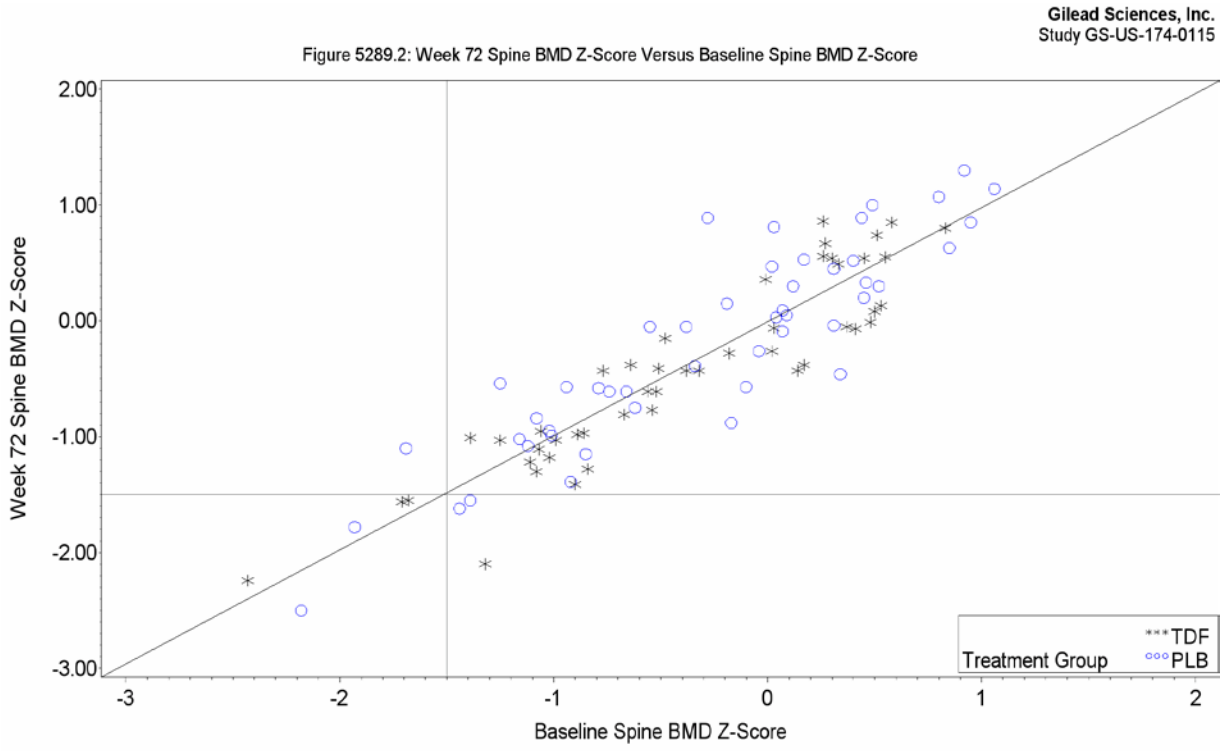
Study week is windowed week relative to study baseline.

Data Extracted: CRF data: 13MAY2011
Source: ...\Version1\intext\f-dexa-z.sas v9.2 Output file: f-bmdzsp.out 09APR2012:22:53

At baseline and over 72 weeks, there was considerable overlap of lumbar spine BMD Z-scores between the TDF and PLB groups. Of note, at baseline the majority of subjects had lumbar spine Z-scores that were below zero (horizontal line) and remained so throughout the 72-week study period. At baseline, the mean (standard deviation [SD]) spine BMD Z-score was lower in the TDF group (-0.43 [0.764]) than the PLB group (-0.28 [0.813]). At Week 72, mean (SD) change from baseline in Z-scores were -0.05 (0.310) and 0.07 (0.377) for the TDF and PLB groups, respectively.

Figure 2 shows individual lumbar spine BMD Z-scores at baseline and Week 72. In the figure, dissecting lines have been included to indicate a Z-score cut of -1.5 at baseline (vertical line), and a Z-score cut of -1.5 at Week 72 (horizontal line). These indicate individuals with lower BMD scores. A diagonal line of unity representing no change in BMD Z-scores has also been included.

