28 February 2019
EMA/239040/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Viread

International non-proprietary name: tenofovir disoproxil

Procedure No. EMEA/H/C/000419/II/0191

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AASLD American Association for the Study of Liver Diseases
ADV adefovir
AE adverse event
ALT alanine aminotransferase
AST aspartate aminotransferase
AUC_{tau} area under the plasma/serum concentration versus time curve over the dosing interval
BMD bone mineral density
CHB chronic hepatitis B
C_{max} maximum observed plasma/serum concentration of drug
EC50 drug concentration that provides half-maximal response
eGFR estimated glomerular filtration rate
EMEA European Medicines Evaluation Agency
ETV entecavir
EU European Union
FDA Food and Drug Administration
GCP Good Clinical Practice
HBeAg hepatitis B e antigen
HBsAg hepatitis B surface antigen
HBV hepatitis B virus
HCC hepatocellular carcinoma
HIV(-1) human immunodeficiency virus (type 1)
ICH International Council for Harmonisation (of Technical Requirements of Pharmaceuticals for Human Use)
LAM lamivudine
LLOQ lower limit of quantitation
MedDRA Medical Dictionary for Regulatory Activities
NDA new drug application
PIP paediatric investigational plan
PK pharmacokinetic(s)
PMR post-marketing request
pol/RT polymerase/reverse transcriptase
SAE serious adverse event
TDF tenofovir disoproxil fumarate
TmP/GFR ratio of renal tubular reabsorption of phosphate/eGFR
SD standard deviation
TFV tenofovir
ULN upper limit of normal
US United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 29 June 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication based on results from interim Week 48 clinical study report (CSR) for Study GS-US-174-0144; a 'Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection'. Following changes have been proposed:

1) Viread film coated tablets (123 mg; 163 mg; 204 mg): new chronic hepatitis B (CHB) indication to include treatment of CHB in paediatric patients aged 6 to < 12 years
2) Viread granules 33 mg/g: extension of the existing CHB indication for Viread granules to include treatment of CHB in paediatric patients aged 2 to < 12 years.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated for Viread 123 mg, 163 mg and 204 mg. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated for Viread 245 mg, whereas Sections 4.1, 4.2, 4.4, 5.1 and 5.2. have been updated for Viread granules 33 mg/g.

The Package Leaflet has been updated accordingly for all the products concerned.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0262/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0262/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

2. Scientific discussion

Recent reports estimate that 250 to 350 million individuals were living with HBV (i.e., hepatitis B surface antigen [HBsAg] positive) in 2010, representing a worldwide prevalence of 3.6%, with considerable geographic variability. In 2013, an estimated 686,000 deaths were due to HBV infection and associated complications, placing it among the top 20 causes of mortality worldwide.

Universal HBV vaccination and blood-donor screening have markedly reduced the rate of chronic infection including in Europe. However, a significant number of children are still infected each year. In Europe, prevalence remains elevated in some European areas (notably in Eastern and Southern Europe) and paediatricians are confronted with an increasing number of children adopted from higher prevalence countries.

Following acute HBV infection, the risk of developing chronic infection varies inversely with age. Chronic HBV infection occurs among about 90% of infants infected at birth, 25 to 50% of children infected at 1 to 5 years of age, and about 5 to 10% of persons infected as teens and adults.

Although most children with chronic HBV infection are asymptomatic and severe liver disease during childhood is rare, children are at risk for developing serious complications later in life, notably cirrhosis and HCC. In addition, HBV carriers can transmit the disease for many years.

Chronic HBV infection is characterised by different phases of infection:

1) the immune tolerant phase, with markedly elevated levels of HBV DNA, detectable HBsAg and HBV e antigen (HBeAg), and normal or low levels of alanine aminotransferase (ALT);

2) the immune active phase, characterised by elevated levels of HBV DNA with persistently elevated ALT, an indicator of ongoing liver damage;

3) the inactive HBsAg carrier phase, with undetectable or low levels of HBV DNA and the presence of anti-HBe antibodies; and

4) the reactivation phase, characterised by HBeAg seronegativity (and anti-HBe seropositivity) but with elevated HBV DNA levels and abnormal ALT.

Management of CHB in children and adolescents is evolving and optimal treatment is not well established. The current consensus is that no treatment is indicated for HBV-infected children in the immune tolerant or inactive HBsAg carrier phases (AASLD 2018, EASL 2017). However, treatment may be warranted for children in the immune active or reactivation phases to suppress viral replication and prevent complications and poor clinical outcomes, including cirrhosis, decompensated liver disease, and HCC. Indeed, studies in adults suggest that a prolonged period of time in the immune active phase is associated with an increased risk of cirrhosis and HCC.

As mentioned in the ESPGHAN clinical practice guidelines (Sokal et al. J of Heatology 2013), for all patients, the ideal end point of treatment is sustained HBsAg clearance, as it stops disease progression and reduces the risk of HCC, although it occurs in a minority of treated subjects. When HBsAg seroclearance is not achieved, sustained off-therapy suppression of viral replication (undetectable HBV DNA levels with a sensitive real time polymerase chain reaction assay), associated with durable anti-HBe seroconversion in originally HBeAg-positive patients, is a good end point, being associated with improved

prognosis, including decreased risk of HCC. In the absence of off-therapy viral suppression, undetectable HBV DNA under long-term antiviral therapy (maintained virological response) is the next desirable end point. Reduction of viremia levels leads to decreased liver inflammation and subsequent normalisation of ALT levels, reducing the risk of disease progression.

Currently, there are two main treatment options for CHB patients: treatment with oral antiviral agents or with IFNa, currently pegylated interferon alfa-2a. The rationale for a PegIFNa based approach is to induce long-term immunological control with a finite duration treatment (EASL 2017); however, pegIFN is associated with important safety and tolerability issues. Entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are potent inhibitors of HBV replication with a high barrier to resistance, and these 3 agents are recommended as preferred monotherapies for CHB in adults regardless of the severity of liver disease (EASL 2017).

Entecavir, TDF and TAF as well as peginterferon alfa-2a are currently approved for use in CHB-infected adolescents in Europe. In children, only entecavir is approved for paediatric patients (from 2 years of age) and Pegasys (from 3 years of age). A study is ongoing with TAF in paediatric patients <12 y.o.

Thus, TDF represents a new treatment option for children 2 to < 12 years old given its potent antiviral activity in CHB, including patients with resistance to other oral antivirals, such as LAM and ETV.

2.1. Introduction

Viread [tenofovir disoproxil fumarate (TDF)] is the oral prodrug of tenofovir (TFV), a nucleotide reverse transcriptase inhibitor. After absorption, TDF is rapidly converted to TFV, which is metabolised intracellularly to the active metabolite, TFV diphosphate, a potent and selective inhibitor of both hepatitis B virus (HBV) polymerase and human immunodeficiency virus type-1 (HIV-1) reverse transcriptase.

Viread is currently approved in the European Union for the treatment of chronic hepatitis B (CHB) in adult and paediatric patients $\geq$ 12 years old and for the treatment of HIV infection in adults and paediatric patients $\geq$ 2 years.

The MAH is now submitting a type II variation to extend the indication of CHB-infected paediatric patients from 2 to 12 years of age. This application is supported by the submission of the 48 weeks results of study GS-US-174-0144. This study is an ongoing Phase 3 study that is evaluating safety, antiviral activity and pharmacokinetics (PK) or TDF in paediatric subjects with CHB.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The environmental risk assessment for TDF has been updated to account for increased environmental exposure due to a paediatric line extension.

The MAH has already performed Phase I studies and Phase II studies (Tier A and Tier B) for the initial MAA in adult / children from 12 years in HBV. In section 5.3 of SmPC, it is noted that the active substance tenofovir disoproxil and its main transformation products are persistent in the environment.

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, no additional studies would be required for this extended indication.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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.

- Tabular overview of clinical studies

Protocol Number	Study Title	Third Country
GS-US-174-0144	*A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection*	India South Korea Taiwan USA

2.3.2. Pharmacokinetics

Bioanalytical Methods

The concentration of TFV in plasma samples was determined using fully validated high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) bioanalytical methods. All samples were analysed within the time frame supported by frozen stability storage data. The assays for TFV were performed using validated methods by QPS, Inc (Newark, DE, USA).

Bioanalytical method validation parameters are summarised in the table below:

Table 6. GS-US-174-0144: Bioanalytical Assay Validation for Tenofovir in Human Plasma

Parameter	TFV
Calibrated range (ng/mL)	5–3000
LLOQ (ng/mL)	5
Interassay precision range (%CV)	2.4% to 6.5%
Interassay accuracy range (%RE)	−4.7% to 2.0%
Stability in frozen matrix (days)	190 at −20°C; 340 at −70°C; 1426 at −80°C

CV = coefficient of variation; LLOQ = lower limit of quantitation; RE = relative error
Source: Appendix 16.1.10, QPS 42-0831 Amendment 6

Bioanalytic methods used in this study were the same than those used previously in adolescents' study.

The calibration standards and QCs of the in-study validation are considered acceptable by the CHMP.

With the exception of two samples (Subject 1021 Week 16 and Subject 1028 Week 4), all study samples were analysed within the established long-term stability of 1426 days at -80°C (please refer to QPS 42-0831 Amendment 6).

The reasons for re-analysis of the samples are also considered adequate by the CHMP (one sample was re-assayed due to no internal standard detected and one sample was re-assayed due to low internal standard).

Incurred sample reanalysis was not performed. This is considered suitable by the CHMP since the ISR was performed in the previous clinical trial.

Absorption, Distribution, Metabolism and Elimination

No new information is submitted since no significant difference in PK characteristics is expected in children as compared to adolescents or adults. This is endorsed by the CHMP.

Pharmacokinetics in paediatric patients (2 to <12 years old) with CHB

In order to characterise the PKs of TFV in paediatric CHB, the MAH developed a population-PK model using sparse and intensive sampling plasma concentrations collected from study GS-US-174-0144. The purpose of this modelling effort was to estimate the steady-state exposures of TFV in paediatric subjects who received TDF 8 mg/kg powder or tablet. The model-derived exposures were utilised to evaluate the PK and exposure-response (efficacy and safety) of TFV to support an expansion of the current indication to include paediatric subjects (2 to <12 years old) with CHB.

Population Pharmacokinetics for TFV

Population PK modelling was conducted to describe the plasma PK for TFV in paediatric CHB subjects receiving TDF, including identification of covariates influencing PK.

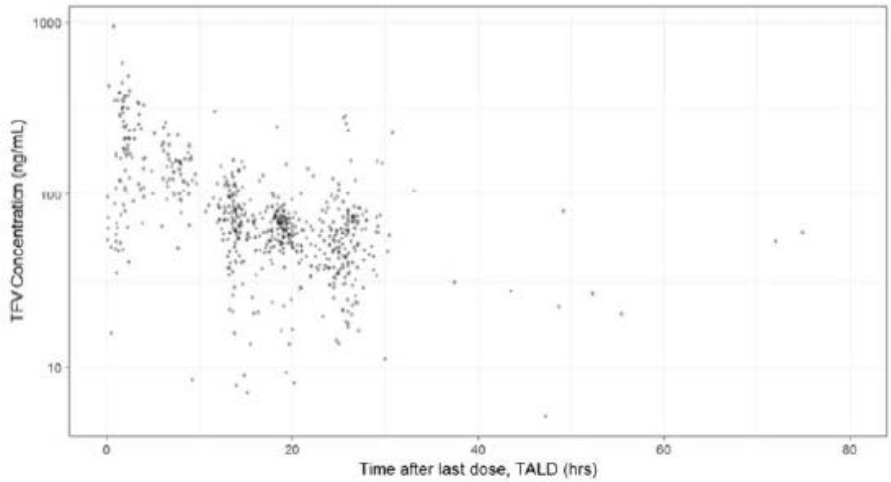
1 / Description of the analysed data set:
The model development dataset included data from subjects in study GS-US-74-0144. The dataset included 700 plasma samples from 60 subjects. A portion of the samples (60 samples) were BLQ, leaving 640 measurable TFV plasma concentrations. The remaining dataset had a total of 640 data points from 58 subjects, and was used for the analysis (Table below). Figure below shows the TFV plasma concentrations versus time profile for all subjects.

Table 2. Number of Observations and Subjects Included in the TFV Population PK Model Development

	Number of Measurable PK Observations	Number of Subjects
Population PK Model Development Dataset	640	58

The population PK model development dataset included pediatric CHB subjects who were randomized to receive TDF and had evaluable PK parameters in Study GS-US-174-0144.

Figure 1. TFV concentration versus time after dose profiles



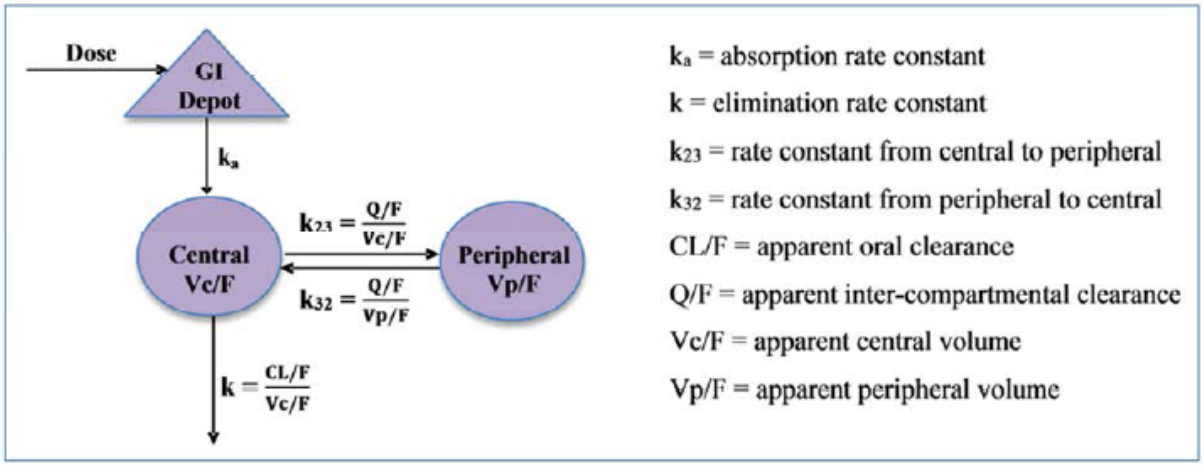
Each symbol represents an individual PK observation

2 / Model development:

- Structure Model:

Based on the previously established adult CHB PopPK model (Vemlidy PopPK model), a two-compartment model was considered the initial base model. The model was further characterised with first order absorption (Ka), and first order elimination from the central compartment and parameterised with apparent oral clearance (CL/F), apparent central volume (Vc/F), apparent inter-compartmental clearance (Q/F), apparent peripheral volume (Vp/F), and first-order absorption rate constant (Ka), with inter-individual variability (IIV) terms on apparent CL/F, Vc/F, and Vp/F. IOV was sequentially evaluated on each PK parameter (CL/F, Vc/F, Vp), and was included on CL/F based on statistically significant change in OFV ($p<0.05$). Overall, TFV plasma concentrations were best described by a 2-compartment model with first order absorption, linear elimination, inter-individual variability term on CL/F, Vc/F and Vp/F, IOV on CL/F, and a combined error model (Figure 2).

Figure 2. TFV PopPK model diagram



- Final Model:

The effects of baseline demographic covariates (age, WT, BMI, sex, race, ethnicity, geographical region), pathophysiological covariates (BCLCRSW), disease related covariates (HBVGT, HBeAg) and FAST and FORM on TFV CL/F, Vc/F and Vp/F were assessed graphically followed by linear regression (continuous covariates) and ANOVA testing (categorical covariates). Individual specific random effects (ETA) for CL/F, Vc/F, and Vp/F were plotted versus the covariates to identify potential relationships. Body weight, age, and HBeAg were found to show significant ($p<0.05$) trends with PK parameters in this screening step and were subsequently examined further using NONMEM for significance on CL/F, Vc/F, and Vp/F.
Testing of covariates in a step-wise forward addition and backward elimination methodology for TFV resulted in the addition of only WT as a statistically covariate ($p<0.001$) on CL/F. BCLCRSW ($p=0.8$) was retained as a covariate on CL/F in the final model, based on renal excretion being the predominant elimination pathway for TFV. FORM (powder versus tablet; $p=0.04$) was retained as a covariate on Ka to improve the characterisation of TFV absorption profile. The final model included covariates of WT and BCLCRSW on CL/F and FORM on Ka.