Figure 4. GU-US-174-0115: Week 72 vs Baseline Spine BMD Z-Scores



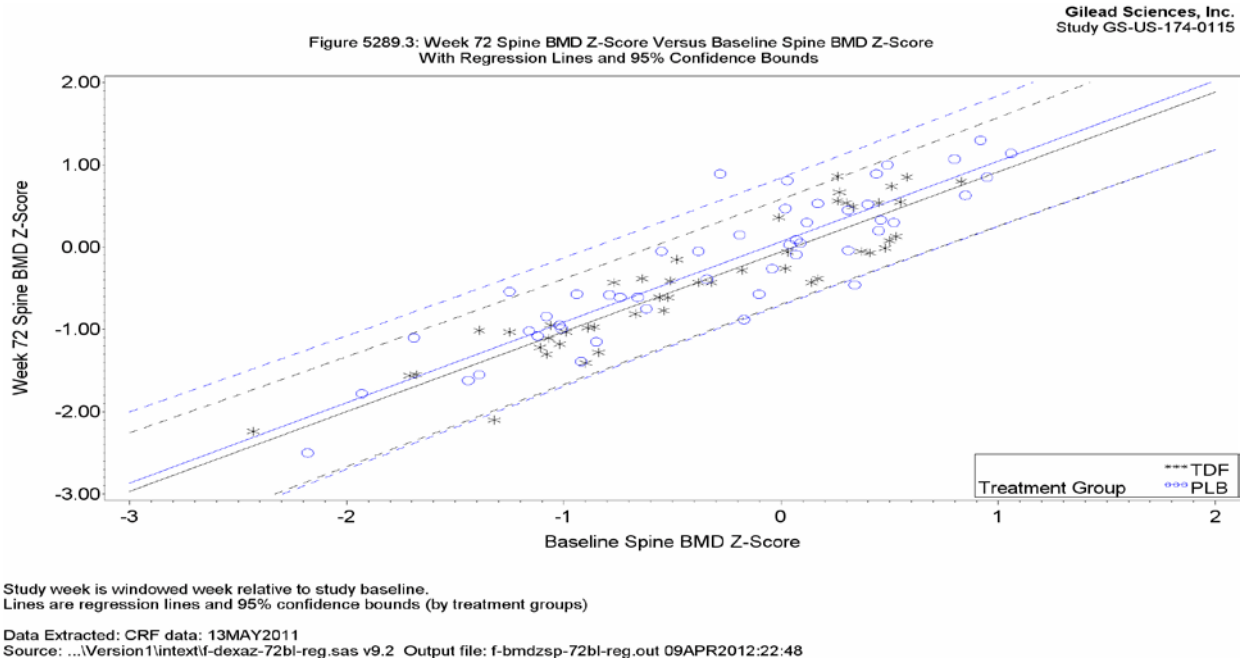
Study week is windowed week relative to study baseline.

Data Extracted: CRF data: 13MAY2011
Source: ...\Version1\intext\f-dexaz-72bl.sas v9.2 Output file: f-bmdzsp-72bl.out 09APR2012:22:54

Overall, the distribution of individual Z-scores is similar between TDF and PLB subjects with the majority of subjects having Z-scores above -1.5 at Week 72. There were a small number of subjects (2 PLB and 3 TDF) who had Z-scores ≤ −1.5 at both baseline and Week 72, and a small number of subjects (2 PLB and 1 TDF) who had baseline Z-scores above -1.5 and who then shifted to a Z-score ≤ -1.5 at Week 72. In summary, at Week 72 there were equal numbers of subjects in each treatment group (4 PLB and 4 TDF) who had Z-scores ≤ −1.5.

To illustrate the changes in the 2 groups, regression lines for both treatment groups, TDF and PLB (dotted lines representing 95% confidence intervals [CIs]) are provided (Figure 3). The regression lines for TDF and PLB are very similar, further indicating a similar trend of Z-score change from baseline to Week 72 in both treatment groups.

Figure 5. GU-US-174-0115: Baseline vs Week 72 Spine BMD Z-Scores



Finally, analysis on the change in Z-score at Week 72 as a function of initial (baseline) Z-score shows again considerable overlap observed in Z-score changes at Week 72 in TDF and PLB subjects vs baseline.

It is to be noted as a particular limitation that the BMD measures were not made according to height and weight (see list of outstanding issues).

Discontinuation due to adverse events

One subject was withdrawn from the study due to an AE (Grade 4 syncope that was not considered to be related to the study drug) in the TDF group.

1.5.1. Discussion on clinical safety

To date, the safety profile of TDF in children and adolescents has been characterized in five clinical studies conducted in patients with HIV. Three have been completed (GS-02-983, GS-01-926, and GS-01-927) and 2 additional studies are ongoing (Study GS-US-104-0321 and Study GS-US-104-0352). Regarding the same population studied (i.e. adolescents), the application in HIV infected adolescents was withdrawn in 2010 due to major objections from the CHMP on safety grounds (bone toxicity) and inadequate efficacy demonstration in GS-US-104-321 study. Study GS-US-104-0352, aimed to demonstrate the efficacy, safety and tolerability of TDF in HIV infected children is being assessed in a parallel procedure.

The main safety concerns of TDF in adult population are related to renal toxicity and bone toxicity.