Final PopPK Model

$$CL_i = \theta_1 * \left(\frac{WT}{21}\right)^{\theta_6} * \left(\frac{BCLCRSW}{167}\right)^{\theta_8} * \exp(\eta_{CL,i} + \eta_{IOV,i} + \eta_{IOVForm,i})$$

$$Vc_i = \theta_2 * \exp(\eta_{Vc,i})$$

$$Q_i = \theta_3$$

$$Vp_i = \theta_4 * \exp(\eta_{Vp,i})$$

$$Ka_i = \theta_5 * \theta_7^{POW} \qquad POW=0 \text{ for tablet, } POW=1 \text{ for powder}$$

$$\eta_{IOVi} = \begin{cases} \eta_{IOVi,1}, if \ \ TIME \leq 1680 \ hrs \\ \eta_{IOVj,2}, if \ TIME \leq 3024 \ hrs \ \ TIME \ > 1680 \\ \eta_{IOVj,2}, if \ TIME \leq 11088 \ hrs \ \ TIME \ > 30234 \\ \eta_{IOVj,4}, if \ TIME \ > 11088 \end{cases}$$

$$\eta_{IOVForm,i} = \begin{cases} \eta_{IOVForm,i,1}, if \ \ TABLET \\ \eta_{IOVForm,i,2}, if \ POWDER \end{cases}$$

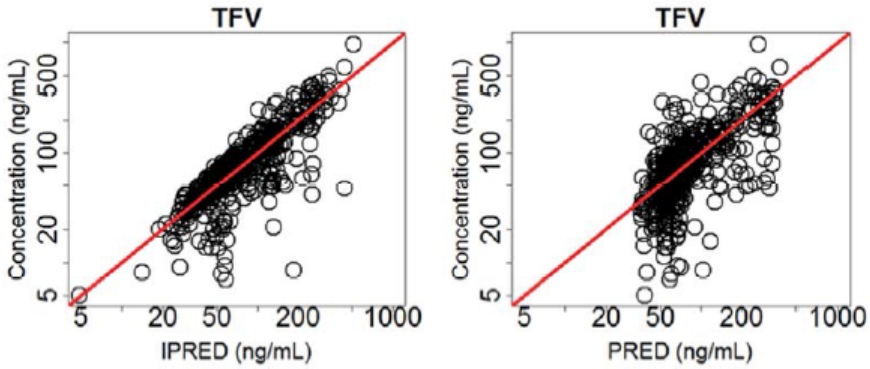
Table 4. Summary of final TFV model PK parameters

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	Inter-Individual Variability (%)
θ_1	Apparent oral clearance, CL/F (L/hr)		75.3	--	23.1
$\theta_1 * \left(\frac{BCLCRSW}{167}\right)^{\theta_8}$	Influence of BCLCRSW on CL/F (L/hr)	5th%ile of BCLCRSW	67.7	-10.0	
		95th%ile of BCLCRSW	84.1	11.7	
$\theta_1 * \left(\frac{WT}{21}\right)^{\theta_6}$	Influence of WT on CL/F (L/hr)	5th%ile of WT	59.1	-21.6	
		95th%ile of WT	101	33.6	
θ_2	Apparent central volume, Vc/F (L)		211	--	111
θ_3	Apparent Inter-compartment clearance, Q/F (L/hr)		105	--	--
θ_4	Apparent peripheral volume, V_p/F (L)		7290	--	133
θ_5	Absorption rate constant, K_a (hr^{-1})		0.313	--	--
$\theta_5 * \theta_7^{POW}$	Influence of FORM on K_a (hr^{-1})	POW=0 (Tablet)	0.313	--	
		POW=1 (Powder)	0.196	-37.5	
θ_6	Influence of WT on CL/F		0.483	--	--
θ_7	Influence of FORM on K_a (hr^{-1})		0.625	--	--
θ_8	Influence of BCLCRSW on CL/F		0.481	--	--
σ_1	Residual error (%)		32.2		

3 / Model evaluation / qualification:

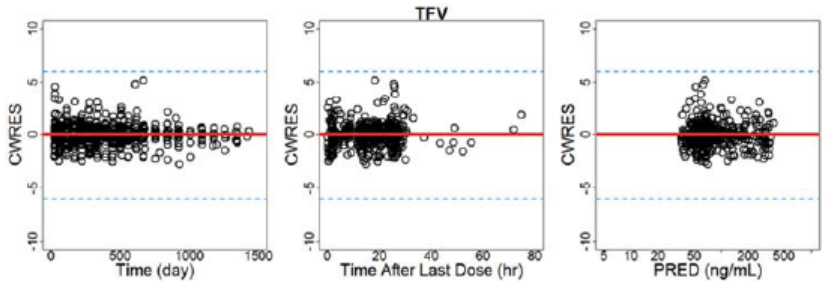
Goodness of fit (GOF):
The general goodness-of-fit plots of the final TFV PopPK model are shown in Figure 3 and Figure 4, where a good agreement between the predicted concentrations and the observed concentrations was observed. Furthermore, no apparent bias was observed in the residuals plots over time, time after previous dose, and across predicted concentrations. Distribution of inter-individual variability is shown in Figure 5.

Figure 3. Predicted versus observed TFV concentration diagnostics for the final TFV PopPK model



Observed versus Individual predicted (IPRED) plasma TFV concentrations (left) and observed versus population predicted (PRED) plasma TFV concentrations (right) for the final PopPK model. Points are individual data, red lines represent loess smooth lines, and the black lines are the unit diagonal.

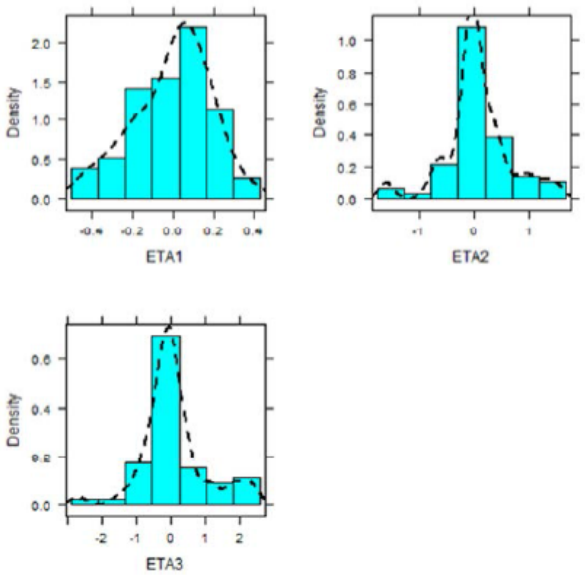
Figure 4. Residual diagnostic plots for the final TFV PopPK model



Conditional weighted residuals (CWRES) versus time after 1st dose (left), time after last dose (middle), and PRED (right). Points are individual data. Black solid lines represent the unit line at zero and red solid lines represent loess smooth lines. Blue dashed lines represent |CWRES| of 6.

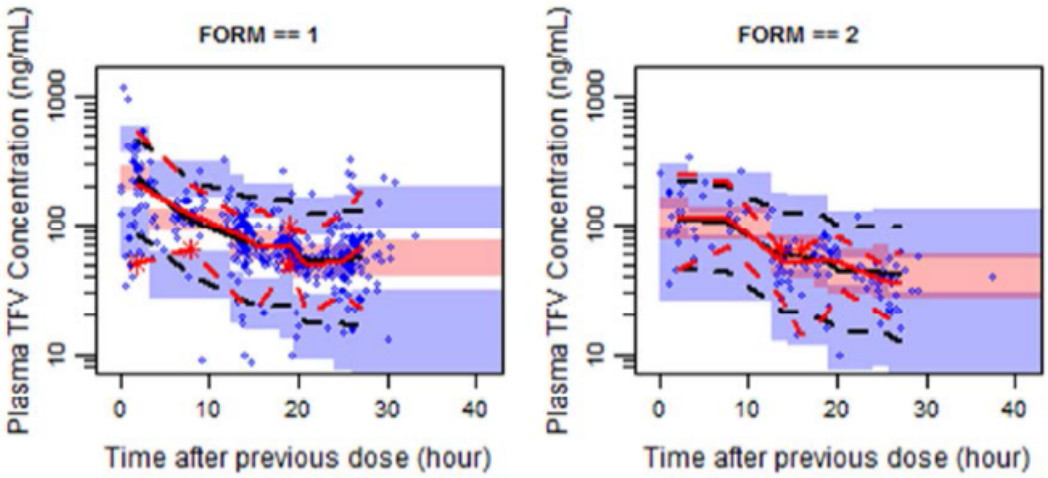
Visual Predictive Check (VPC):

Figure 5. **ETA histograms for the final TFV PopPK model**



ETA1: Individual ETA for CL/F; ETA2: Individual ETA for V_c/F; and ETA3: Individual ETA for V_p/F

Figure 10. **pcVPC of TFV plasma concentration-time profiles**



FORM=1 is tablet, FORM=2 is powder formulation. pcVPC plots show the observed concentrations (points), median (solid red lines) and spread (5^{th} to 95^{th} percentile, dashed red line) of the observed concentrations, and median (solid black lines) and spread (5^{th} to 95^{th} percentile, dashed black lines) of the simulated concentrations in all subjects. The red area is the 95% confidence interval of the simulated median and the blue area is the 95% confidence interval of the simulated 5^{th} and 95^{th} percentiles.

Table 5 shows the median and 95% CIs of the PK parameter estimates derived from bootstrap method (N = 500). Median values following bootstrapping were very similar to the parameter estimates of the original dataset and the 95% CIs overlapped with those of the original datasets, indicating that the final PopPK model was stable with good precision of parameter estimation.

Table 5. Comparison of TFV final model estimates and bootstrap results

Parameter	Parameter Description	Final model estimate	Bootstrap estimate Median	Bootstrap 5 %	Bootstrap 95 %
θ_1	Apparent oral clearance, CL/F (L/hr)	75.3	73.8	66.6	81.2
θ_2	Apparent central volume, V_c/F (L)	211	180	59.5	402.9
θ_3	Apparent inter-compartment clearance, Q/F (L/hr)	105	98.6	68.9	139.2
θ_4	Apparent peripheral volume, V_p/F (L)	7290	7336	4419	14200
θ_5	Absorption rate constant, K_a (hr^{-1})	0.313	0.306	0.213	0.441
θ_6	Influence of WT on CL/F	0.483	0.475	0.306	0.642
θ_7	Influence of FORM on K_a (hr^{-1})	0.625	0.643	0.408	1.17
θ_8	Influence of BCLCRSW on CL/F	0.481	0.466	0.174	0.862
$\omega_{CL/F}$	IIV of CL/F (%)	23.1	21.6	15.5	27.0
$\omega_{Vc/F}$	IIV of V_c/F (%)	111	122	65.9	186
$\omega_{Vp/F}$	IIV of V_p/F (%)	133	134	85.8	169
ω_{IOVCL}	IOV of CL/F (%)	14.1	10.5	2.11	19.0
$\omega_{IOVFORM}$	IOV_{FORM} of CL/F (%)	8.50	12.5	4.15	18.8
σ	Residual error (%)	33.2	32.5	29.0	36.6

Shrinkage:
Shrinkage of the final model parameters is presented in Table 7. The η-shrinkage for CL/F was 18%, Vc/F was 47%, and Vp/F was 31% which were considered reasonable. Thus, the final PopPK model generated reliable Bayesian estimates for CL/F, Vc/F and Vp/F.

Table 7. Shrinkage estimates of inter-individual and intra-individual variability in the final TFV model

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	18.2
$\omega_{Vc/F}$	IIV of Vc/F	47.1
$\omega_{Vp/F}$	IIV of Vp/F	31.4

4/ Model-based prediction:

- Impact of WT on TFV Exposure:

Body weight was identified as a statistically significant covariate on TFV CL/F in the final model (Table 4). The impact of WT on TFV exposure is presented in Table 9. In paediatric CHB subjects between 10.5 to 51.1 kg, TFV exposures demonstrated approximately 2-fold change between the lowest and highest AUC_{tau}, C_{max} and C_{tau} quartiles. These differences were not considered clinically significant, based on the factors mentioned previously.

Table 9. Impact of WT on mean (%CV) steady-state TFV exposure in pediatric subjects

	WT Quartiles			
Characteristics	Q1	Q2	Q3	Q4
WT (kg: min, median, max)	10.5, 15, 16.4	17, 19.05, 21	21.2, 24.55, 27	28.4, 36, 51.1
No. of subjects (%)	15 (25.9)	14 (24.1)	14 (24.1)	15 (25.9)
AUC_{tau} (hr*ng/mL)	1401 (33.3)	1922 (32.7)	2164 (27.5)	2474 (14.6)
C_{max} (ng/mL)	116.2 (23.5)	186.9 (27.5)	216 (31.4)	278.1 (12.1)
C_{tau} (ng/mL)	30.01 (47.3)	41.93 (49.1)	45.16 (44.5)	43.18 (32.8)

- Impact of BCLCRSW (Estimated creatinine clearance derived by the Schwartz equation) on TFV Exposure:

BCLCRSW was included as a covariate on TFV CL/F in the final model (Table 4). The impact of BCLCRSW on TFV exposure is presented in Table 10. In paediatric subjects across the range of BCLCRSW values (114 to 237 mL/min/1.73m^2), TFV exposures demonstrated approximately ≤40% difference between the lowest and highest AUC_{tau}, C_{max} and C_{tau} quartiles. These differences were not considered clinically significant, based on the factors mentioned previously.

Table 10. Impact of BCLCRSW on mean (%CV) steady-state TFV exposure in pediatric subjects

	BCLCRSW Quartiles			
Characteristics	Q1	Q2	Q3	Q4
BCLCRSW (ml/min/1.73m^2 : min, median, max)	114, 142, 146	147, 158, 165	167, 176, 187	189, 201, 237
No. of subjects (%)	15 (25.9)	13 (22.4)	15 (25.9)	15 (25.9)
AUC_{tau} (hr*ng/mL)	2349 (26.2)	2128 (26.8)	1818 (41.5)	1677 (25.8)
C_{max} (ng/mL)	243.5 (29.9)	211.8 (32.5)	174.4 (43.9)	168.9 (37.2)
C_{tau} (ng/mL)	47.32 (31.5)	43.39 (45.5)	36.56 (62.3)	32.98 (31.8)

- Impact of FORM on TFV Exposure:

Formulation was included as a covariate on TFV Ka in the final model (Table 4). The impact of FORM on TFV exposure is presented in Table 11. Paediatric subjects with CHB who received the tablet formulation had higher (≤50%) AUC_{tau}, C_{max} and C_{tau} compared with subjects who received the powder formulation. The difference in exposures is reflective of the effect of body weight, which explains the majority of variability in TFV exposures. These differences were not considered clinically significant, based on the factors mentioned previously.

Table 11. Impact of FORM on mean (%CV) steady-state TFV exposure in pediatric subjects

Characteristics	Tablet (TDF 8mg/kg)	Powder (TDF 8mg/kg)	Both[a] (TDF 8mg/kg)
No. of subjects (%)	35 (60.3)	14 (24.2)	9 (15.5)
AUC_{tau} (hr*ng/mL)	2290 (23.6)	1430 (34.2)	1710 (34.1)
C_{max} (ng/mL)	242 (23.8)	116 (24.5)	160 (33.3)
C_{tau} (ng/mL)	44.5 (40.6)	31.1 (46.8)	35.9 (50.4)

[a]Subjects who switched formulations during the 48 Week treatment of TDF.

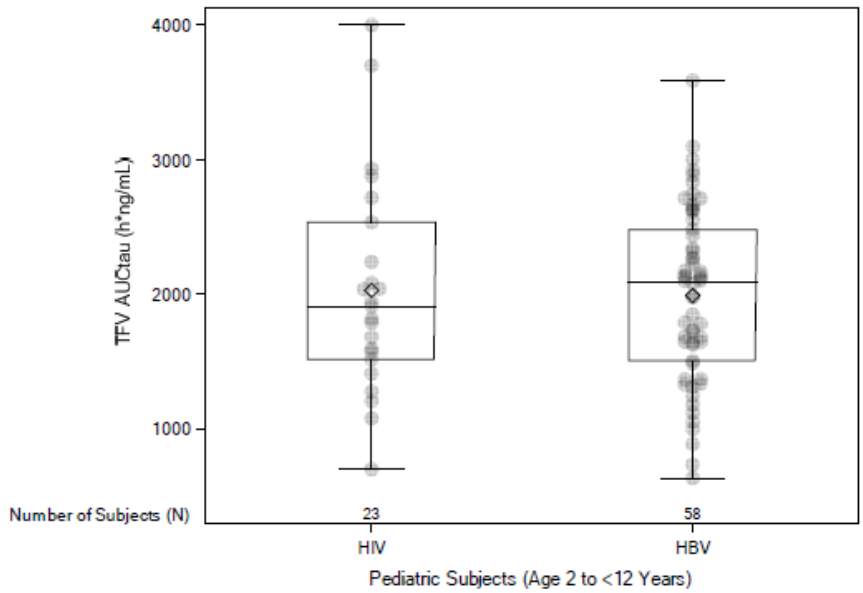
Pharmacokinetics of TFV for Paediatric CHB Subjects 2 to < 12 Years Old Relative to Paediatric HIV Subjects

Predicted systemic TFV exposures in paediatric CHB subject 2 to < 12 years old receiving TDF 8 mg/kg were compared with those from paediatric HIV subjects of the same age who received TDF 8 mg/kg in combination with ritonavir-boosted lopinavir (LPV/r) or nelfinavir (GS-US- 104-0352 Interim Week 48 CSR).

TDF is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). LPV/r, an inhibitor of P-gp and BCRP, has been shown to moderately increase mean TFV concentrations (32%). Therefore, observed TFV AUC_{tau} for paediatric HIV subjects who received TDF with LPV/r were scaled by $AUC_{tau}/1.32$ to account for LPV/r-induced increases in TFV AUC_{tau}. Observed TFV AUC_{tau} for paediatric HIV subjects who received TDF with nelfinavir were not adjusted, as nelfinavir is not an inhibitor of P-gp or BCRP.

Figure below presents the comparison of population PK-predicted systemic TFV AUC_{tau} in pediatric CHB subjects 2 to < 12 years old receiving TDF 8 mg/kg with exposures in paediatric HIV subjects of the same age who received TDF 8 mg/kg in combination with LPV/r or nelfinavir.

Figure 2. Steady-State TFV AUC_{tau} Following Administration of TDF in Pediatric CHB and HIV Subjects 2 to < 12 Years Old



Horizontal lines on the box plots are median and interquartile ranges; circles represent individual values, diamonds represent mean values, and vertical lines are maximum and minimum values within 1.5 × the interquartile range.
TFV AUC_{tau} for pediatric HBV is the population PK-predicted exposure for subjects receiving TDF 8 mg/kg in Study GS-US-174-0144.

TFV exposures (AUC_{tau} and C_{max}) were similar for the paediatric HBV and HIV subjects:

Table 3. Statistical Comparisons of TFV PK Parameters for Pediatric CHB Subjects (Test) Versus Pediatric HIV Subjects (Reference) (Population PK Model Dataset)

TFV PK Parameter	TDF 8 mg/kg in Pediatric Subjects 2 to < 12 Years Old Mean (%CV)		Test/Reference %GLSM Ratio[c] (90% CI)
	Test: CHB Subjects[a] (N = 58)	Reference: HIV subjects (scaled)[b] (N=23)	
AUC_{tau} (h•ng/mL)	1988.4 (32.5)	2027.7 (39.6)	99.5 (85.2, 116.1)
C_{max} (ng/mL)	199.2 (37.8)	238.7 (53.4)	87.9 (73.1, 105.8)

CHB = chronic hepatitis B; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean; HIV = human immunodeficiency virus

a Population PK-predicted exposures for subjects receiving TDF in Study GS-US-174-0144.

b Pediatric HIV subjects in Study GS-US-104-0352. PK parameters were calculated by scaling the observed exposures by AUC_{tau}/1.32 for subjects with TDF administered with LPV/r. Observed values were used for subjects administered TDF with nelfinavir.

c GLSMs were obtained by the back-transformation of least-squares means of the parameters from an ANOVA using a mixed model based on the natural logarithmic scale.

The CHMP noted that the AUC was comparable between CHB paediatric population (estimated by PKpop) and HIV paediatric population (historical data) of the same age receiving the same dose of TDF.