Regarding study GS-US-174-0115:

- No renal adverse events have been reported in the TDF group. However, results from studies with tenofovir in HIV children, show that renal events, especially tubulopathies present a late onset (no event occurred before week 48). Thus, long term exposure data are required to better evaluate renal toxicity.

- No patient met the primary safety endpoint (ie decrease of at least 6% in lumbar spine BMD). However, a 6% decrease when an increase is expected, since bone mass is known to accumulate rapidly during childhood, does not seem to be an appropriate threshold.

  At week 72, 8/39 (21%) patients aged 15-18 years experienced a decrease of BMD in the TDF group compared to 5/36 (14%) in the placebo group, including 3/39 (7.6%) subjects in the TDF group (vs 2/36 (5.6%) in the placebo group) with a decrease of > 4% in spine BMD.

  The results at week 72 showed a lower increase of total mean lumbar spine BMD and total BMD in the TDF group compared to the placebo group. 25% of the patients in the TDF 15-18 years group experienced a -0.28 lumbar spine BMD Z-score and a -0.41 whole body BMD Z-score decrease, including 5/38 (13%) patients with respectively a -0.97, -0.81, -0.70, -0.69, -0.65.

  The above results raised concerns. In response the MAH has provided further analyses to address this issue. The following conclusions were derived:

  Small decreases in median BMD Z-scores have been observed following treatment with TDF. Equal numbers of subjects in each treatment group (4 PLB and 4 TDF) had spine BMD Z-scores ≤ −1.5 at Week 72

  Minimal differences between TDF or comparator groups were seen in changes from baseline in spine BMD Z-scores. Small decreases in total body BMD Z-score were observed for subjects who received TDF compared to subjects who received placebo in Study GS-US-174-0115.

  Interpretation of the long-term data available in paediatric subjects is restricted by the small sample size and the lack of control group beyond 72 weeks of treatment (data beyond 72 weeks of treatment in Study GS-US-174-0115 are not available).

  The decreases in total body BMD Z-scores observed following the initiation of TDF do not appear to be associated with an increased fracture rate (1 pathological fracture/103 patients treated with TDF). Low BMD per se is not a unique marker in identifying clinical concerns/consequences. The long-term clinical relevance of these observations is unknown, and no signal of BMD alteration justifying treatment withdrawal can be proposed. Decisions regarding (dis)continuation of treatment with TDF in paediatric patients should be made by the treating physician, taking into account the benefits and risks for the individual patient.

  In adolescent subjects with chronic HBV infection, there is insufficient evidence for reversibility or lack of reversibility of renal events (eg. hypophosphatemia) and reductions in BMD when TDF is withdrawn.

  The association of lower levels of BMI and lower levels of vitamin D at baseline by univariate analysis is suggestive of poor nutritional status being a potential risk factor for lower BMD. In a multivariate analysis, baseline spine BMD Z-score was found to be the only statistically significant predictor of spine BMD Z-scores ≤ -1.5 at Week 72; study treatment was not a statistically significant predictor.

  In view of the limited data, no specific recommendations can be made at this time regarding vitamin D supplementation for patients receiving TDF.

  Overall due to the lack of long-term safety data and difficulties in assessing the clinical relevance of BMD decrease in children, bone toxicity related to TDF remains a particular concern for paediatric use.

1.5.2. Conclusions on the clinical safety

The safety profile characterised by bone toxicity makes tenofovir an “a priori” non optimal candidate for the paediatric population. An extension of the Marketing Authorisation for Viread (EMEA/H/C/00419/X/105/G in the treatment of HIV infection in children aged 2 to < 12 years old is under parallel evaluation and major objections on renal and bone toxicity were also raised. A SAG has been requested by the CHMP in order to provide a position on the risk of bone and renal toxicity of Viread in the context of its use in both HIV and HBV infected paediatric and adult patients. PDCO members as experts provided input to the scientific discussion at the SAG.

The SAG meeting was held the 3 May 2012. The discussion focused on the safety burden of tenofovir in the paediatric population and gave important information on the safety monitoring of the use of tenofovir in paediatric patients. Overall, SAG members highlighted the lack of correlation between DXA measurements and bone events and the difficulties to provide specific recommendation as regards supplementation.

As regards renal toxicity in paediatric patients, the SAG members did not foresee any specific reason for the renal toxicity in adults being different in children and adolescents. Only the phosphate loss resulting from the tubulopathy could be of differential impact given that paediatric patients are in active process of bone modelling. The current recommendation of renal toxicity monitoring in adults are judged conservative enough and could overall be aligned for paediatric patients, especially having in mind that this paediatric population is expected to be closely managed in clinical practice. As regards the need for treatment interruption in paediatric patients, it was considered that instead of stating a specific threshold for withdrawal, as in adults, it would be more appropriate to give a general message that significant laboratory abnormality suggestive of renal toxicity during treatment should trigger specialised consultation.

As regards bone toxicity, the SAG members have considered that it is currently questioned whether the observed toxicity of the drug could be of any long term consequence. Therefore the discussion on the benefit/risk could then amount balancing theoretical risks versus established benefit (virological suppression). When considering the need for specific monitoring, the SAG members refute the value of any BMD monitoring given the lack of established correlation with clinical event, all the more that it represents a burden for paediatric patients and raises practical and technical issues. As regards the need for phosphate and Vitamin D supplementation, the SAG members have considered that there was no apparent reason to deviate from the general attitude which prevails in clinical practice for a population in active modelling process (i.e. supplementation is considered in case of significant depletion).

The CHMP has agreed with the SAG views. The SmPC was revised to reflect the uncertainties associated with the long term effects of bone and renal toxicity. Since, the reversibility of renal toxicity cannot be fully ascertained a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment and to decide on the appropriate monitoring during treatment (including decision for treatment withdrawal) and to consider the need for supplementation.

To address bone safety concerns the applicant proposed a BMD monitoring at baseline and during therapy in at risk patients. The CHMP did not agree to impose a BMD given the lack of established correlation with clinical event and given the burden it represents for paediatric patients as well acknowledging practical and technical issues.

The MAH was requested to perform additional studies. A separate post-authorisation safety study with a representative sample of HIV- and HBV infected children to help establish evidence-based strategies

for management of TDF-associated renal and bone toxicity (protocol synopsis to be submitted by 31 December 2012) and a Drug Utilisation Study in HIV-1 and HBV-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures (draft synopsis to be submitted by 25 October 2012). In addition, the CHMP considered that the MAH should submit the following safety data: a cumulative review of renal tubulopathy reports in HIV-1 and HBV infected adult patients by 31 December 2012.

Details of these studies are detailed in the RMP.

1.6. Pharmacovigilance

Risk management plan

The MAH submitted an updated Risk Management Plan, which included a risk minimisation plan. The RMP addressed the safety concerns identified with tenofovir.

Risk minimisation plan

The MAH proposed an educational brochure for adolescents to address renal and bone toxicity and to include dosing recommendations on this population, in addition to the educational brochure for adults. The CHMP recognises the need of this educational material and formalised the ongoing activities in annex II of the product information. The key messages are reflected in Annex II. The CHMP requested the review of the HBV educational brochure for adolescents aged 12 to <18 years.

Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
Important Identified Risks		
Renal Toxicity	Routine pharmacovigilance activities including a renal tubulopathy targeted follow-up questionnaire for postmarketing reports Observational study (GS-US-104-0353) Cumulative review of reversibility of renal tubulopathy in HIV-1 and HBV infected adult patients Monitoring of renal parameters in HIV-1 and HBV infected adult and pediatric subjects in clinical studies who discontinue tenofovir DF due to renal tubulopathy Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in	<u>Routine Risk Minimization Activities</u> Current approved Viread SmPC text is as follows: Statements in Section 4.2 of the Viread SmPC: *Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with moderate and severe renal impairment (creatinine clearance <50 ml/min) and long term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Dose interval adjustments are recommended for patients with creatinine clearance <50 ml/min.* *Mild renal impairment (creatinine clearance 50–80 ml/min): Limited data from clinical studies support once daily dosing of tenofovir disoproxil fumarate in patients with mild renal impairment.* *Moderate renal impairment (creatinine clearance 30–49 ml/min): Administration of 245 mg tenofovir disoproxil (as fumarate) every 48 hours is recommended based on modeling of single-dose pharmacokinetic data in HIV negative and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring haemodialysis, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.* *Severe renal impairment (creatinine clearance <30 ml/min) and haemodialysis patients: Adequate dose adjustments cannot be applied due to lack of alternative tablet strengths, therefore use in this group of patients is not recommended. If no alternative treatment is available, prolonged dose intervals may be used as follows:* *Severe renal impairment: 245 mg tenofovir disoproxil (as fumarate) may be administered every 72–96 hours (dosing twice a week).*