2.3.3. PK/PD modelling

Exposure-response relationships for efficacy (HBV DNA < 69 IU/mL, ALT normalisation) and safety (change from baseline in spine and whole body bone mineral density [BMD])at Week 48 were evaluated using TFV exposure estimates (AUC_{tau} and C_{max}) derived from population PK modelling.

Subjects with missing data for specific analysed endpoints were excluded from that analysis.

Five subjects were excluded from the PK/PD efficacy analysis due to missing HBV DNA values at Week 48 (missing = excluded [M = E]). One subject was excluded from the PK/PD efficacy and safety analyses due to missing ALT and whole body BMD data at Week 48, respectively (M = E).

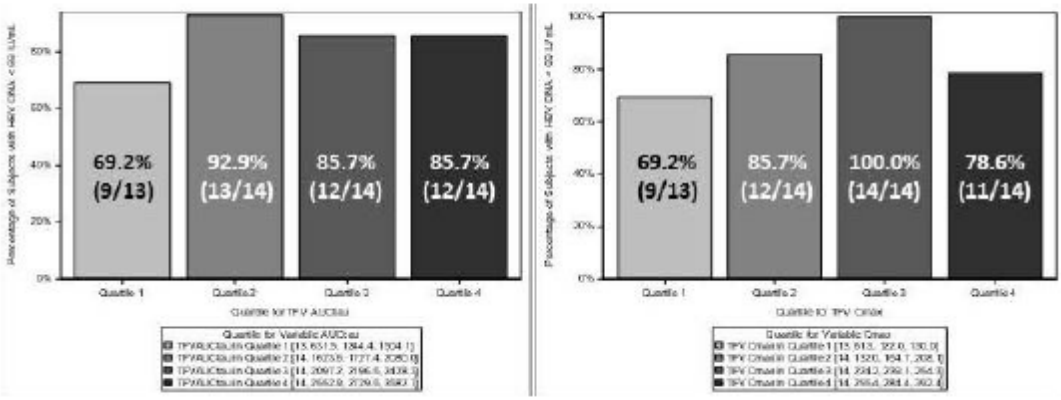
Exposure-Response for Efficacy

The exposure-efficacy relationship for TFV was evaluated by determining the proportion of subjects who achieved the primary (HBV DNA < 69 IU/mL at Week 48) and secondary (normalised ALT at Week 48) efficacy endpoints as a function of TFV exposure quartiles (AUC_{tau} and C_{max}). Further analyses determined the proportion of subjects stratified by age (< 6 years and ≥ 6 years) who achieved these efficacy endpoints as a function of median TFV exposures for that age group (i.e., above or below the age group median).

- by TFV AUC_{tau} and C_{max} Quartiles

Overall, high virologic response rates were observed across all quartiles, with no statistically significant trends observed in the exposure-response relationship (p = 0.44 for TFV AUC_{tau}, p = 0.14 for TFV C_{max}). Of the 4 subjects in Q1 who did not meet the primary efficacy endpoint at Week 48, 2 subjects achieved HBV DNA< 69 IU/mL at Week 56 or 72.

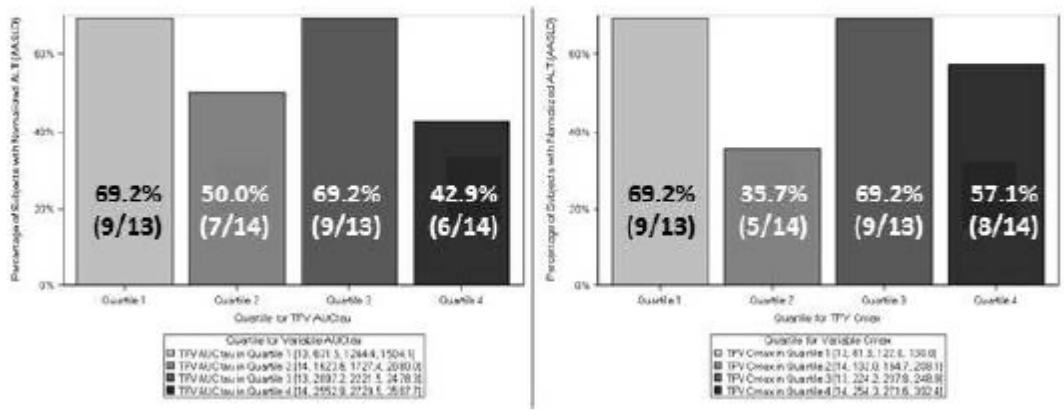
Figure 3. **Proportion of Pediatric CHB Subjects with HBV DNA < 69 IU/mL at Week 48 by TFV AUC_{tau} and C_{max} Quartiles (PK/PD Analysis Set)**



Analysis were based on an M = E approach.
The numbers presented in brackets are the sample size, minimal, median, and maximal values of the TFV PK parameter.

For both TFV AUC_{tau} and C_{max}, a numerically higher proportion of subjects in Q1 and Q3 compared with Q2 and Q4 had ALT normalisation at Week 48. The reason for these numerical differences is unclear; there were no statistically significant differences in the proportion of subjects with ALT normalisation at Week 48 observed across quartiles (p =0.42 for TFV AUC_{tau}, p = 0.25 for TFV C_{max})

Figure 5. **Proportion of Pediatric CHB Subjects with Normalized ALT (AASLD Criteria) at Week 48 by TFV AUC_{tau} and C_{max} Quartiles (PK/PD Analysis Set)**

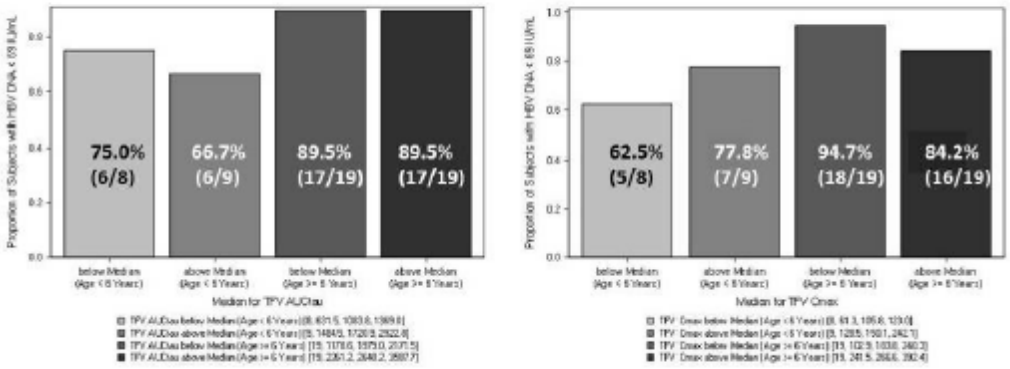


Analysis were based on an M = E approach.
The numbers presented in brackets are the sample size, minimal, median, and maximal values of the TFV PK parameter.

- by Age (2 to < 6 years and ≥ 6 to < 12 years)

For subjects in the 2 to < 6 years old group, there were no statistically significant differences in response rates for those with TFV exposures above or below the age group medians (p = 1.00 TFV AUC_{tau}, p = 0.62 for TFV C_{max}). Similarly, for subjects in the ≥ 6 to 12 years old group, the differences in response rates for subjects with TFV exposures above or below the age group medians were not statistically significant (p = 1.00 for TFV AUC_{tau}, p = 0.60 for TFV C_{max}).

Figure 4. **Proportion of Pediatric CHB Subjects with HBV DNA < 69 IU/mL at Week 48 by Age (TFV AUC_{tau} and C_{max} Above and Below the Age Group Median) (PK/PD Analysis Set)**

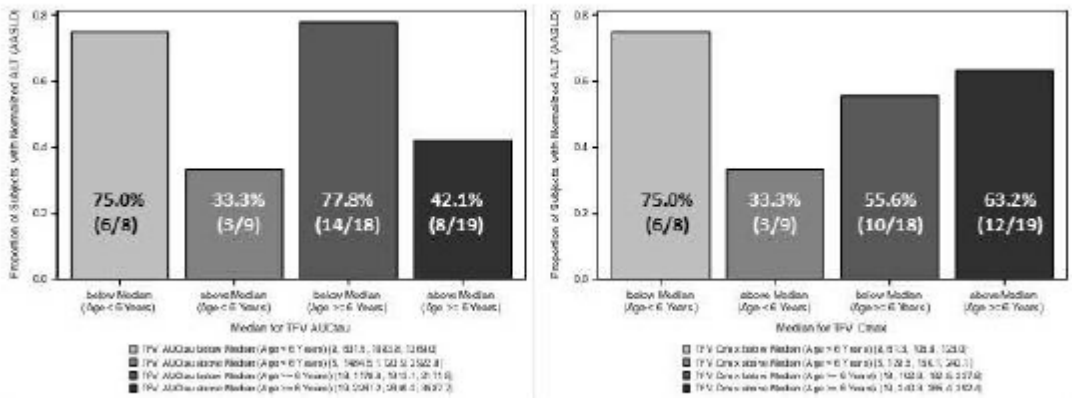


Analysis were based on an M = E approach.
The numbers presented in brackets are the sample size, minimal, median, and maximal values of the TFV PK parameter.

A numerically higher proportion of subjects in the both age groups with TFV AUC_{tau} below the age group median had ALT normalisation at Week 48 compared with subjects with AUC_{tau} above the age group median. The difference was statistically significant for the ≥ 6 years old group (p = 0.045) but not for the < 6 years old group (p = 0.15). The proportion of subjects with ALT normalisation at Week 48 was similar for those < 6 years and ≥ 6 years with AUC_{tau} below the age group median.

A numerically higher proportion of subjects < 6 years old with TFV C_{max} below the age group median compared with above the age group median had ALT normalisation at Week 48. The proportion of subjects ≥6 years old with ALT normalisation at Week 48 was similar for those above or below the age group median; no statistically significant differences were observed in the proportion of subjects with ALT normalisation by C_{max} (p = 0.15 and p = 0.74 for subjects < 6 years and ≥ 6 years, respectively)

Figure 6. **Proportion of Pediatric CHB Subjects with Normalized ALT (AASLD Criteria) at Week 48 by Age (TFV AUC_{tau} and C_{max} Above and Below the Age Group Median) (PK/PD Analysis Set)**



Analysis were based on an M = E approach.
The numbers presented in brackets are the sample size, minimal, median, and maximal values of the TFV PK parameter.

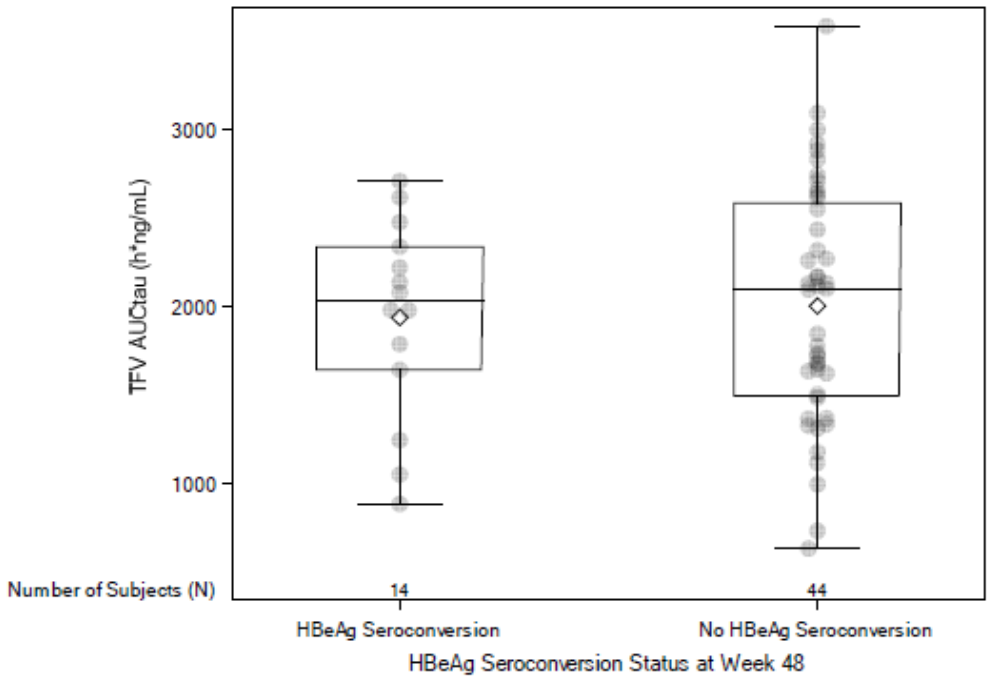
- Pharmacokinetics of TFV for Paediatric CHB Subjects With and Without HBeAg Seroconversion at W48

Due to small sample sizes, the same exposure-response analyses (by quartiles, age, etc.) were not

planned for HBeAg seroconversion; instead a comparison of TFV exposure by subjects who did or did not have HBeAg seroconversion at Week 48 was performed.

A comparison of the population PK model-predicted systemic TFV AUC_{tau} between subjects who had HBeAg seroconversion and those who did not have HBeAg seroconversion at Week 48. The TFV AUC_{tau} of subjects with seroconversion was within the range of the exposure of subjects without seroconversion. Similar results were observed for TFV C_{max}.

Figure 7. **Pharmacokinetics of TFV for Pediatric CHB Subjects 2 to < 12 Years Old With and Without HBeAg Seroconversion at Week 48 (PK/PD Analysis Set)**



Horizontal lines on the box plots are median and interquartile ranges; circles represent individual values, diamonds represent mean values, and vertical lines are maximum and minimum values within 1.5 × the interquartile range.

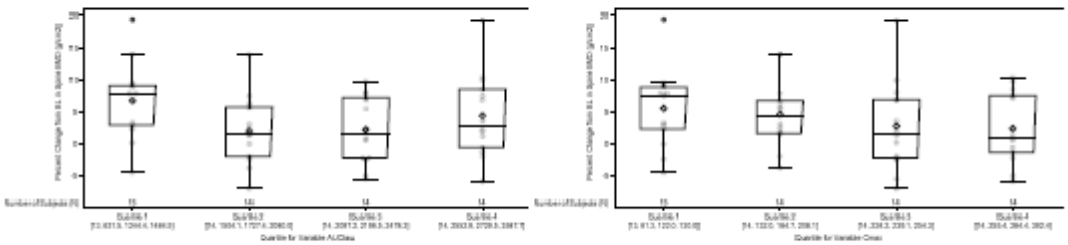
Exposure-Response for Safety

The exposure-efficacy relationship for TFV was evaluated by determining the percent change from baseline in spine and whole body BMD as a function of TFV exposure quartiles (AUC_{tau} and C_{max}). Further analyses determined the proportion of subjects stratified by age (< 6 years and ≥ 6 years) who achieved these safety endpoints as a function of median TFV exposures for that age group (i.e., above or below the age group median).

- By TFV AUC_{tau} and C_{max} Quartiles

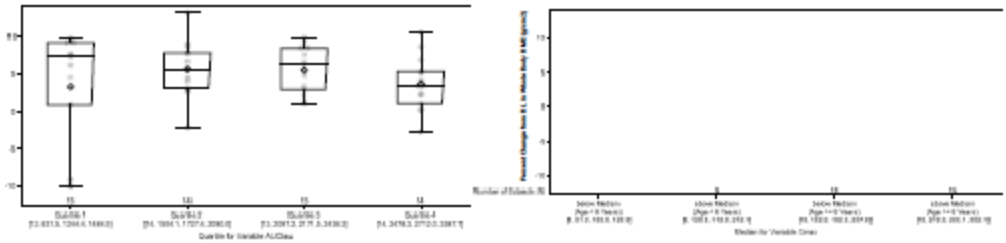
The median percent changes from baseline in spine and whole body BMD were similar across quartiles of TFV AUC_{tau} and $C_{max,}$ indicating the lack of an exposure-safety relationship (spine BMD: p = 0.100 for TFV AUC_{tau}, p = 0.40 for TFV C_{max}; whole body BMD: p=0.47 for TFV AUC_{tau}, p = 0.50 for TFV C_{max}).

Figure 8. **Percent Change from Baseline in Spine BMD at Week 48 by TFV AUC_{tau} and C_{max} Quartiles (PK/PD Analysis Set)**



Analysis were based on an M = E approach.
Horizontal lines on the box plots are median and interquartile ranges; circles represent individual values, diamonds represent mean values, and vertical lines are maximum and minimum values within 1.5 × the interquartile range.
Numbers in brackets below each plot are sample size, minimum, median, and maximum values for TFV AUC_{tau} or C_{max} for subjects included in the subgroup.

Figure 9. **Percent Change from Baseline in Whole Body BMD at Week 48 by TFV AUC_{tau} and C_{max} Quartiles (PK/PD Analysis Set)**



Analysis were based on an M = E approach.

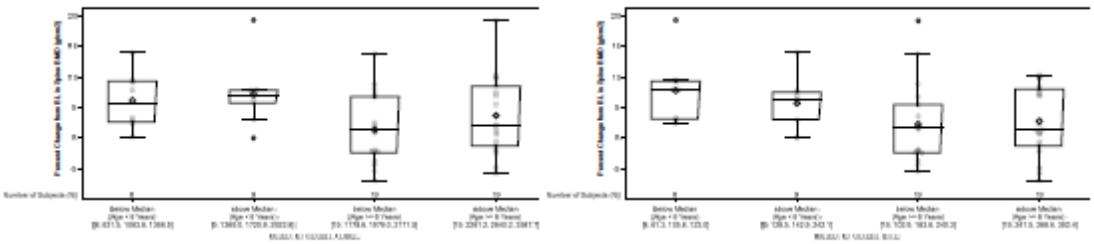
- By Age

For both age groups, the percent changes from baseline in spine BMD were numerically similar for subjects with TFV AUC_{tau} and C_{max} above or below the age group median. Within age groups, there were no significant differences in percent change from baseline in spine BMD for subjects < 6 years old (p = 1.00 for TFV AUC_{tau} and p = 0.27 for TFV C_{max}) or subjects ≥ 6 years old (p = 0.22 for TFV AUC_{tau} and p = 0.62 for TFV C_{max}).

For both age groups, the percent changes from baseline in whole BMD were numerically similar for subjects with TFV AUC_{tau} and C_{max} above or below the age group median. Within age groups, there were no significant differences in percent change from baseline in whole body BMD for subjects < 6 years old (p = 0.89 for TFV AUC_{tau} and p = 0.53 for TFV C_{max}) or subjects ≥ 6 years old (p = 0.75 for TFV AUC_{tau} and p = 0.80 for TFV C_{max}).