	HIV-1 and HBV infected pediatric patients	*Haemodialysis patients: 245 mg tenofovir disoproxil (as fumarate) may be administered every 7 days following completion of a haemodialysis session*.* *These dose adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Therefore clinical response to treatment and renal function should be closely monitored.* ** Generally, once weekly dosing assuming three haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis.* *No dosing recommendations can be given for non-haemodialysis patients with creatinine clearance < 10 ml/min.* Warnings in Section 4.4 of the Viread SmPC: *Co-administration of other medicinal products: Viread should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate.* *Renal function: Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance <80 ml/min).* *It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.* *Patients with creatinine clearance <50 ml/min, including haemodialysis patients: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function. Therefore, tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance <30 ml/min) and in patients who require haemodialysis use of tenofovir is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored.* *If serum phosphate is <1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to <50 ml/min in any patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with tenofovir disoproxil fumarate in patients with creatinine clearance decreased to <50 ml/min or decreases in serum phosphate to <1.0 mg/dl (0.32 mmol/l).* *Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.* *Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transporter proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4 might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.* *Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (see section 4.4).* *c. Description of selected adverse reactions* *HIV-1 and hepatitis B:* *Renal impairment: As Viread may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8a).* *e. Other special population(s)*

		Patients with renal impairment: Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Viread (see sections 4.2, 4.4 and 5.2). Adverse reactions in Section 4.8b of the Viread SmPC: *Renal and urinary disorders:* *Uncommon: increased creatinine* *Rare: acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus* *Metabolism and nutrition disorders:* *Very common: hypophosphataemia** *Uncommon: hypokalaemia** *Musculoskeletal and connective tissue disorders:* *Uncommon: rhabdomyolysis*, muscular weakness** *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)*, myopathy** ** This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* Update of labeling as appropriate Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows (based on proposed updates to the Viread 245 mg SmPC): Statement in Section 4.2 of the Viread SmPC: *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.4).* Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Renal effects* *Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to <12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).* *Renal monitoring* *Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment and monitored during treatment as in adults (see above).* *Renal management* *If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil fumarate treatment.* *Co-administration and risk of renal toxicity* *The same recommendations apply as in adults (see above).* *Renal impairment* *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.* Statement in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1* *Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy.* Statements in Section 5.1 of the Viread SmPC *Paediatric population:* *HIV-1:* *In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure was 104 weeks).*

		Additional Risk Minimization Activities Educational initiatives ('HIV and the Kidney' educational program, renal educational program for HBV, educational brochures distributed to prescribers). Update of educational program as appropriate Following the approval of the pediatric applications, renal risk minimization activities will be updated to include information on HIV-1 infected children and adolescents and HBV infected adolescents. Educational brochures specific to the use of Viread in these pediatric populations will be distributed to pediatric prescribers.
Bone events due to proximal renal tubulopathy/loss of bone mineral density	Routine pharmacovigilance activities including monitoring and review in PSURs. Clinical studies (GS-99-903, GS-US-236-0103 GS-US-174-0102, GS-US-174-0103, GS-US-174-0115, GS-US-174-0121, GS-US-104-0321, GS-US-104-0352) Retrospective analyses of pediatric BMD Z-scores adjusted by height (GS-US-174-0115, GS-US-104-0321, GS-US-104-0352) Planned clinical study in HBV infected pediatric patients (GS-US-174-0144) Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients Planned cross-sectional study to assess BMD in HIV-1 infected patients of interest who include those over 50 years of age, particularly women, and who have been exposed to tenofovir DF for at least 3 years (GS-US-104-0423).	Routine Risk Minimization Activities Current approved Viread SmPC text is as follows: Statements in Section 4.4 of the Viread SmPC: *Bone effects: In HIV infected patients, in a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.* *Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.* *Paediatric population: Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).* Statements in Section 4.8 of the Viread SmPC *a. Summary of the safety profile* *HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (see section 4.4).* Adverse reactions in Section 4.8b of the Viread SmPC *Musculoskeletal and connective tissue disorders:* *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)*[1,2] [1] *This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* [2] *This adverse reaction was identified through post-marketing surveillance but not observed in randomized controlled clinical trials or the tenofovir disoproxil fumarate expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil fumarate in randomized clinical trials and the expanded access program (n = 7,319).* Statements in Section 5.1 of the Viread SmPC *Paediatric population:* *HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.* Update of labeling as appropriate Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows: Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population*

		There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation. *Bone effects:* *If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.* Statement in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1* *Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).* *Chronic hepatitis B* *Reductions in BMD have been observed in HBV-infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).* Statements in Section 5.1 of the Viread SmPC *In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks.* *Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.* *Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10^5 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks.* *No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. BMD Z-scores were not adjusted for height and weight. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo. The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.*
Post-treatment hepatic flares in HBV monoinfected	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Statement in Section 4.2 of the Viread SmPC: *If Viread is discontinued in patients with chronic hepatitis B with or without HIV co-infection, these patients should be closely monitored for evidence of exacerbation of*