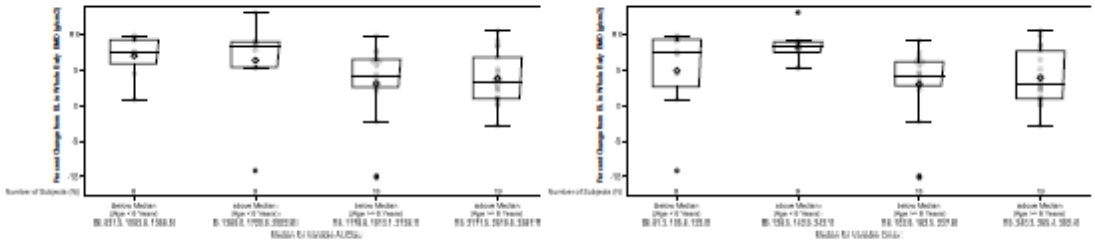
These results indicated an overall lack of exposure-response relationship between TFV exposures (AUC_{tau} and C_{max}) and percent changes from baseline in spine and whole body BMD at Week 48 by age group.

Figure 10. **Mean (SD) Percent Change from Baseline in Spine BMD by Age Group (TFV AUC_{tau} and C_{max} Above and Below the Age Group Median) (PK/PD Analysis Set)**



Analysis were based on an M = E approach.
Horizontal lines on the box plots are median and interquartile ranges; circles represent individual values, diamonds represent mean values, and vertical lines are maximum and minimum values within 1.5 × the interquartile range.
Numbers in brackets below each plot are sample size, minimum, median, and maximum values for TFV AUC_{tau} or C_{max} for subjects included in the subgroup.

Figure 11. **Percent Change from Baseline in Whole Body BMD by Age Group (TFV AUC_{tau} and C_{max} Above and Below the Age Group Median)**



Analysis were based on an M = E approach.
Horizontal lines on the box plots are median and interquartile ranges; circles represent individual values, diamonds represent mean values, and vertical lines are maximum and minimum values within 1.5 × the interquartile range.
.Numbers in brackets below each plot are sample size, minimum, median, and maximum values for TFV AUC_{tau} or C_{max} for subjects included in the subgroup.

The CHMP noted that the Relationship between TFV exposure (AUC and C_{max}) and efficacy (HBV DNA <69 IU/ml, ALT normalisation, HBeAg seroconversion) and safety (spine and whole body BMD) was explored by PK pop analysis and that no clinically significant differences were observed in exposure-response relationship.

2.3.4. Discussion on clinical pharmacology

The PK of TFV in paediatric CHB subjects was evaluated using all sparse and intensive plasma concentration data available from Study GS-US-174-0144. Tenofovir exposures (AUC_{tau} and C_{max}) were estimated using a population PK approach, and compared with historical data in paediatric subjects infected with HIV who were receiving the same dose of TDF (i.e., 8 mg/kg).

2.3.5. Conclusions on clinical pharmacology

Tenofovir exposures in CHB paediatric subjects were estimated using a population PK approach and were found similar to historical data in HIV infected paediatric subjects. Clarification was required by the CHMP on the PK pop analysis before concluding on the reliability of the exposure estimation.

2.4. Clinical efficacy

2.4.1. Main study – GS-US-174-0144

Title of Study:

Study GS-US-174-0144 is a Phase 3, randomised, double-blind, multicentre study to evaluate the antiviral efficacy, safety and tolerability of TDF versus Placebo in paediatric patients aged 2 to <12 years with chronic hepatitis B infection.

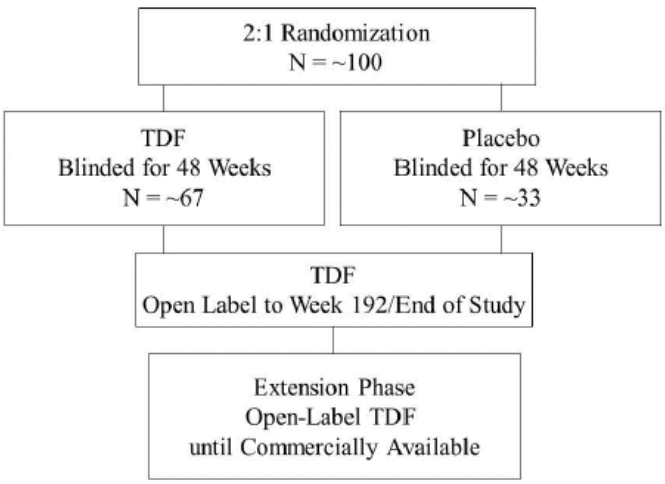
Methods

The study is ongoing.

Approximately 100 TDF-naive subjects with HBV DNA > 10^5 copies/mL and ALT >1.5 × the upper limit of normal (ULN) at screening were to be randomised in a 2:1 ratio to 1 of the following treatments:

- TDF once daily by mouth for 48 weeks
- Placebo-to-match TDF once daily by mouth for 48 weeks

Figure 1. GS-US-174-0144: Study Schema



Randomisation was stratified by age (< 6 years, ≥ 6 years) and geographic region (North America/Europe and Asia).

In the original study protocol (22 July 2011), subjects received double-blind TDF or placebo for 72 weeks, after which subjects received open-label TDF for an additional 120 weeks (to Week 192/end of treatment). Subjects who were randomised into the study following protocol Amendment 3 (29 February 2016) received double-blind TDF or placebo for 48 weeks, after which subjects received open-label TDF for an additional 144 weeks (to Week 192/end of treatment). Subjects who were beyond Week 48 of double-blind treatment when protocol Amendment 3 became effective continued double-blind treatment to Week 72 (as originally planned) and switched to open-label TDF at the Week 72 visit.

All subjects who completed the study to Week 192 were offered continuation of open-label TDF in an extension phase until TDF became commercially available for patients of their age and weight in the country of their enrolment. During the extension phase, subjects were to attend study visits every 12

weeks to assess efficacy and safety, conduct study drug accountability, and dispense study drug.

The interim Week 48 analysis was conducted after all randomised subjects had completed the Week 48 study visit or had prematurely discontinued study drug. All data collected by the Week 48 data cut (10 August 2017), except bone mineral density (BMD) and clinical laboratory data, which were collected up to the data finalisation date (16 January 2018), were included in the interim report provided in support of the extension of indication.

Study participants

Inclusion Criteria:

- Male or female

- 2 years to < 12 years of age (consent of parent or legal guardian required)

- Body weight $\geq$ 10 kg

- Documented chronic HBV infection, defined as positive serum HBsAg for $\geq$ 6 months

- HBeAg-positive or HBeAg-negative

- HBV DNA $\geq$ 10^5 copies/mL

- ALT $\geq$ 1.5 × ULN at screening

- Estimated glomerular filtration rate (eGFR) (creatinine clearance [CLcr]) $\geq$ 80 mL/min/1.73 m^2 (using the Schwartz formula)

- Adequate hematologic function (absolute neutrophil count $\geq$ 1500/mm^3; haemoglobin $\geq$ 10.0 g/dL)

- Negative serum Beta-HCG pregnancy test (for females of childbearing potential only)

- Male and female subjects of childbearing potential who chose to become sexually active agreed to utilise highly effective contraception methods or to abstain from heterosexual intercourse while on study treatment and for 30 days following the last dose of study drug

- No prior TDF therapy (subjects may have received prior interferon alfa and/or other oral anti-HBV nucleoside/nucleotide therapy; subjects must have discontinued interferon alfa therapy $\geq$ 6 months prior to screening; subjects experienced on other anti-HBV nucleoside/nucleotide therapy must have discontinued therapy $\geq$ 16 weeks prior to screening to avoid flare if randomised to the placebo arm)

Exclusion Criteria:

- Pregnant or lactating, Sexually-active male or female of childbearing potential who is not willing to use a highly effective method of contraception during the study

- Decompensated liver disease defined as prothrombin time > 1.2 x ULN, platelets < 150,000/mm^3, serum albumin < 3.5 g/dL, or prior history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy, variceal haemorrhage).

- Interferon (pegylated or not pegylated) therapy within 6 months of the screening visit

- Anti-HBV nucleoside/nucleotide therapy within 16 weeks of the screening visit

- Alpha-fetoprotein > 50 ng/mL

- Evidence of HCC

- Coinfection with HIV, acute hepatitis A virus, hepatitis C virus, or hepatitis D virus

- Chronic liver disease of non-HBV aetiology (e.g., hemochromatosis, alpha-1 antitrypsin deficiency, cholangitis)

- History of significant renal disease (e.g., nephrotic syndrome, renal dysgenesis, polycystic kidney disease, congenital nephrosis, acute tubular necrosis, other renal disease)

- History of significant bone disease (e.g., osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochrondroses, multiple bone fractures)

- Significant cardiovascular, pulmonary, or neurological disease

- Evidence of a gastrointestinal malabsorption syndrome that may interfere with absorption of orally administered medications

- History of solid organ or bone marrow transplantation

- Ongoing therapy with any of the following: nephrotoxic agents, parenteral aminoglycoside antibiotics (e.g., gentamicin, tobramycin, amikacin), cidofovir, cisplatin, foscarnet, intravenous (IV) amphotericin B, IV pentamidine, oral or IV ganciclovir, cyclosporine, tacrolimus, IV vancomycin

- Chronic daily nonsteroidal anti-inflammatory drug therapy, including competitors of renal excretion (e.g., probenecid), systemic chemotherapeutic agents, systemic corticosteroids (pulmonary administration via metered-dose inhaler[MDI]/nebuliser and oral steroids administered for < 5 days were permitted), interleukin-2 (IL-2) and other immunomodulating agents, and investigational agents (except with the expressed approval of the study sponsor). Administration of any of these medications must have been discontinued ≥ 45 days prior to the baseline visit and for the duration of the study.

- Known hypersensitivity to the study drugs, metabolites, or formulation excipients

- Any other condition (including alcohol or substance abuse) or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.

Treatments

Subjects were randomised to receive TDF (150, 200, 250, or 300 mg tablets or 40 mg/gram powder) or placebo to match TDF tablets and powder once daily with or without food followed by 240 mL of water.

The recommended oral dose of TDF for HIV infected paediatric patients ≥ 2 years is 8 mg/kg of body weight, to a maximum of 300 mg/day (≥ 35 kg).

In this study,

- paediatric subjects who weighed > 17 kg and were able to swallow tablets received weight-based TDF as a 150, 200, 250, or 300 mg tablet (or matching placebo tablet) once daily.
- Subjects who weighed ≥ 17 kg but were unable to swallow a tablet and subjects who weighed ≤ 17 kg received weight-based TDF as oral powder (or matching placebo powder).

Throughout the study, and depending on country-specific regulations, subjects were required to take a daily multivitamin. Multivitamins were supplied by the study site and contained ≥ 400 IU of vitamin D.

Blinding

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 exceptions were if a Grade 4 ALT event was maintained for 16 weeks or an ALT flare occurred, both of which were considered situations of medical need; in those cases, serial HBV DNA values from screening through the duration of the event were made available to the investigator.

Blinding of study treatment was critical to the integrity of the study; therefore, if a subject's treatment assignment was disclosed to the investigator, the subject was discontinued from blinded study treatment and offered open-label TDF.

Objectives

The primary objective of this study was:

- To evaluate the antiviral efficacy of TDF versus placebo in paediatric subjects (aged 2 to < 12 years at the time of enrolment) with CHB

The key secondary objective of this study was :

- To evaluate the proportion of subjects with HBeAg seroconversion at Week 48 for subjects with baseline HBeAg seropositivity.

Other secondary objectives of this study were:

- To characterise the safety and tolerability profile of TDF in paediatric subjects (aged 2 to < 12 years at the time of enrolment) with CHB

- To evaluate the biochemical and serological responses to TDF versus placebo

- To evaluate the incidence of potential resistance mutations to TDF in HBV polymerase/reverse transcriptase (pol/RT)

- To assess the pharmacokinetics (PK) of tenofovir (TFV) in subjects receiving the tablet formulation of TDF and those receiving the oral powder formulation of TDF.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects in the FAS with HBV DNA < 69 IU/mL at Week 48 (according to the PCR-based assay).

The M = F approach was used for missing data. Accordingly, all missing HBV DNA data were treated as failing to achieve the primary efficacy endpoint (i.e., HBV DNA was ≥ 69 IU/mL).

The primary efficacy analysis was conducted for the FAS after all randomised subjects had completed the Week 48 study visit or had prematurely discontinued study drug. The difference in the proportion of subjects who achieved the primary endpoint in each treatment group was calculated using a Cochran-Mantel-Haenszel (CMH) test controlling for the stratification factors age at baseline (< 6 years, > 6 years) and region (North America/Europe, Asia).

Sample size

A sample size of 100 subjects (67 subjects in the TDF group, 33 subjects in the Placebo group) would provide at least 85% power to detect a 20% treatment difference between TDF and placebo for the primary endpoint, assuming that the response rate for the TDF group would be 21% and the response rate for the Placebo group would be 1%. This calculation was based on a 2-sided Fisher's exact test with a significance level of 0.05. A similar placebo-response rate was observed in Study GS-US-174-0115 (0% at Week 48).

Due to difficulty enrolling subjects, and to limit exposure of subjects to placebo, the FDA agreed that approximately 90 subjects would be sufficient to conduct the study. The reduced sample size was unlikely to impact the power of the study, even adjusting for a change in the primary endpoint from Week 72 to Week 48, as the originally assumed response rate for the TDF group was only 21%. If the assumed response rate for the TDF group was adjusted to 80%, which is similar to the observed TDF-response rate in Study GS-US-174-0115 (86.5% at Week 48), the study would have well over 85% power with a sample size of 90 subjects. Initially, the primary efficacy endpoint should evaluate the difference between the TDF and Placebo treatment groups using a 2-sided Fisher's exact test. Instead, a CMH test was used that controlled for the randomisation stratification factors of age group and region. A 2-sided Fisher's exact test was used to perform sensitivity analyses of the primary endpoint.

The individual efficacy measurements used in this study were standard for evaluating the antiviral activity of a drug in adults and paediatric patients with CHB. Reductions in HBV DNA levels indicate suppression of active viral replication, and permanent HBsAg seroconversion and normalisation of liver enzyme levels are usually accepted indicators of therapeutic benefit. The Roche COBAS TaqMan HBV test for use with the High Pure System was used to measure plasma HBV DNA in this study. It is the same assay used in the Phase 3 studies that led to TDF registration for treatment of CHB infection (Studies GS-US-174-0102 and GS-US-174-0103) and the same assay used to assess the antiviral efficacy of TDF compared with placebo in adolescent subjects with CHB (GS-US-320-0115). While the lower limit of quantitation (LLOQ) of the assay is 29 IU/mL, the primary endpoint was based on a cut-off of 69 IU/mL (i.e., 400 copies/mL) as this was considered the standard of care at the time this study was initiated {Allice 2007}. The LLOQ of the assay (29 IU/mL) was included as a secondary efficacy endpoint. An endpoint of HBV DNA suppression is widely recognised as a useful marker for the assessment of antiviral activity in CHB patients {Lok 2001}. Levels of HBsAg were quantified using the Abbott ARCHITECT assay, with an LLOQ of ≤ 0.05 IU/mL {Covance Central Laboratory Services 2014, Lou 2011}.

Results

Recruitment – Disposition of patients

Study GS-US-174-0144 was conducted at a total of 24 study centres in 6 countries (6 sites in India, 6 sites in South Korea, 6 sites in the US, 3 sites in Romania, 2 sites in Taiwan, and 1 site in Bulgaria).

A total of 90 eligible subjects were randomised, and 89 randomised subjects received at least 1 dose of study drug and were included in the Full Analysis Set (60 subjects in the TDF group and 29 subjects in the Placebo group). A total of 7 prematurely discontinued double-blind study treatment (4 subjects in the TDF group and 3 in the Placebo group).

	TDF	Placebo	Total
Subjects Screened	—	—	176
Subjects Not Randomized	—	—	86
Screen Failure Subjects Not Randomized	—	—	78
Subjects Who Met All Eligibility Criteria and Were Not Randomized	—	—	8
Reasons Subjects Not Randomized	—	—	
Subject Withdrew Consent	—	—	5
Investigator's Discretion	—	—	1
Outside of Visit Window	—	—	1
Other	—	—	1
Subjects Randomized	60	30	90
Subjects Randomized and Not Treated	0	1	1
Subjects in Safety Analysis Set	60	29	89
Double-Blind Phase			
Completed Double-Blind Study Drug	56 (93.3%)	26 (89.7%)	82 (92.1%)
At Week 72	45 (75.0%)	21 (72.4%)	66 (74.2%)
At Week 48	11 (18.3%)	5 (17.2%)	16 (18.0%)
Premature Discontinuation of Double-Blind Study Drug	4 (6.7%)	3 (10.3%)	7 (7.9%)
Reasons for Premature Discontinuation of Double-Blind Study Drug			
Adverse Event	0	2 (6.9%)	2 (2.2%)
Subject Noncompliance	1 (1.7%)	0	1 (1.1%)
Withdrew Consent/Assent	3 (5.0%)	1 (3.4%)	4 (4.5%)
Open-Label Phase			
Entered at Week 72	45 (75.0%)	20 (69.0%)	65 (73.0%)
Entered at Week 48	11 (18.3%)	5 (17.2%)	16 (18.0%)
Continuing Open-Label Study Drug	46 (76.7%)	20 (69.0%)	66 (74.2%)
Entered Open-Label Extension	13 (21.7%)	6 (20.7%)	19 (21.3%)
Completed Open-Label Study Drug	9 (15.0%)	3 (10.3%)	12 (13.5%)
Premature Discontinuation of Open-Label Study Drug	1 (1.7%)	2 (6.9%)	3 (3.4%)
Reasons for Premature Discontinuation of Open-Label Study Drug			
Investigator Decision	1 (1.7%)	0	1 (1.1%)
Withdrew Consent/Assent	0	2 (6.9%)	2 (2.2%)

	TDF	Placebo	Total
Entered TFFU Phase	7 (11.7%)	3 (10.3%)	10 (11.2%)
Completed TFFU Phase	4 (6.7%)	1 (3.4%)	5 (5.6%)
Entered TFFU Phase and Discontinued due to Starting Another HBV Therapy	0	0	0
Study Completion Status			
Continuing Study	48 (80.0%)	22 (75.9%)	70 (78.7%)
Completed Study	5 (8.3%)	1 (3.4%)	6 (6.7%)
Premature Discontinuation from Study	7 (11.7%)	6 (20.7%)	13 (14.6%)
Reasons for Premature Discontinuation from Study			
Investigator Decision	1 (1.7%)	0	1 (1.1%)
Subject Noncompliance	1 (1.7%)	1 (3.4%)	2 (2.2%)
Withdrew Consent/Assent	5 (8.3%)	5 (17.2%)	10 (11.2%)

The denominator for percentages was the number of subjects in the Safety Analysis Set.
One subject completed double-blind study drug but did not enter the open-label phase of the study and discontinued from study due to noncompliance.