and HIV/HBV coinfected patients		*hepatitis (see Section 4.4).* Warning in Section 4.4 of the Viread SmPC: *Flares after treatment discontinuation: Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.* *Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section 4.4).* *c. Description of selected adverse reactions* *Exacerbations of hepatitis after discontinuation of treatment: In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).* Update of labeling as appropriate.
Interaction with didanosine	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Warning in Section 4.4 of the Viread SmPC (interaction also described in Section 4.5): *Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40–60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Co- administration of Viread and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).* *c. Description of selected adverse reactions* *Interaction with didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.* Update of labeling as appropriate.
Pancreatitis	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Pancreatitis is listed in Section 4.8b of the Viread SmPC: *Gastrointestinal disorders:* *Uncommon: pancreatitis* There are also warning statements in Sections 4.4, 4.5 and 4.8 of the Viread SmPC regarding the risk of pancreatitis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lactic acidosis and severe hepatomegaly with steatosis	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Warning in Section 4.4 of the Viread SmPC: *Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. The preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues, is low for tenofovir disoproxil fumarate. However, as tenofovir is structurally related to nucleoside analogues, this risk cannot be excluded. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of*

		treatment. *Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.* *Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol).* *Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.* *Patients at increased risk should be followed closely.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate (see sections 4.4 and 4.8c).* *c. Description of selected adverse reactions* *Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (see section 4.4).* Lactic acidosis is listed in Section 4.8b of the Viread SmPC: *Metabolism and nutrition disorders:* *Rare: lactic acidosis* There are also warning statements in Section 4.4, 4.5 and 4.8 of the Viread SmPC regarding the risk of lactic acidosis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lipodystrophy	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Precautionary statements in Section 4.4 of the Viread SmPC: *Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.* *Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve HIV infected patients indicate that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate than with stavudine when administered with lamivudine and efavirenz.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate (see sections 4.4 and 4.8c).* *c. Description of selected adverse reactions* *Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).* *In a 144-week controlled clinical study in antiretroviral-naïve patients that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz, patients who received tenofovir disoproxil had a significantly lower incidence of lipodystrophy compared with patients who received stavudine. The tenofovir disoproxil fumarate arm also had significantly smaller mean increases in fasting triglycerides and total cholesterol than the comparator arm.* Update of labeling as appropriate.

Important Potential Risks		
Development of resistance during long-term exposure in HBV infected patients	Routine pharmacovigilance activities Clinical studies (GS-US-174-0102, GS-US-174-0103, GS-US-174-0121)	Routine Risk Minimization Activities Section 5.1 of the Viread SmPC states the following: *Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified. In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC_{50} values 1.5-fold that of wild-type virus.* *Clinical resistance: Four hundred and twenty-six HBeAg negative (GS-US-174-0102, n = 250) and HBeAg positive (GS-US-174-0103, n = 176) patients were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients initially randomised to the tenofovir disoproxil fumarate arm (i.e excluding patients who received double-blind adefovir dipivoxil and then switched to open-label tenofovir disoproxil fumarate) with HBV DNA > 400 copies/ml at week 48 (n = 39), week 96 (n = 24) and week 144 (n = 6) and week 192 (n = 5) on tenofovir disoproxil fumarate monotherapy, showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.* *In study GS-US-174-0108, 45 patients (including 9 patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline) received tenofovir disoproxil fumarate for up to 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.* Update of labeling as appropriate.
Important Missing Information		
Safety in children (including long-term safety)	Routine pharmacovigilance activities Clinical studies in HIV-1 infected children (GS-US-104-0321, GS-US-104-0352) Clinical study in HBV infected adolescents (GS-US-174-0115) Planned clinical study, including a PK substudy, in HBV infected children aged 2 to < 12 years (GS-US-174-0144) Planned PK bioavailability study of TDF oral granules in the fed state Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients	Routine Risk Minimization Activities Current approved Viread SmPC text is as follows: Statement in Section 4.2 of the Viread SmPC: *Paediatric population: Viread is not recommended for use in children The clinical data available in HIV-1 infected adolescents are inadequate to support the use of tenofovir disoproxil fumarate in this population and no data are currently available in younger children.* *No data are currently available in paediatric patients infected with chronic hepatitis B.* Statement in Section 4.4 of the Viread SmPC: *Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.* Statement in Section 4.8 of the Viread SmPC: *d. Paediatric population* *Assessment of adverse reactions is based on one randomised trial (study GS-US-104-0321) in 87 HIV-1 infected adolescent patients (aged 12 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with other antiretroviral agents for 48 weeks.* Statements in Section 5.1 of the Viread SmPC: *Paediatric population:* *HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate,*

		BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. *The efficacy and safety data derived from this study do not support the use of Viread in adolescents.* Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows (based on proposed updates to the Viread 245 mg SmPC): Statements in Section 4.2 of the Viread SmPC: *Paediatric population* *HIV-1: The safety and efficacy of tenofovir disoproxil fumarate in HIV-1 infected children under 2 years of age have not been established. No data are available.* *Chronic hepatitis B: The safety and efficacy of tenofovir disoproxil fumarate in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established. No data are available.* *Special populations* *Renal impairment: The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.4).* Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Renal effects* *Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to <12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).* *Renal monitoring* *Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment and monitored during treatment as in adults (see above).* *Renal management* *If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil fumarate treatment.* *Co-administration and risk of renal toxicity* *The same recommendations apply as in adults (see above).* *Renal impairment* *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.* *Bone effects:* *If bone abnormalities are detected or suspected in paediatric patients,, consultation with an endocrinologist and/or nephrologist should be obtained.* Statements in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1:* *Assessment of adverse reactions is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).* *Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).* *Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due*

		to adverse reactions consistent with proximal renal tubulopathy. *Chronic hepatitis B:* *Assessment of adverse reactions is based on one randomised study (study GS-US-174-0115) in 106 adolescent patients (12 to < 18 years of age) with chronic hepatitis B receiving treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks. The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).* *Reductions in BMD have been observed in HBV-infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).* Statements in Section 5.1 of the Viread SmPC *In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks.* *Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.* *In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure was 104 weeks).* *Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10^5 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks.* *No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo. BMD Z-scores were not adjusted for height and weight. The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.* The proposed Viread oral granules SmPC also contains statements indicating that limited clinical data are available at the 6.5 mg/kg dose of the oral granules and therefore close monitoring of efficacy and safety is needed, and that investigations are planned to further substantiate the dose in children from 2 years of age. Following the approval of the pediatric applications, renal risk minimization activities will be updated to include information on HIV-1 infected children and adolescents and HBV infected adolescents. Educational brochures specific to the use of Viread in these pediatric populations will be distributed to pediatric prescribers (see Renal Safety Concern).
Safety in pregnancy	Routine pharmacovigilance activities Epidemiological studies (Antiretroviral	<u>Routine Risk Minimization Activities</u> Statements in Section 4.6 of the Viread SmPC:

	Pregnancy Registry; Cross-sectional study to assess the risk of mitochondrial disease in children exposed to NRTIs in utero [MITOC group])	*Pregnancy* *A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of tenofovir disoproxil fumarate may be considered during pregnancy, if necessary.* Update of labeling as appropriate.
Safety in patients with renal impairment	Routine pharmacovigilance activities Clinical study in HBV infected patients including patients with mild to moderate renal impairment (GS-US-174-0121) Planned clinical study in HBV infected patients with moderate to severe renal impairment (GS-US-174-0127)	Routine Risk Minimization Activities See Renal Safety Concern. A Type II variation application for tenofovir DF 40 mg/g oral granules is planned to be submitted by Q4 2012 to enable adjustment of daily dose as well as dose interval of tenofovir DF in HIV-1 infected and HBV infected adult patients with moderate or severe renal impairment.
Safety in elderly patients	Routine pharmacovigilance activities	Routine Risk Minimization Activities Warning in Section 4.4 of the Viread SmPC (also in section 4.8e): *Elderly; Tenofovir disoproxil fumarate has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate.* Update of labeling as appropriate.
Safety in lactation	Routine pharmacovigilance activities	Routine Risk Minimization Activities Statements in Section 4.6 of the Viread SmPC: *Breast-feeding* *Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore Viread should not be used during breast-feeding.* *As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.* Update of labeling as appropriate.
Safety in black HBV infected patients	Routine pharmacovigilance activities	Routine Risk Minimization Activities Update of labeling as appropriate.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Conduct a separate post-authorisation safety study with a representative sample of HIV- and HBV infected children to help establish evidence-based strategies for management of TDF-associated renal and bone toxicity.	Submit the protocol synopsis by 31 December 2012. Interim study results: 31 December 2014 Final study results: 31 December 2016
To conduct a Drug Utilisation Study in HIV-1 and HBV-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures.	Submit draft synopsis by 25 October 2012 Feasibility assessment alongside a full draft protocol expected: by 28 February 2013. Interim study results: 31 December 2014 Final study results: 31 December 2017

The CHMP, having considered the data submitted, was of the opinion that the below additional risk minimisation activities are required for the management of the safety profile of the product:

Physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

1.7. Changes to the Product Information

The PI was updated accordingly and has been consolidated with parallel procedures X/105/G and II/119.

Section 4.1 "Therapeutic indication"

This section was revised and the indication was restricted to better delineate the population of children most in need for immediate treatment. The therapeutic indication was extended for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with: compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.

Section 4.2 "Posology and method of administration"

This section was updated to include dose recommendations for treatment of adolescents infected with HBV.

Section 4.4 "Special warnings and precautions for use"

Warnings on the management of renal and bone effects were revised.

This section was revised to inform on the uncertainties associated with the long term effects of bone and renal toxicity and to mention that the reversibility of renal toxicity cannot be fully ascertained. Therefore warnings were introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation.

Furthermore physicians are alerted that significant laboratory abnormality suggestive of renal toxicity during treatment should trigger specialised consultation.

Section 4.8 "Undesirable effects"

This section was updated to reflect safety data from study GS-US-174-0115.

Section 5.1 "Pharmacological properties"

This section was updated to reflect data from study GS-US-174-0115.

Annex IIB Conditions of the marketing authorisation

Annex II was updated to reflect key messages that should be included HIV and HBV renal educational brochures.

The PL was updated to reflect the above mentioned SmPC changes.

2. conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

In adults, tenofovir has become a standard of care (besides entecavir) for the treatment of chronic hepatitis B, due to its potency and high genetic barrier (no emerging resistance at 5 years). From the efficacy point of view, it is expected to show similar results in paediatric patients. In this pivotal study GS-US-174-0115 a striking superiority of TDF over placebo was demonstrated on the primary endpoint (proportion of patients with HBV DNA <400 copies/ml).

Uncertainty in the knowledge about the beneficial effects.

Beyond the sustained virologic suppression, the ultimate goal for treatment is to achieve HBs Ag seroconversion (translating a cure) or at least a stable HBeAg seroconversion. TDF showed greater potency over placebo not only on the primary endpoint but also on all secondary endpoints. However, this is not translated into a major differential in terms of HBeAg seroconversion rate, illustrating the need for a life long treatment for the vast majority of adolescents.

Risks

Unfavourable effects

The renal and bone toxicity are a source of particular concern for the long-term use of TDF. This is true for both adults and paediatric patients especially considering that they are in evolving modelling process.

Uncertainty in the knowledge about the unfavourable effects

The long-term effect of TDF on bone modelling and the potential reversibility of bone toxicity cannot be determined from the non clinical and clinical data available. However, it is acknowledged that given the lack of correlation between BMD and clinical events, it remains theoretical risk. Moreover, the reversibility of the renal toxicity cannot be fully ascertained.

Warnings were added to the SmPC to alert physicians on the uncertainties on the long term effect of bone and renal toxicity and the fact that reversibility of renal toxicity cannot be fully ascertained. A statement was introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation. Promoting multidisciplinary approach appears pragmatic based on the SAG input that management is to be tailored to the child and mostly refer to good clinical practice in paediatric.

Discussion on the benefit-risk balance

Overall based on the MAH's responses and SAG input the CHMP consider that Viread can be approved in adolescents according to the following indication:

Hepatitis B infection
Viread 245 mg film coated tablets are indicated for the treatment of chronic hepatitis B in adults with:

- *compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).*

- *decompensated liver disease (see sections 4.4, 4.8 and 5.1).*

Viread 245 mg film coated tablets are indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with:

- *compensated liver disease and evidence of immune active disease, i.e. active viral replication persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis. (see sections 4.4, 4.8 and 5.1).*

The SmPC was revised to include warnings to alert physicians on the uncertainties on the long term effect of bone and renal toxicity and the fact that reversibility of renal toxicity cannot be fully ascertained. A statement was introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation. Promoting multidisciplinary approach appears pragmatic based on the SAG input that management is to be tailored to the paediatric patient and mostly refer to good clinical practice in paediatric.

Further studies are included in the RMP that will help to better understand the safety in this population.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order extend the indication for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age. The annex II, Labelling and Package Leaflet are updated accordingly.

The requested variation proposed amendments to the Update of Summary of Product Characteristics, annex II, labelling and package leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Viread in adults and/or paediatric patients are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

The HIV and HBV renal educational brochures in adult should contain the following key messages:

- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks
- The importance of dose interval adjustment of Viread in adult patients with creatinine clearance of 30-49 ml/min
- That Viread is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min). If no alternative treatment is available, prolonged dose intervals may be used.
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule.
- That patients should have their baseline renal function assessed prior to initiating Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function should be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then consideration should be given to interrupting Viread therapy.
- Instructions on the use of the creatinine clearance slide ruler

The HIV and HBV paediatric educational brochure should contain the following key messages:

- That a multidisciplinary approach is recommended for the management of paediatric patients
- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread is not recommended for use in paediatric patients with renal impairment

- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule.
- That patients should have their baseline renal function assessed prior to initiating Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week. If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Viread treatment
- That Viread may cause a reduction in BMD and the effects of Viread associated changes in BMD on long term bone health and future fracture risk are currently unknown in paediatric patients
- That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/180/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.