Conduct of the study

Protocol amendments

The original study protocol (22 July 2011) was amended 4 times. Key changes to the protocol for each amendment were as follows:

- The protocol was amended for the first time on 07 March 2012; changes at Amendment 1 were primarily updates to/clarification of study objectives, eligibility criteria, study procedures, and use of concomitant medications and oral contraception. Administrative changes were also made (change in medical monitor, updated schedule of data monitoring committee [DMC] meetings).

- The protocol was amended for the second time on 08 November 2012. Key changes in Amendment 2 included updates to the design and conduct of the PK substudy in response to regulatory authority comments. Subject dosing diaries, a section defining special situations and instructions for reporting special situations, and criterion and instructions for unblinding an investigator in the event of a medical emergency were also introduced. Other changes included a change in medical monitor and clarification of study objectives, eligibility criteria, and procedures.

- The protocol was amended for the third time on 29 February 2016. At this time, due to difficulty enrolling subjects, to limit exposure of subjects to placebo, and upon agreement of the FDA that approximately 90 subjects would be sufficient to conduct the study, the primary efficacy endpoint was changed from Week 72 to Week 48. The amendment specified that upon completing 48 weeks of blinded treatment, all subjects would switch to open-label TDF for the remainder of the study, and subjects who were beyond Week 48 under the previous protocol would switch to open-label TDF at Week 72 (as originally planned). All subjects would receive open-label TDF until Week 192 (end of study). Other amendments to the protocol included a change in the medical monitor, updates to the schedule of study assessments, and modifications to improve clarity and consistency throughout the protocol.

- The protocol was amended for the fourth time on 04 August 2016. At that time, an extension phase was added, whereby all subjects who completed the study were offered the opportunity to continue receiving open-label TDF until the time that TDF became commercially available for patients of their age and weight in the country of their enrolment. During the extension period, subjects were to attend study visits every

12 weeks. Study procedures were updated accordingly. Protocol Amendment 4 also clarified the requirements for dual-energy X-ray absorptiometry (DXA) scans and biochemical bone marker assessments performed at Week 192/end of study or premature discontinuation of study drug and updated the physical description of TDF 300 mg tablets.

Protocol deviations

A total of 43 subjects had at least 1 important protocol deviation (IPD), and the IPD categories were similar for the TDF and Placebo groups. Overall, the most common IPDs were due to treatment compliance (33.3% of subjects), off-schedule procedures (11.1% of subjects), and deviations from eligibility criteria (10.0% of subjects).

	TDF (N=60)	Placebo (N=30)	Total (N=90)
Subjects With at Least 1 Important Protocol Deviation	26 (43.3%)	17 (56.7%)	43 (47.8%)
Other treatment compliance issue	19 (31.7%)	11 (36.7%)	30 (33.3%)
Off-schedule procedure	4 (6.7%)	6 (20.0%)	10 (11.1%)
Eligibility criteria	6 (10.0%)	3 (10.0%)	9 (10.0%)
Informed consent	1 (1.7%)	1 (3.3%)	2 (2.2%)
Missing data	1 (1.7%)	1 (3.3%)	2 (2.2%)
Other	2 (3.3%)	0	2 (2.2%)
Wrong treatment or incorrect dose	2 (3.3%)	0	2 (2.2%)

Subjects with multiple important protocol deviations were counted only once in each protocol deviation category.
Most of the other treatment compliance issues were due to IP kits not returned and subject noncompliance.

Most of the other treatment compliance issues were due to IP kits not returned and subject noncompliance.

None of these IPDs was considered to have affected the overall quality or interpretation of the study data.

Baseline data

Demographic Characteristics

Demographic and baseline characteristics were similar for the TDF and Placebo groups. Overall, the median age was 6 years (range: 2 to 12 years; 1 subject in the Placebo group turned 12 years old prior to the baseline/Day 1 visit), and the majority of subjects were male (56.2%), Asian (65.2% [including 15.7% Indian]); only 30% were White and there were no subject Hispanic or Latino. The median BMI value at baseline was 15.5 kg/m^2 (range: 11.6 to 26.7 kg/m^2), and the median BMI Z-score was −0.12 (range: −5.57 to 2.97).

Table 11. GS-US-174-0144: Demographic and Baseline Characteristics (Safety Analysis Set)

	TDF (N=60)	Placebo (N=29)	Total (N=89)	P-value
Age (years)				
N	60	29	89	0.224
Mean (SD)	6 (2.5)	7 (3.2)	6 (2.8)	–
Median	6	7	6	–
Q1, Q3	4, 8	5, 10	4, 9	–
Min, Max	2, 11	2, 12	2, 12	–
Age Category (years)				
<6	22 (36.7%)	11 (37.9%)	33 (37.1%)	0.908
>=6	38 (63.3%)	18 (62.1%)	56 (62.9%)	–
Sex				
Male	33 (55.0%)	17 (58.6%)	50 (56.2%)	0.748
Female	27 (45.0%)	12 (41.4%)	39 (43.8%)	–
Race				
Asian	41 (68.3%)	17 (58.6%)	58 (65.2%)	0.555
Indian	9 (15.0%)	5 (17.2%)	14 (15.7%)	–
Non-Indian	32 (53.3%)	12 (41.4%)	44 (49.4%)	–
Black or African American	4 (6.7%)	1 (3.4%)	5 (5.6%)	–
White	15 (25.0%)	11 (37.9%)	26 (29.2%)	–
Ethnicity				
Not Hispanic or Latino	60 (100.0%)	29 (100.0%)	89 (100.0%)	NA
Region				
North America/Europe	27 (45.0%)	13 (44.8%)	40 (44.9%)	0.988
Asia	33 (55.0%)	16 (55.2%)	49 (55.1%)	–

Baseline Disease Characteristics

Baseline disease characteristics were similar for the 2 treatment groups. The median (Q1, Q3) baseline HBV DNA value was 8.2 (7.8, 8.7) log10 IU/mL, and median (Q1, Q3) HBsAg was 4.49 (3.97, 4.72) log10 IU/mL. Overall, 83.1% of subjects had baseline ALT > 1.5 × ULN based on central laboratory criteria, and the median (Q1, Q3) baseline eGFR by the Schwartz formula was 166.7 (144.4, 187.5) mL/min/1.73 m^2.

Most subjects were infected with HBV genotype C (43.8%), reflective of the high proportion of non-Indian Asian subjects, or genotype D (41.6%), reflective of Indian and North American/European subjects. The majority of subjects (95.5%) were HBeAg positive at baseline.

Four subjects in the TDF group were HBeAg-negative and anti-HBe positive at baseline; 1 of these subjects was HBeAg positive at screening. Overall, 75.3% of subjects were naive to prior HBV treatment, and a greater proportion of subjects in the Placebo group compared with the TDF group had received prior HBV treatment (41.4% vs 16.7%, respectively; p = 0.012), primarily with interferon alfa and/or lamivudine.

Table 12. GS-US-174-0144: Baseline Disease Characteristics (Safety Analysis Set)

	TDF (N=60)	Placebo (N=29)	Total (N=89)	P-value
HBV DNA (log_{10} IU/mL)				
N	60	29	89	0.156
Mean (SD)	8.089 (0.7208)	8.133 (1.2538)	8.103 (0.9214)	–
Median	8.169	8.297	8.196	–
Q1, Q3	7.759, 8.606	7.948, 8.843	7.848, 8.673	–
Min, Max	5.744, 9.384	2.589, 9.182	2.589, 9.384	–
HBsAg (log_{10} IU/mL)				
N	60	29	89	0.530
Mean (SD)	4.293 (0.4984)	4.205 (1.0744)	4.264 (0.7318)	–
Median	4.475	4.579	4.493	–
Q1, Q3	3.959, 4.716	4.156, 4.716	3.965, 4.716	–
Min, Max	2.926, 4.716	-0.824, 4.716	-0.824, 4.716	–
HBsAg				
Positive	60 (100.0%)	29 (100.0%)	89 (100.0%)	NA
Negative	0	0	0	–
HBeAg				
Positive	56 (93.3%)	29 (100.0%)	85 (95.5%)	0.157
Negative	4 (6.7%)	0	4 (4.5%)	–
HBeAb				
Positive	4 (6.7%)	0	4 (4.5%)	0.157
Negative or Missing	56 (93.3%)	29 (100.0%)	85 (95.5%)	–

	TDF (N=60)	Placebo (N=29)	Total (N=89)	P-value
ALT (U/L)				
N	60	29	89	0.687
Mean (SD)	129 (101.3)	112 (70.1)	123 (92.3)	–
Median	85	97	93	–
Q1, Q3	58, 167	55, 146	56, 161	–
Min, Max	31, 522	29, 337	29, 522	–
ALT (U/L) Category - Central Lab				
≤ 1.5 × ULN	9 (15.0%)	6 (20.7%)	15 (16.9%)	0.488
> 1.5 × ULN to 5 × ULN	37 (61.7%)	19 (65.5%)	56 (62.9%)	–
> 5 × ULN to 10 × ULN	10 (16.7%)	4 (13.8%)	14 (15.7%)	–
> 10 × ULN	4 (6.7%)	0	4 (4.5%)	–
ALT (U/L) Category - AASLD				
≤ 1.5 × ULN	7 (11.7%)	5 (17.2%)	12 (13.5%)	0.757
> 1.5 × ULN to 5 × ULN	35 (58.3%)	18 (62.1%)	53 (59.6%)	–
> 5 × ULN to 10 × ULN	14 (23.3%)	5 (17.2%)	19 (21.3%)	–
> 10 × ULN	4 (6.7%)	1 (3.4%)	5 (5.6%)	–
Years Positive for HBV				
N	55	28	83	0.553
Mean (SD)	3 (2.5)	3 (3.2)	3 (2.7)	–
Median	2	2	2	–
Q1, Q3	1, 5	1, 5	1, 5	–
Min, Max	1, 11	1, 10	1, 11	–
Previous HBV Medication Exposure				
Yes	10 (16.7%)	12 (41.4%)	22 (24.7%)	0.012
No	50 (83.3%)	17 (58.6%)	67 (75.3%)	–
HBV Genotype				
A	4 (6.7%)	2 (6.9%)	6 (6.7%)	0.635
B	5 (8.3%)	1 (3.4%)	6 (6.7%)	–
C	28 (46.7%)	11 (37.9%)	39 (43.8%)	–
D	22 (36.7%)	15 (51.7%)	37 (41.6%)	–
E	1 (1.7%)	0	1 (1.1%)	–
eGFR by Schwartz Formula (mL/min/1.73 m^2)				
N	60	29	89	0.423
Mean (SD)	169.22 (25.881)	162.68 (31.617)	167.09 (27.868)	–
Median	167.62	166.45	166.69	–
Q1, Q3	146.59, 188.23	135.74, 187.53	144.40, 187.53	–
Min, Max	114.15, 236.70	102.67, 218.10	102.67, 236.70	–

Of note, ALT ULN was defined using 2 criteria: that of the central laboratory and that of the American Association of the Study of Liver Diseases (AASLD):

- Central laboratory ALT ULN was 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and 43 U/L for males aged 10-15 years old.
- AASLD ALT ULN was 30 U/L for paediatric subjects between 0-12 years old.

Treatment Compliance

Median (Q1, Q3) adherence to double-blind dosing was 98.9% (94.0%, 100.0%) for the TDF group and 99.4% (97.0%, 100.0%) for the Placebo group. Most subjects in the TDF (95.0%) and Placebo (89.7%) groups had ≥ 80% adherence to double-blind study drug, and a greater proportion of subjects in the Placebo group had adherence < 80% (10.3%) compared with the TDF group (5.0%).

Analysis sets

Table 14. GS-US-174-0144: Analysis Sets (Randomized Analysis Set)

	TDF (N=60)	Placebo (N=30)	Total (N=90)
Randomized Analysis Set	60 (100.0%)	30 (100.0%)	90 (100.0%)
Safety Analysis Set	60 (100.0%)	29 (96.7%)	89 (98.9%)
Full Analysis Set	60 (100.0%)	29 (96.7%)	89 (98.9%)
Per Protocol Analysis Set	52 (86.7%)	25 (83.3%)	77 (85.6%)
Reasons for Exclusion from Per Protocol Analysis Set			
Subject never dosed	0	1	1
Subject did not have on-treatment HBV DNA assessed within Week 48 analysis window	5	4	9
Subject with adherence rate below 80% at Week 48	4	1	5
Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion	56 (93.3%)	29 (96.7%)	85 (94.4%)
Serologically Evaluable Full Analysis Set for HBsAg Loss/Seroconversion	60 (100.0%)	29 (96.7%)	89 (98.9%)
Spine DXA Analysis Set	60 (100.0%)	29 (96.7%)	89 (98.9%)
Whole Body DXA Analysis Set	60 (100.0%)	29 (96.7%)	89 (98.9%)

Outcomes and estimation

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects with HBV DNA < 69 IU/mL at Week 48.

A significantly greater proportion of subjects treated with TDF group compared with Placebo achieved HBV DNA < 69 IU/mL at Week 48 (76.7% vs 6.9%, p < 0.001).

The between-group difference was also observed when HBV DNA < 29 IU/mL at Week 48 was evaluated. Only 3 of 46 subjects in the TDF group with HBV DNA < 69 IU/mL at Week 48 did not achieve complete suppression (i.e., HBV DNA < 29 IU/mL). A similar percentages of subjects in the TDF (8.3%) and Placebo (10.3%) groups were considered treatment failures at Week 48 due to missing data.

Table 4. GS-US-174-0144: Summary of HBV DNA Outcomes at Week 48 (Missing = Failure) (Full Analysis Set)

	TDF (N = 60)	Placebo (N = 29)	P-Value[a]	P-Value[b]
HBV DNA at Week 48				
< 69 IU/mL	46/60 (76.7%)	2/29 (6.9%)	< 0.001	< 0.001
95% CI	64.0% to 86.6%	0.8% to 22.8%	—	
< 29 IU/mL	43/60 (71.7%)	2/29 (6.9%)	< 0.001	
29 to < 69 IU/mL	3/60 (5.0%)	0/29	—	
≥ 69 IU/mL	9/60 (15.0%)	24/29 (82.8%)	—	
Missing	5/60 (8.3%)	3/29 (10.3%)	—	

a P-value was based on a 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline and region strata.
b P-value was based on the Fisher's exact test without adjusting for strata at baseline.
The denominator for percentages was the number of subjects in the Full Analysis Set.

The results were similar when the primary efficacy endpoint analysis was conducted using the missing = excluded (M = E) approach (TDF 83.6%, 46 of 55 subjects; Placebo 7.7%, 2 of 26 subjects; p < 0.001) and when using the Per Protocol Analysis Set with a missing = failure (M = F) approach (TDF 84.6%, 44 of 52 subjects; Placebo 8.0%, 2 of 25 subjects; p < 0.001).

Additionally, a Breslow-Day test of homogeneity confirmed the assumption of homogenous odds ratios for subjects with HBV DNA < 69 IU/mL at Week 48 in the TDF group versus the Placebo group across randomisation strata (p = 0.129), indicating that the CMH test of group differences was appropriate.

Sensitivity Analysis of the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint using a M = F approach were conducted to evaluate what effect, if any, changing the duration of double-blind treatment from 72 weeks to 48 weeks under protocol Amendment 3 had on the primary efficacy endpoint.

For the subset of subjects included in the sensitivity analysis who completed Week 48 or discontinued blinded study drug prior to protocol Amendment 3, a statistically significant greater proportion in the TDF group compared with the Placebo group achieved HBV DNA < 69 IU/mL at Week 48 and Week 72 as follows:

- Week 48 TDF: 73.5%, 36 of 49 subjects, 95% CI 58.9% to 85.1%; Placebo: 4.2%, 1 of 24 subjects, 95% CI 0.1% to 21.1%; p < 0.001

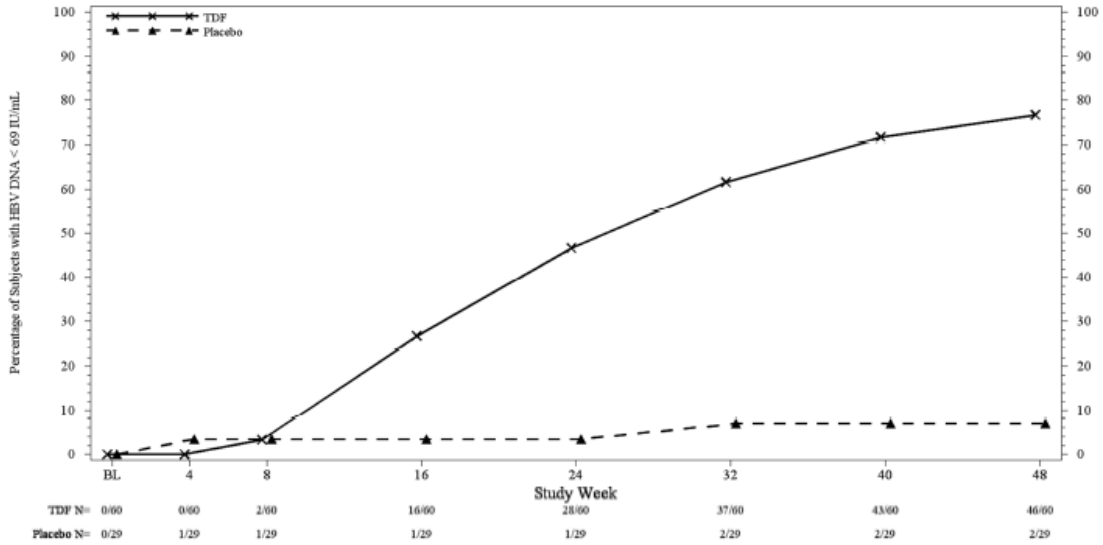
- Week 72 TDF: 79.6%, 39 of 49 subjects, 95% CI 65.7% to 89.8%; Placebo 12.5%, 3 of 24 subjects, 95% CI 2.7% to 32.4%; p < 0.001

Secondary endpoints

Virologic suppression

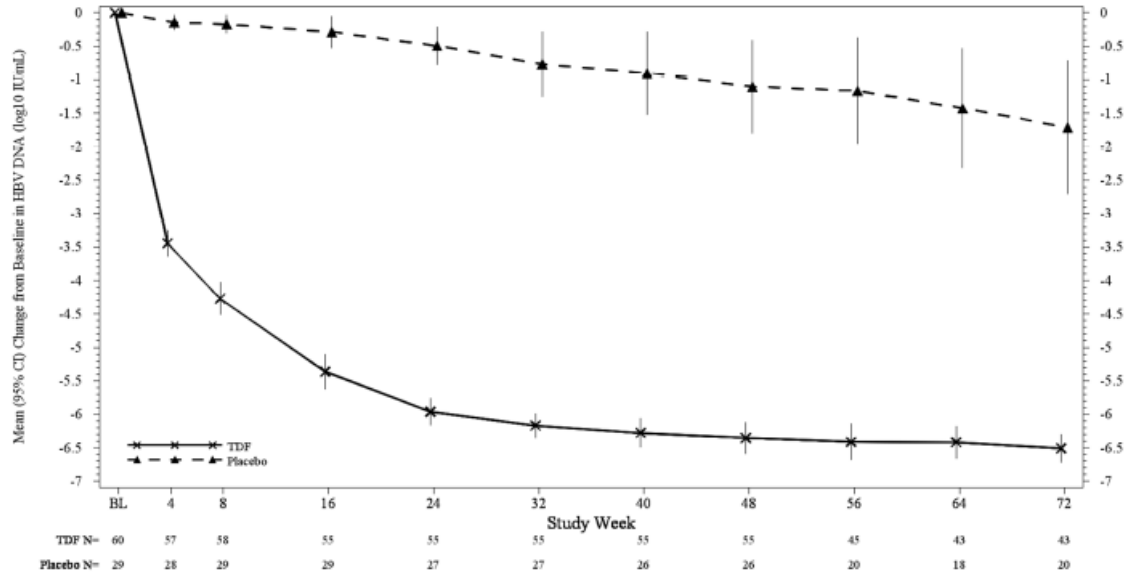
Between-group differences in the proportion of subjects with HBV DNA < 69 IU/mL were statistically significant at all assessments from Week 16 through Week 48.

Figure 1. **GS-US-174-0144: Proportion of Subjects with HBV DNA < 69 IU/mL by Visit to Week 48, Missing = Failure (Full Analysis Set)**



Treatment with TDF resulted in rapid decreases in HBV DNA. At every assessment from Week 4 through 48, the decline from baseline in HBV DNA was significantly greater for the TDF group compared with the Placebo group.

Figure 2. **GS-US-174-0144: Mean (95% CI) Change from Baseline in HBV DNA (log_{10} IU/mL) by Visit (Observed Data) (Full Analysis Set))**



BL = baseline
HBV DNA values below the lower limit of quantitation were imputed as 28 IU/mL (or 1.45 log_{10} IU/mL)

The CHMP noted that the kinetic of the virologic response is comparable to the one previously reported in adults study.

HBeAg and HBsAg Loss and Seroconversion

The proportions of subjects with HBeAg loss and HBeAg seroconversion progressively increased from baseline over 48 weeks of double-blind treatment and the proportion of subjects with HBeAg loss and seroconversion were similar for each treatment group at each time-point evaluated.

At Week 48, 30.4% of subjects in the TDF group and 27.6% of subjects in the Placebo group had achieved HBeAg loss, and 25.0% and 24.1%, respectively, had achieved HBeAg seroconversion. No statistically significant between-group differences in HBeAg loss or seroconversion were observed at any time point evaluated.

According to the MAH ad-hoc analysis showed that prior anti-HBV treatment did not appear to have an effect on the rate of HBeAg loss or seroconversion.

The proportion of subjects with HBsAg loss and seroconversion was minimal for both the TDF and Placebo groups (3.3% and 3.4%, respectively, at Week 48). No subjects in either group achieved HBsAg seroconversion during 48 weeks of treatment.

Alanine Aminotransferase Normalisation

Nearly all subjects had abnormal ALT levels at baseline, including 96.7% in the TDF group and 93.1% in the Placebo group by central laboratory criteria, and 100.0% in the TDF group and 96.6% in the Placebo group by AASLD criterion (≤ 30 U/L).

By both criteria, the proportion of subjects with ALT normalisation was significantly greater for the TDF group compared with the Placebo group at Week 48.

Table 4. GS-US-174-0144: Proportion of Subjects with Normalized ALT and Normal ALT at Week 48, Missing = Failure (Full Analysis Set with Baseline Abnormal ALT, Full Analysis Set)

	TDF (N=60)	Placebo (N=29)	P-Value
Normalized ALT at Week 48[a]			
Central laboratory	38/58 (65.5%)	4/27 (14.8%)	<0.001
AASLD	31/60 (51.7%)	5/28 (17.9%)	0.002
Normal ALT at Week 48			
Central laboratory	39/60 (65.0%)	5/29 (17.2%)	<0.001
AASLD	31/60 (51.7%)	5/29 (17.2%)	0.001

ALT = alanine amino transferase; AASLD = American Association for the Study of Liver Diseases
a The denominator for percentages was the Full Analysis Set including only those subjects who had abnormal ALT (ALT > ULN) at baseline.
Central laboratory normal ALT was defined as ≤ 34 U/L for females 2–15 years or males 1–9 years old, and ≤ 43 U/L for males 10–15 years.
AASLD normal ALT was defined as ≤ 30 U/L for males and females 0–12 years.
P-values were based on 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata.

The CHMP noted that the biochemical response was significantly higher in the TDF arm.

Composites of Secondary Efficacy Endpoints

When composite endpoints that included HBV DNA < 69 IU/mL, normal ALT, normalised ALT, and/or HBeAg loss or seroconversion were assessed, a significantly greater proportion of subjects with abnormal ALT at baseline in the TDF group compared with the Placebo group had achieved both ALT normalisation and HBV < 69 IU/mL at Week 48.

In contrast, there were no between-group differences observed for any of the composite endpoints that included HBeAg loss or seroconversion and HBV DNA < 69 IU/mL. However, the proportion of subjects was numerically higher in the TDF group compared with the Placebo group for each of the 3-endpoint composites of HBV DNA < 69 IU/mL plus ALT normalisation (by central laboratory or AASLD criteria), plus HBeAg loss or seroconversion at Week 48.

Table 7. **GS-US-174-0144: Composite Outcomes of the Proportions of Subjects with HBV DNA < 69 IU/mL and/or HBeAg Loss or Seroconversion and/or Normal/Normalized ALT Proportion of Subjects with Normalized ALT and HBV DNA at Week 48, Missing = Failure**

Outcome at Week 48	TDF (N = 56)	Placebo (N = 29)	P-Value	Source GS-US-174-0144 Week 48 Interim CSR:
Number (%) of subjects with:				
Composite of 2 Endpoints at Week 48				
HBV DNA < 69 IU/mL and normal ALT (Central Lab)	32/60 (53.3%)	2/29 (6.9%)	<0.001	Table 15.9.7.1.1
HBV DNA < 69 IU/mL and normal ALT (AASLD)	28/60 (46.7%)	2/29 (6.9%)	<0.001	Table 15.9.7.1.2
HBV DNA < 69 IU/mL and normalized ALT (Central Lab)	31/58 (53.4%)	2/27 (7.4%)	<0.001	Table 15.9.11.1.1
HBV DNA < 69 IU/mL and normalized ALT (AASLD)	28/60 (46.7%)	2/28 (7.1%)	<0.001	Table 15.9.11.1.2
Composite of 3 Endpoints at Week 48				
HBV DNA < 69 IU/mL and normal ALT (Central Lab) and HBeAg Loss	10/56 (17.9%)	2/29 (6.9%)	0.177	Table 15.9.8.1.1
HBV DNA < 69 IU/mL and normal ALT (AASLD) and HBeAg Loss	9/56 (16.1%)	2/29 (6.9%)	0.237	Table 15.9.8.1.2
HBV DNA < 69 IU/mL and normalized ALT (Central Lab) and HBeAg Loss	9/54 (16.7%)	2/27 (7.4%)	0.258	Table 15.9.12.1.1
HBV DNA < 69 IU/mL and normalized ALT (AASLD) and HBeAg Loss	9/56 (16.1%)	2/28 (7.1%)	0.246	Table 15.9.12.1.2
HBV DNA < 69 IU/mL and normal ALT (Central Lab) and HBeAg Seroconversion	9/56 (16.1%)	2/29 (6.9%)	0.240	Table 15.9.9.1.1
HBV DNA < 69 IU/mL and normal ALT (AASLD) and HBeAg Seroconversion	8/56 (14.3%)	2/29 (6.9%)	0.320	Table 15.9.9.1.2
HBV DNA < 69 IU/mL and normalized ALT (Central Lab) and HBeAg Seroconversion	8/54 (14.8%)	2/27 (7.4%)	0.347	Table 15.9.13.1.1
HBV DNA < 69 IU/mL and normalized ALT (AASLD) and HBeAg Seroconversion	8/56 (14.3%)	2/28 (7.1%)	0.332	Table 15.9.13.1.2

AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; HBeAg = hepatitis B virus e antigen
P-values were based on 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata.
95% CIs were calculated using the Clopper-Pearson method.
HBeAg loss was defined as a change from HBeAg positive at baseline to HBeAg negative with baseline HBeAb negative or missing.
HBeAg seroconversion was defined as HBeAg loss and a change from HBeAb negative or missing at baseline to HBeAb positive.
Central laboratory normal ALT was ≤ 34 U/L for females 2-15 years old or males 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old.
AASLD normal ALT was ≤ 30 U/L for males and females 0-12 years old.

Subgroup Analysis of the Primary Efficacy Endpoint

Analysis of the proportion of subjects who achieved HBV DNA < 69 IU/mL by selected demographic and disease characteristics demonstrated that, with the exception of subjects with baseline ALT ≤ 2 × the upper limit of normal (ULN; by either central laboratory or AASLD criteria), between-group differences were statistically significant for each of the subgroups evaluated, with a greater proportion of subjects in the TDF group achieving HBV DNA < 69 IU/mL at Week 48.

For subjects with ALT ≤ 2 × ULN at baseline, the proportion of subjects with HBV DNA < 69 IU/mL at Week 48 was numerically higher in the TDF group compared with the Placebo group; the small number of subjects included in the baseline ALT ≤ 2 × ULN category likely contributed to the lack of a statistically significant between-group difference, as evidenced by the wide 95% CIs.

Table 19. GS-US-174-0144: Proportion of Subjects with HBV DNA < 69 IU/mL at Week 48 by Subgroup, Missing = Failure (Full Analysis Set)

Number (%) of Subjects with HBV DNA < 69 IU/mL at Week 48 by:	TDF (N = 60)	Placebo (N = 29)	P-Value
ALT at Baseline (AASLD)			
≤ 2 × ULN	9/17 (52.9%)	2/ 9 (22.2%)	0.238
95% CI	27.8% to 77.0%	2.8% to 60.0%	
Missing	2/17 (11.8%)	1/ 9 (11.1%)	
> 2 × ULN	37/43 (86.0%)	0/20	< 0.001
95% CI	72.1% to 94.7%	0.0% to 16.8%	
Missing	3/43 (7.0%)	2/20 (10.0%)	
ALT at Baseline (Central Laboratory)			
≤ 2 × ULN	12/20 (60.0%)	2/10 (20.0%)	0.051
95% CI	36.1% to 80.9%	2.5% to 55.6%	
Missing	2/20 (10.0%)	1/10 (10.0%)	
> 2 × ULN	34/40 (85.0%)	0/19	< 0.001
95% CI	70.2% to 94.3%	0.0% to 17.6%	
Missing	3/40 (7.5%)	2/19 (10.5%)	
Sex			
Male	27/33 (81.8%)	0/17	< 0.001
95% CI	64.5% to 93.0%	0.0% to 19.5%	
Missing	3/33 (9.1%)	1/17 (5.9%)	
Female	19/27 (70.4%)	2/12 (16.7%)	0.002
95% CI	49.8% to 86.2%	2.1% to 48.4%	
Missing	2/27 (7.4%)	2/12 (16.7%)	
Age at Baseline			
< 6 years	12/22 (54.5%)	1/11 (9.1%)	0.013
95% CI	32.2% to 75.6%	0.2% to 41.3%	
Missing	5/22 (22.7%)	1/11 (9.1%)	
≥ 6 years	34/38 (89.5%)	1/18 (5.6%)	<0.001
95% CI	75.2% to 97.1%	0.1% to 27.3%	
Missing	0/38	2/18 (11.1%)	

Number (%) of Subjects with HBV DNA < 69 IU/mL at Week 48 by:	TDF (N = 60)	Placebo (N = 29)	P-Value
Region			
North America/Europe	17/27 (63.0%)	0/13	<0.001
95% CI	42.4% to 80.6%	0.0% to 24.7%	
Missing	3/27 (11.1%)	1/13 (7.7%)	
Asian	29/33 (87.9%)	2/16 (12.5%)	<0.001
95% CI	71.8% to 96.6%	1.6% to 38.3%	
Missing	2/33 (6.1%)	2/16 (12.5%)	
Baseline HBV DNA			
< 8 $\log_{10}$ IU/mL	22/25 (88.0%)	2/ 8 (25.0%)	0.002
95% CI	68.8% to 97.5%	3.2% to 65.1%	
Missing	2/25 (8.0%)	1/ 8 (12.5%)	
≥ 8 $\log_{10}$ IU/mL	24/35 (68.6%)	0/21	<0.001
95% CI	50.7% to 83.1%	0.0% to 16.1%	
Missing	3/35 (8.6%)	2/21 (9.5%)	

AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; ULN = upper limit of normal
The denominator for percentages was the Full Analysis Set.
Central laboratory ALT ULN was 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and 43 U/L for males aged 10-15 years old.
AASLD ALT ULN was 30 U/L for pediatric subjects between 0-12 years old.
P-values were based on 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata.
95% CIs were calculated using the Clopper-Pearson method.

Ancillary analyses

Virologic Resistance

Population sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT; amino acids 1–344) was attempted on serum samples obtained from all subjects at baseline and from subjects with HBV DNA ≥ 69 IU/mL at Week 48 or at the time of early discontinuation of study drug for subjects with at least 24 weeks of double-blind treatment. This included subjects treated with TDF and those treated with placebo, since the study remained blinded through 48 weeks of treatment.

Virologic breakthrough was defined as confirmed HBV DNA ≥ 69 IU/mL after having had HBV DNA < 69 IU/mL during double-blind treatment or a ≥ 1.0 log10 increase from nadir in HBV DNA. Phenotypic resistance evaluations were performed for all subjects in the TDF group who either developed substitutions at a conserved site or had virologic breakthrough.

A total of 10 subjects qualified for sequence analysis in the TDF group at W48: 8 subjects had HBV DNA ≥ 69 IU/mL in the absence of virologic breakthrough, 1 subject (Subject 8993-1074) experienced an unconfirmed virologic blip, and 1 subject (Subject 9045-1043) experienced a virologic breakthrough.

Of 10 subjects in the TDF treatment group who qualified for sequence analysis at Week 48, 4 had no change from baseline sequence, 4 had polymorphic site substitutions, 1 had a conserved site substitution, and 1 was unable to be sequenced due to sample unavailability. No substitutions were detected in more than 1 subject in the TDF group.

Table 10. HBV Sequence Analysis at Week 48 for TDF-Treated Subjects

Subject	Baseline HBV DNA[a]	Week 48 HBV DNA[a]	Week 48 Changes in HBV pol/RT[b]
Subjects with virologic breakthrough at Week 48			
9045-1043	8.35	5.69	No change from baseline
Subjects with a virologic blip			
8993-1074	8.33	3.03[c]	Not available[f]
Subjects with persistent viremia at Week 48 or last visit			
3986-1010	9.38	3.43	rtN118N/D
3986-1024	9.17	2.71	rtT128N, **[rtR193R/G]**
3986-1032	8.65	3.16	No change from baseline
4598-1025	8.29	2.39	rtV27V/A
7161-1001	8.88	1.91[d]	rtC314Y
8656-1050	9.28	4.16	No change from baseline
8757-1047	7.76	2.12	rtT222T/S
8993-1079[e]	9.19	2.00	No change from baseline

a HBV DNA is expressed as $\log_{10}$ IU/mL
b Conserved site changes are noted in **bold with brackets**
c Subject 8993-1074 discontinued study drug early, and the Week 24 sample was analyzed
d Subject 7161-1001 was missing HBV DNA data for the Week 48 sample (accession number W769913) subjected to sequence analysis; a second Week 48 sample (accession number Z455134) was used to obtain the HBV DNA level.
e Subject 8993-1079 did not have a baseline serum sample available and the Week 4 sample was substituted for baseline analysis
f Subject 8993-1074 had no serum sample available at Week 24; therefore, sequence results were not available.

Of 26 subjects in the Placebo group who qualified for sequence analysis at Week 48, 18 had no change from baseline sequence.

Two subjects in the TDF group met the criteria for phenotypic evaluation. One subject qualified at Week 48, with a conserved site substitution in the absence of virologic breakthrough. The other subject qualified due to virologic breakthrough with no sequence changes from baseline detected.

All post-baseline virus pools that were successfully tested remained sensitive to TFV based on fold change from baseline in EC50. Results from sequence analyses and phenotypic evaluation demonstrate no development of resistance to TDF at Week 48.

Table 12. Phenotypic Evaluation of Qualified Subjects in the TDF Group

Isolate	Baseline and Changes from Baseline in HBV pol/RT[a]	TFV EC_{50} (μM)	Fold Change[b]
3986-1024 - BL	NA	1.53	NA
3986-1024 - Week 48	rtT128N, [rtR193R/G]	1.33	0.84
3986-1024 - Week 48 - Clone 4	[rtR193G]	AF	NA[c]
9045-1043 - BL	NA	4.90	NA
9045-1043 - Week 48	No change from baseline	4.25	0.86
Controls			
pHY92	Wild-type	2.77	NA
ADV-R	rtA181V+rtN236T	8.21	3.01

AF = assay failure; BL = baseline; EC_{50} = half maximal concentration; NA = not applicable; pol/RT = polymerase/reverse transcriptase

a Conserved site changes are noted in bold with brackets.

b Defined as the EC_{50} fold change from reference of the last on treatment sample/EC_{50} fold change from reference of the baseline sample. A value < 2-fold was within assay variability.

c Not available due to low replication capacity

The CHMP noted that:

- among the 10 children who qualified for resistance analysis, only 1 experienced a virologic breakthrough (no information is given on the adherence of the patient), 1 had virologic blip and the 8 remaining children had persistent viremia without breakthrough. No patients had TDF resistance-associated mutation through week 48 in this study.
- The study is ongoing with a FU of 192 weeks and will provide longer term data on resistance to TDF in children.

2.4.2. Discussion on clinical efficacy

To support the extension of the indication for VIREAD in children chronically infected with HBV, the MAH is submitting the interim Week 48 analysis (primary endpoint) of the ongoing study GS-US-174-0144. This study is a Phase 3, double-blind, randomised, placebo-controlled study of the safety, efficacy and pharmacokinetics of Tenofovir DF in paediatric patients aged 2 to <12 years old.

The study was initiated in December 2012 and was primarily conducted in Asia and North America/Europe (the EU centres being in Romania and Bulgaria). At the time of the study initiation, entecavir was not yet approved in children and the study was designed as a placebo controlled study. The study therefore compared TDF and placebo over 48 weeks, at which time children from the placebo arm could switch to open-label TDF. Given the significant rate of spontaneous HBeAg seroconversion in children and the concern around the bone and renal toxicity of TDF in children, a placebo-controlled study is appropriate. The open-label phase of the study (until Week 192) will provide useful information on the longer-term safety and durability of virologic response.

To select a paediatric population with immune-active disease, children should have ALT>1.5 ULN at screening. The cut-off was chosen based on recommendation from US experts panel and ESPGHAN guidelines. However, while US and EU experts recommends ALT should be persistently elevated (>1.5 ULN on at least 2 occasions over 6 months), children were eligible in the study if ALT were >1.5 ULN at screening without confirmation required. Therefore, whether all paediatric patients included in this study were in active immune phase is questionable, all the more there was no biopsy requirement in this study.

The study population consists mostly in male (56%), mean age of 6 y.o (even though 63% were >6 y.o) of Asian origin (65%). Patients from US/Europe represents 45% of the study population and vertical transmission account for 73% of the source of contamination.

Contrarily to the study in HBV-infected adolescent, for which 85% of patients had prior exposure to anti-HBV agents, the majority of children were treatment naïve in this study. Of note, a significantly higher proportion of patients having received prior HBV treatment in the Placebo group (41.4% versus 16.7% in the Viread group). Moreover, all but 4 children had HBeAg+ disease. The MAH nevertheless applies for an unqualified (large) indication, which is acceptable when considering the efficacy of tenofovir in adults is regarded as established in both HBeAg+ and HBeAg- disease and prior exposure to anti-HBV agents did not impact response to TDF in adults and adolescents.

The primary objective of the study is to confirm the antiviral efficacy of Viread in children as a surrogate of the clinical benefit of the drug. Even though the association between viral suppression and reduction of the risk of progression of liver disease is less documented in paediatric patients, durable suppression of viral replication is acknowledged to be an appropriate marker in children.

As expected, a striking superiority of TDF over placebo was demonstrated on the primary endpoint (proportion of patients with HBV DNA <69 IU/ml, equivalent to <400 copies/ml at Week 48). Patients with abnormal ALT at baseline had notably greater rate of response as compared to patients who had normal ALT at baseline. Response rate was also higher in children aged >6 y.o as compared to younger children.

Biochemical response was also significantly higher in the TDF arm. However, as previously raised for adolescents and for adults, the superior virological potency of TDF did not translate into a superior rate of HBeAg seroconversion. As a matter of fact, the rate of HBeAg seroconversion was similar in the TDF and the placebo arm at W48, and was around 25%. A similar very low proportion of patients (3%) achieved HBsAg loss and no patients achieved HBs seroconversion.

Similarly to adults, TDF seems to have a high genetic barrier in children as no patients had TDF resistance-associated mutation through week 48 in this study.

Overall, the antiviral activity of TDF appears as high in children as in adolescents and in adults. Only 25% of TDF-treated patients achieved HBeAg seroconversion, a rate comparing similarly to the spontaneous rate of seroconversion reported in the placebo arm. This illustrates the need for a long-time treatment in the majority of children therefore calls for a cautious assessment of the benefit versus the risk of resistance and bone/renal toxicity in these young growing children.

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/safety and resistance of TDF in HBV-infected children.

2.4.3. Conclusions on the clinical efficacy

Even though TDF did not improve HBeAg seroconversion rate as compared to spontaneous seroconversion, a striking superiority of TDF over placebo was demonstrated on the primary endpoint (proportion of patients with HBV DNA <69 IU/ml, equivalent to <400 copies/ml) at Week 48. Virologic endpoint has been admitted as appropriate surrogate endpoint in HBV-infected adults but also in adolescent and younger children, for which Baraclude has already been approved for use in this population.

Patients with abnormal ALT at baseline had notably greater rate of response as compared to patients who had normal ALT at baseline. Response rate was also higher in children aged >6 y.o as compared to younger children.

2.5. Clinical safety

Safety data are presented for 89 subjects treated with TDF (n = 60) or Placebo (n = 29) included in study GS-US-174-0144 as of the data cut for the Week 48 interim analysis (10 August 2017), except bone mineral density (BMD) and clinical laboratory data, which were collected up to the data finalisation date (16 January 2018).

Patient exposure

Median (Q1, Q3) weeks of exposure to blinded study drug was 71.9 (59.8, 72.3) weeks for subjects in the TDF group and 71.9 (48.7, 72.1) weeks for subjects in the Placebo group. The majority of subjects in each treatment group had received blinded study drugs for ≥ 48 weeks at the time of the Week 48 data cut date (TDF 85.0%, 51 of 60 subjects; placebo 86.2%, 25 of 29 subjects).

Demographic and baseline characteristics were similar for the TDF and Placebo treatment groups. Overall, the median age was 6 years and the majority of subjects were male (56.2%), Asian (65.2%). The median body mass index (BMI) value at baseline was 15.5 kg/m^2 (range: 11.6 to 26.7 kg/m^2), and the median BMI Z-score was −0.12 (range: −5.57 to 2.97).

Adverse events

Overview of adverse events

Overall Summary of Adverse Events During the Double-Blind Treatment Phase

	TDF (N=60)	Placebo (N=29)
Subjects Experiencing Any		
Adverse Event	47 (78.3%)	17 (58.6%)
Grade 2, 3, or 4 Adverse Event	15 (25.0%)	5 (17.2%)
Grade 3 or 4 Adverse Event	4 (6.7%)	2 (6.9%)
Adverse Event Related to Study Drug	9 (15.0%)	4 (13.8%)
Grade 2, 3, or 4 Adverse Event Related to Study Drug	3 (5.0%)	2 (6.9%)
Grade 3 or 4 Adverse Event Related to Study Drug	1 (1.7%)	2 (6.9%)
Serious Adverse Event	10 (16.7%)	2 (6.9%)
Serious Adverse Event Related to Study Drug	3 (5.0%)	2 (6.9%)
Adverse Event Leading to Premature Discontinuation of Study Drug	0	2 (6.9%)
Adverse Event Leading to Temporary Interruption of Study Drug	1 (1.7%)	1 (3.4%)
Death	0	0

Most frequently reported AEs

Adverse Events Reported for at ≥ 5% of Subjects in Either Treatment Group During the Double-Blind Treatment Phase (Safety Analysis Set)

System Organ Class and Preferred Term	TDF (N=60)	Placebo (N=29)
Adverse Events Occurring in ≥ 5% of Subjects in Either Treatment Group	40 (66.7%)	16 (55.2%)
Gastrointestinal disorders	7 (11.7%)	2 (6.9%)
Abdominal pain	3 (5.0%)	1 (3.4%)
Diarrhoea	3 (5.0%)	1 (3.4%)
Vomiting	3 (5.0%)	1 (3.4%)
General disorders and administration site conditions	9 (15.0%)	2 (6.9%)
Pyrexia	9 (15.0%)	2 (6.9%)
Infections and infestations	26 (43.3%)	9 (31.0%)
Upper respiratory tract infection	8 (13.3%)	5 (17.2%)
Nasopharyngitis	9 (15.0%)	2 (6.9%)
Pharyngitis	3 (5.0%)	3 (10.3%)
Otitis media	3 (5.0%)	1 (3.4%)
Ear infection	3 (5.0%)	0
Tonsillitis	3 (5.0%)	0
Varicella	3 (5.0%)	0
Investigations	5 (8.3%)	4 (13.8%)
Alanine aminotransferase increased	5 (8.3%)	4 (13.8%)
Nervous system disorders	2 (3.3%)	2 (6.9%)
Headache	2 (3.3%)	2 (6.9%)
Respiratory, thoracic and mediastinal disorders	5 (8.3%)	1 (3.4%)
Cough	5 (8.3%)	1 (3.4%)
Skin and subcutaneous tissue disorders	0	2 (6.9%)
Dermatitis atopic	0	2 (6.9%)

Drug-related AEs

Nine subjects (15.0%) in the TDF group and 4 subjects (13.8%) in the Placebo group had AEs that were assessed as related to study drug by the investigator. The only treatment-related AE that was

reported for > 1 subject in either treatment group was increased ALT: 4 subjects (6.7%) in the TDF group and 2 subjects (6.9%) in the Placebo group.

Serious adverse event / deaths

No deaths had been reported at the time of the interim analysis.

A total of 16.7% of subjects in the TDF group and 6.9% in the Placebo group had an SAE. The only SAE reported for > 1 subject in either treatment group was ALT increased (4 subjects in the TDF group and 1 subject in the Placebo group).

Three SAEs in the TDF group (ALT increased) and one SAE in the placebo group (hypoglycaemia) were considered as related to study drug by the investigator.

Adverse events of specific interest

Renal Safety

Renal adverse events

Two subjects both in the TDF group experienced AEs under the SOC Renal and urinary disorders, one 5-year-old Asian male patient had Grade1 AEs of hydronephrosis and pelvi-ureteric obstruction and one 3-year-old Asian male had a non-serious Grade 1 AE of dysuria. None of them were considered as related to study drug by the investigator.

Serum creatinine

At baseline, serum creatinine levels were comparable between TDF and placebo arms. Slight increases from baseline were reported in both treatment groups at week 48 of +0.05 (0.092) mg/dL in TDF group and +0.01 (0.082) mg/dL in placebo group.

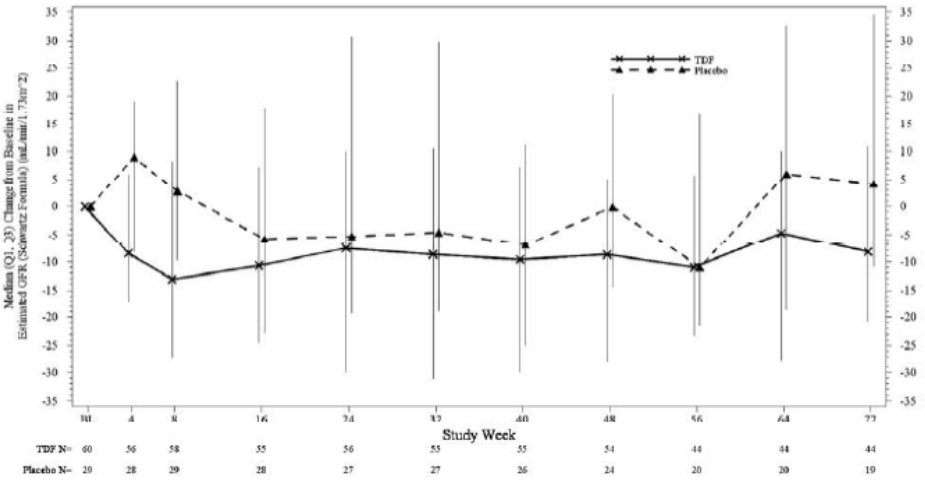
There were no confirmed increases from baseline in serum creatinine ≥ 0.3 mg/dL or decreases from baseline in serum phosphorus < 2 mg/dL

Estimated Glomerular Filtration Rate

At baseline, median eGFR was similar for the TDF and Placebo groups. As shown in the figure below, the median (Q1, Q3) decrease from baseline in eGFR at week 48 was significantly greater for the TDF group (−8.71 [−27.86, 4.99] mL/min/1.72 m^2) compared with the Placebo group (−0.09 [−14.44, 20.20] mL/min/1.72 m^2); p = 0.047.

Median (Q1, Q3) Change from Baseline in eGFR (Schwartz Formula) by Visit

(Observed Data), Safety Analysis



During the double-blind treatment phase, 2 subjects in the TDF group (3.3%) and 1 subject in the Placebo group (3.4%) had eGFR (CLcr; using the Schwartz formula) < 70 mL/min/1.73 m^2. The same Placebo subject also had an event of CLcr < 50 mL/min/1.73 m^2.

Bone safety

Bone-Related Adverse Events

Bone-related AEs were reported for 4 subjects (6.7%) in the TDF group and 1 subject (3.4%) in the Placebo group during the double-blind treatment phase:

A 6-year-old Asian male experienced a fracture of left arm) on Day 2 of double-blind treatment after experiencing a fall in the placebo group.

The four bone-related AEs in the TDF arm are presented thereafter:

- A -7-year-old Asian female receiving TDF experienced a Grade 1 non serious **pain in jaw** concurrent with Grade 1 headache on Day 356. The AEs were assessed as unrelated to study drug by the investigator; study drug was not interrupted or discontinued, and both jaw pain and headache were resolved on Day 371. At the end of double-blind, this subject demonstrated an overall decrease from baseline in spine BMD (−2.12%) and an overall increase from baseline in whole body BMD (+2.06%).Spine and whole body BMD Z scores were within the normal range for age at all time points evaluated.
- A 7-year-old Asia, male receiving TDF had a Grade 2, non-serious **tibia fracture** on Day 14. Whether the fracture was related to trauma was not reported The AE was assessed as unrelated to study drug by the investigator; study drug was not interrupted or discontinued, and the AE was considered resolved on Day 98. At the end of double-blind treatment, this subject demonstrated an overall increase from baseline in spine BMD (+6.75%) and an overall decrease from baseline in whole body BMD (−10.13%). Spine and whole body BMD Z scores were within the normal range for age at all time points evaluated.
- A 7-year-old Asian male in the TDF group, had Grade 1, non-serious **BMD decreased** on Day 170. The subject was treated with calcium phosphate. The AE was assessed as related to study drug by the investigator; study drug was not interrupted or discontinued. At the end of double-blind treatment, this subject demonstrated an overall increase in spine BMD (+8.82%) and an overall decrease in whole body BMD (−9.93%). This subject's spine BMD Z-scores were

within the normal range for age at all time points evaluated; however, whole body BMD Z-scores were below the normal range for age at every time point evaluated (range −2.86 to −3.15).

- A 9-year-old Asian male in the TDF group, had a Grade 1, non-serious AE of **osteopenia** reported on Day 169 that was assessed as related to study drug by the investigator. The subject was treated with risedronate sodium and calcium citrate with colecalciferol. Study drug was not interrupted or discontinued. Osteopenia was ongoing at the time of the Week 48 data cut. This subject also experienced a Grade 1, non-serious traumatic (per investigator report) **fracture of the sternum** on Day 836 during the open-label dosing period. The sternum fracture was assessed as unrelated to study drug by the investigator and was considered resolved on Day 867. At the end of double-blind treatment, this subject demonstrated overall increases from baseline in spine (+6.47%) and whole body (+7.77%) BMD. Spine and whole body BMD Z-scores were within the normal range for age for the duration of double-blind treatment, with the exception of the spine BMD Z-score at Week 24, which was below the normal range (−2.06)

Cumulative Incidence of ≥ 4% Decrease from Baseline in Spine and Whole Body Bone Mineral Density

The following table presents the cumulative incidence of ≥ 4% decreases from baseline in spine and whole body BMD at Weeks 24 and 48 by treatment group. At each time point evaluated, the proportion of subjects with ≥ 4% decreases in spine and whole body BMD was numerically higher for subjects in the TDF group compared with the Placebo group; the between-group differences were not statistically significant. With 1 exception (spine BMD for a TDF subject), subjects in both groups who experienced ≥ 4% decreases from baseline in BMD did so at Week 24

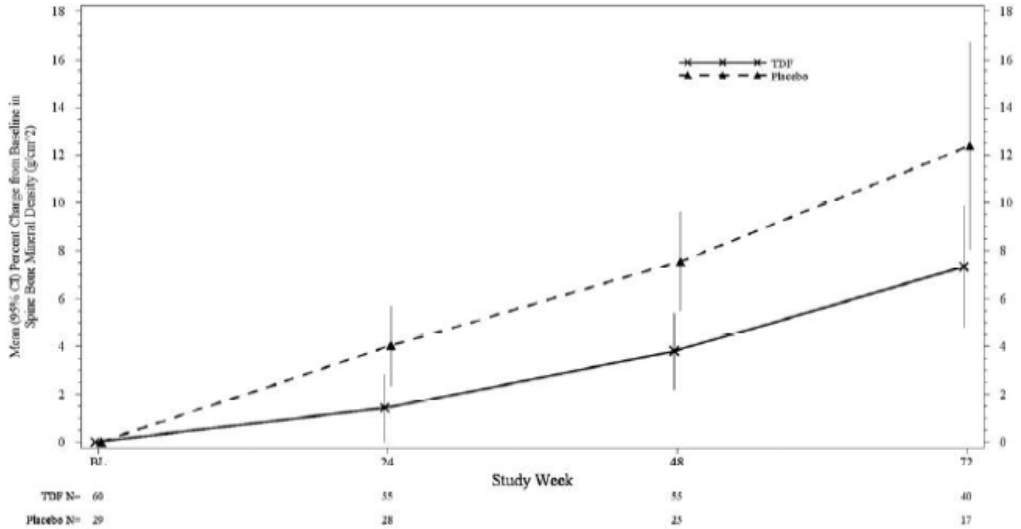
Cumulative Incidence of ≥ 4% Decrease from Baseline in Spine and total body Bone Mineral Density At Weeks 24 and 48 (Observed Data) (Spine and Whole Body DXA Analysis Sets)

	TDF (N = 60)	Placebo (N = 29)	Proportional Difference (95% CI)
Spine BMD, n/N (%)			
Week 24	10/60 (16.7%)	2/29 (6.9%)	9.8% (−7.7% to 23.2%)
Week 48	11/60 (18.3%)	2/29 (6.9%)	11.4% (−6.9% to 25.1%)
Whole Body BMD, n/N (%)			
Week 24	4/60 (6.7%)	0/29	6.7% (−6.9% to 16.5%)
Week 48	4/60 (6.7%)	0/29	6.7% (−6.9% to 16.5%)

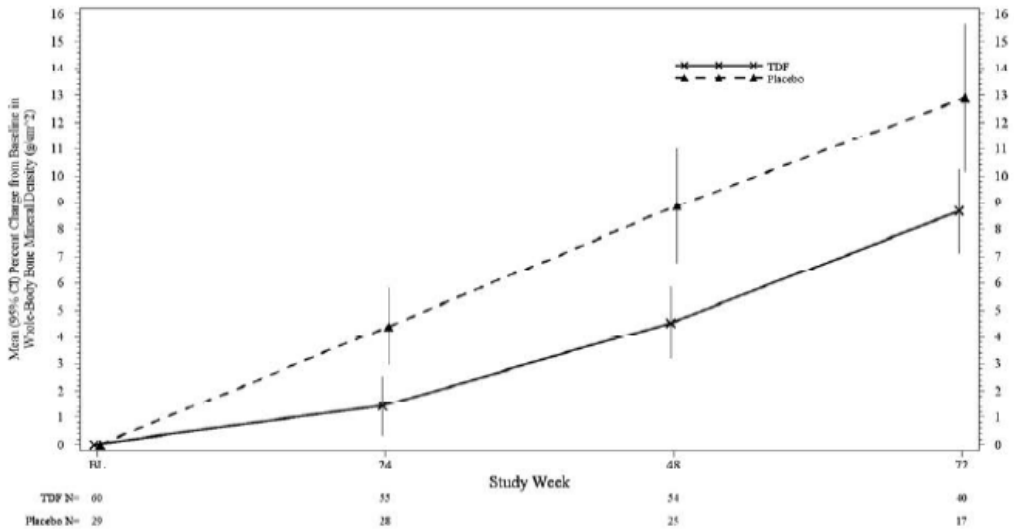
Change from Baseline in Spine and Whole Body Bone Mineral Density

The figures below display the mean percent changes from baseline in spine and whole body BMD, respectively, at Weeks 24 and 48, and 72 for each treatment group.

Means and 95% CIs of Percent Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data) (Spine DXA Analysis Set)



Mean and 95% CI of Percent Change from Baseline in Whole Body BMD by Visit (Observed Data) (Whole Body DXA Analysis Set)



Mean spine BMD values were similar for the TDF and Placebo groups at baseline, and spine BMD increased for both treatment groups during double-blind treatment. The increases in spine BMD were significantly smaller for the TDF group compared with the Placebo group at Weeks 24 and 48. The mean (SD) percent

increase from baseline in spine BMD at Week 48 was + 3.8% (5.91%) for the TDF group and + 7.6% (4.98%) for the Placebo group (p value = 0.007).

Mean whole body BMD values were similar for the TDF and Placebo groups at baseline, and whole body BMD increased from baseline for both treatment groups during double-blind treatment. The mean percent increases from baseline in whole body BMD were significantly smaller for the TDF group compared with the Placebo group at Weeks 24 and 48. The mean (SD) percent increase from baseline in spine BMD at Week 48 was + 4.5% (4.86%) for the TDF group and + 8.9% (5.12%) for the Placebo group (p value < 0.001).

Categorical Percent Change from Baseline in Spine and Whole Body Bone Mineral Density at Week 48 (Spine and Whole Body DXA Analysis Sets)

	TDF (N = 60)	Placebo (N = 29)	P-Value TDF vs Placebo
Spine BMD			
Percentage Change (%) at Week 48, n (%)			0.005
≤ −6% decrease	1/55 (1.8%)	0/25	
> −6% to ≤ −4% decrease	4/55 (7.3%)	0/25	
> −4% to ≤ −2% decrease	5/55 (9.1%)	0/25	
> −2% to ≤ 0% decrease	5/55 (9.1%)	1/25 (4.0%)	
> 0% to ≤ 2% increase	9/55 (16.4%)	0/25	
> 2% to ≤ 4% increase	7/55 (12.7%)	5/25 (20.0%)	
> 4% to ≤ 6% increase	2/55 (3.6%)	7/25 (28.0%)	
> 6% increase	22/55 (40.0%)	12/25 (48.0%)	
Missing	5	4	
Whole Body BMD			
Percentage Change (%) at Week 48, n (%)			
≤ −6% decrease	3/54 (5.6%)	0/25	0.023
> −6% to ≤ −4% decrease	0/54	0/25	
> −4% to ≤ −2% decrease	2/54 (3.7%)	0/25	
> −2% to ≤ 0% decrease	0/54	0/25	
> 0% to ≤ 2% increase	6/54 (11.1%)	1/25 (4.0%)	
> 2% to ≤ 4% increase	10/54 (18.5%)	3/25 (12.0%)	
> 4% to ≤ 6% increase	9/54 (16.7%)	4/25 (16.0%)	
> 6% increase	24/54 (44.4%)	17/25 (68.0%)	
Missing	6	4	

Spine BMD was calculated using the 'SpineTotalAdequate' region. Whole body BMD was calculated using the 'BodyTotalNoHead' region
The denominator for each visit was based on the number of subjects in the Safety Analysis Set with nonmissing BMD measurements at that visit.
Percent change was the change from baseline at a postbaseline visit divided by the baseline value * 100
Only subjects with nonmissing spine and whole body BMD at baseline were included in the spine and whole body DXA analysis sets, respectively.
P-values were based on the Cochran-Mantel-Haenszel test for ordinal data using the row mean scores differ statistic.

Change from Baseline in Spine and Whole Body Bone Mineral Density Z-Scores

The table below presents changes from baseline in BMD Z-scores at Week 48 for subjects with available DXA data

Change from Baseline in Spine and Whole Body Bone Mineral Density Z-Scores at Baseline and Week48 (Spine and Whole Body DXA Analysis Sets)

	TDF (N = 60)	Placebo (N = 29)
Spine BMD		
Baseline		
N	48	23
Mean (SD)	0.02 (0.977)	−0.29 (1.229)
Median (Q1, Q3)	−0.28 (−0.73, 0.60)	−0.10 (−0.90, 0.48)
Change from Baseline at Week 48		
N	45	20
Mean (SD)	−0.12 (0.411)	0.14 (0.330)
Median (Q1, Q3)	−0.12 (−0.49, 0.17)	0.11 (−0.06, 0.33)
Whole Body BMD		
Baseline		
N	17	12
Mean (SD)	0.11 (0.743)	−0.05 (1.497)
Median (Q1, Q3)	0.07 (−0.36, 0.68)	0.40 (−0.51, 0.83)

	TDF (N = 60)	Placebo (N = 29)
Change from Baseline at Week 48		
N	16	10
Mean (SD)	−0.18 (0.334)	0.22 (0.446)
Median (Q1, Q3)	−0.22 (−0.41, 0.05)	0.07 (−0.15, 0.56)

BMD = bone mineral density
Spine BMD was calculated using the 'SpineTotalAdequate' region.
Whole body BMD was calculated using the 'BodyTotalNoHead' region
BMD measurements and corresponding Z-scores were corrected for longitudinal changes in the scanner calibration.
Missing Z-scores were either due to data not available in the manufacturer's references tables, or subjects were analyzed on an older DPX-NT machine which performs analysis using the BASIC rather than the ENHANCED mode.
Only subjects with nonmissing spine and whole body BMD at baseline were included in the spine and whole body DXA analysis sets, respectively.

In the TDF group, based on the observed data, none of the evaluable subjects had a spine or whole body BMD Z-score < −2 at baseline, and no subjects had a decrease in spine or whole body BMD Z-score to < −2 at Week 48. Two subjects with whole body Z-scores < −2 at Week 48 were captured as "missing" in the shift tables, as they did not have whole body Z-scores at baseline. In the Placebo group, 2 subjects had a spine BMD Z-score < −2 and 1 subject had a whole body BMD Z-score < −2 at baseline. BMD Z-score categories improved for these subjects during treatment.

Biochemical Bone Markers

The below table presents the percent change from baseline in biochemical bone markers at Week 48.

Median (Q1, Q3) Percent Change from Baseline in Laboratory Parameters Related to Bone and Renal Function at Week 48 (Safety Analysis Sets)

Bone Laboratory Parameter	TDF (N = 60)		Placebo (N = 29)		P-Value
	N	Median (Q1, Q3)	N	Median (Q1, Q3)	
Serum					
Fasting Creatinine (mg/dL)					
Baseline	52	0.37 (0.32, 0.44)	27	0.43 (0.34, 0.48)	0.078
% Change at Week 48	39	16.13 (2.86, 26.42)	19	4.55 (-4.65, 17.65)	0.082
Fasting Phosphate(mg/dL)					
Baseline	52	5.0 (4.6, 5.3)	27	5.2 (4.6, 5.5)	0.462
% Change at Week 48	39	3.8 (-2.1, 11.4)	19	-4.3 (-10.5, 0)	**0.008**
C-Telopeptide (ng/mL)					
Baseline	58	1.46 (1.09, 1.75)	29	1.39 (1.14, 1.63)	0.682
% Change at Week 48	46	13.58 (-8.27, 36.98)	21	-7.79 (-25.44, 8.00)	**0.010**
Osteocalcin (ng/mL)					
Baseline	59	71.79 (58.47, 91.88)	28	81.15 (61.50, 93.77)	0.605
% Change at Week 48	45	23.08 (-4.94, 40.50)	19	6.21 (-24.61, 20.58)	0.058

Bone Laboratory Parameter	TDF (N = 60)		Placebo (N = 29)		P-Value
	N	Median (Q1, Q3)	N	Median (Q1, Q3)	
bsAP (µg/L)					
Baseline	60	80.30 (63.60, 108.69)	29	79.42 (56.93, 100.91)	0.503
% Change at Week 48	56	-14.44 (-26.56, 5.69)	23	-5.63 (-24.66, 19.45)	0.308
Parathyroid hormone (pg/mL)					
Baseline	60	26.6 (19.3, 34.8)	29	30.8 (25.0, 43.6)	0.065
% Change at Week 48	50	3.4 (-22.1, 50.6)	22	16.1 (-23.4, 53.8)	0.976
25-OH Vitamin D (ng/mL)					
Baseline	60	20.0 (14.8, 25.6)	29	18.4 (14.0, 28.8)	0.593
% Change at Week 48	55	52.9 (15.6, 73.8)	25	16.0 (6.9, 35.7)	**0.004**
1,25-OH Vitamin D (ng/mL)					
Baseline	58	69.8 (53.1, 83.5)	29	68.1 (53.1, 79.6)	0.702
% Change at Week 48	52	9.7 (-17.0, 41.7)	22	2.2 (-20.4, 54.8)	0.727
Urine					
Bicarbonate (mmol/L)					
Baseline	60	4 (4, 4)	29	4 (4, 4)	0.684
% Change at Week 48	54	0 (0, 0)	25	0 (0, 0)	0.736
Creatinine (mg/dL)					
Baseline	60	69 (48, 109)	29	77 (46, 135)	0.847
% Change at Week 48	54	7 (−35, 71)	25	−1 (−32, 48)	0.477
Phosphate (mg/dL)					
Baseline	60	58.6 (29.5, 103.2)	29	66.9 (26.0, 106.4)	0.882
% Change at Week 48	54	−11.3 (−38.3, 80.5)	25	−20.0 (−64.1, 100.4)	0.426
N-Telopeptide (nmol/BCE/L)					
Baseline	60	2865.1 (1341.2, 5696.6)	29	3850.5 (1125.0, 5530.5)	0.927
% Change at Week 48	54	16.4 (-31.0, 158.5)	25	-9.2 (-46.1, 19.5)	0.074
TmP/GFR (mg/dL)					
Baseline	49	5.59 (5.10, 6.06)	27	5.42 (5.12, 6.52)	0.896
% Change at Week 48	36	2.41 (-6.56, 12.27)	17	-4.51 (-15.26, 6.68)	0.219

bsAP = bone-specific alkaline phosphatase; TmP/GFR = ratio of renal tubular reabsorption of phosphate/eGFR

Relationship between Bone Mineral Density and Renal Laboratory Parameters

To address a post-marketing requirement of the FDA relating to the further investigation whether changes in bone mineral density observed with TDF are secondary to renal phosphate excretion or effects

on bone, the MAH evaluated in this study the relationship between select renal biomarkers (i.e serum and urine creatinine and phosphate (fasting and non-fasting); calculated eGFR (CLcr) by the Schwartz formula and TmP to eGFR and changes from baseline in spine and whole body BMD at Week 48.

Cross-sectional correlations between renal parameters and spine and whole body BMD at baseline and Week 48 were also evaluated. Both analyses were supplemented with exploratory tests for interactions of treatment and renal parameters with spine or whole body BMD as response.

Change from baseline in TmP/GFR and change from baseline in fasting serum phosphate were both negatively associated with percent change from baseline in whole body BMD at Week 48, both across and within treatment groups. Treatment (TDF or placebo) had no statistically significant effect on the magnitude of these associations. No other consistently significant associations or interactions with treatment were observed for change from baseline in renal parameters and percent change from baseline in spine or whole body BMD at Week 48.

Serum creatinine was positively associated with spine and whole body BMD at baseline and Week 48 when the analysis included all subjects (i.e., across groups) and when the analysis was conducted by treatment group. Treatment with TDF decreased the magnitude of the positive association between serum creatinine and spine and whole body BMD at Week 48 compared with placebo.

The MAH concludes that the clinical relevance of these observations is unclear. During 48 weeks of treatment with TDF, changes in BMD did not appear to be clinically related to changes in renal parameters in this population of paediatric CHB subjects.

Laboratory findings

A total of 58 subjects in the TDF group (96.7%) and 29 subjects in the Placebo group (100.0%) had at least 1 graded laboratory abnormality. For the majority of subjects in each treatment group, the highest grade laboratory abnormality was Grade 1 (mild) or Grade 2 (moderate): 55.0% of subjects in the TDF group and 55.2% of subjects in the Placebo group. Grade 3 (severe) was the highest grade laboratory abnormality for 19.0% of subjects in the TDF group and 24.1% of subjects in the Placebo group. Seven subjects (12.1%) in the TDF group and 4 subjects (13.8%) in the Placebo group had a Grade 4 (life threatening) laboratory abnormality.

The following table presents Grade 3 and 4 chemistry and coagulation laboratory abnormalities that were reported for > 5% of subjects in either treatment group.

Grade 3 or 4 Chemistry and Coagulation Laboratory Abnormalities Reported for > 5% of subjects in Either Treatment Group (Safety Analysis Set)

	TDF (N=60)	Placebo (N=29)
Chemistry		
Alanine Aminotransferase (U/L) (increased)	58	29
Grade 3	9 (15.5%)	4 (13.8%)
Grade 4	5 (8.6%)	2 (6.9%)
Amylase (U/L)	58	29
Grade 3	0	2 (6.9%)
Grade 4	0	0
Aspartate Aminotransferase (U/L)	58	29
Grade 3	3 (5.2%)	3 (10.3%)
Grade 4	1 (1.7%)	0
Potassium (mEq/L) - Hyper	58	29
Grade 3	0	0
Grade 4	0	2 (6.9%)
Coagulation		
Prothrombin Time (sec)	39	23
Grade 3	2 (5.1%)	0
Grade 4	0	0

The denominator for percentages was the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value for each test.
Severity grades were defined by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1 (01 April 2015).
For maximum postbaseline toxicity grade, the most severe graded abnormality from all tests was counted for each subject.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a subject.
Treatment-emergent laboratory abnormalities during the double-blind phase were defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the earlier of the last dose date of blinded study drug + 3 days or first dose date of open-label study drug.

ALT flares and exacerbation of hepatitis

ALT flare and exacerbation of hepatitis were evaluated during the double-blind treatment phase according to the following criteria:

- ALT > 2 x study baseline and > 10 x the upper limit of normal (ULN), with or without associated symptoms
- Confirmed ALT elevation (defined as 1 grade increase or 2 changes outside of the normal range in other laboratory parameters suggestive of worsening hepatic function (i.e., abnormal prothrombin time ≥ 2 seconds greater than study baseline; INR ≥ 0.5 over study baseline, abnormal serum albumin ≥ 1 g/dL below study baseline, or elevated serum lactate ≥ 2 x ULN).

☐ previous v

During double-blind treatment, 5 subjects (8.3%) in the TDF group and 1 subject (3.4%) in the Placebo group (none of whom had prior HBV treatment experience) met the first criterion for ALT flare and exacerbation of hepatitis (i.e., ALT > 2 x study baseline and > 10 x ULN, with or without associated symptoms). No subjects in either group met Criterion 2 for ALT flare a,d exacerbation of hepatitis (second bullet).

The MAH states that all of the above five subjects with ALT flares had graded elevations in ALT at baseline. Total bilirubin values remained normal for all subjects with ALT flare and no subjects with ALT flare had increases in HBV DNA; and all remained HBsAg positive.

No subjects in the TDF group experienced off-treatment ALT flare or exacerbation of hepatitis.

Body Weight and Height

Body weight Z-scores were similar for the TDF and Placebo groups at baseline. During double-blind treatment, Z-scores decreased slightly for the TDF group and increased slightly for the Placebo group, with mean (SD) changes of −0.061 (0.3876) for the TDF group and +0.259 (0.5080) for the Placebo group at Week 48 (p = 0.005).

Height Z-scores were similar for the TDF and Placebo groups at baseline. During double-blind treatment, Z-scores decreased slightly for both groups, with mean (SD) changes of −0.171 (0.4048) for the TDF group and −0.115 (0.4408) for the Placebo group at Week 48.

Tanner staging

As expected for the study population of 2- to 12-year-olds, the majority of males and females in both treatment groups were categorised at Tanner Stage 1(prepubertal) at enrolment for each category (male genitalia size and lack of pubic hair and female breast size and lack of pubic hair), and most of the subjects remained at Tanner Stage 1 at Week 48.

Discontinuation due to adverse events

No subjects prematurely discontinued TDF due to AEs. Two subjects prematurely discontinued placebo due to AEs: 1 subject due to hypoglycaemia, and 1 subject due to increased ALT

Post-marketing experience

No post-marketing data are submitted with this application.

2.5.1. Discussion on clinical safety

Safety data derived from this study pertains to 60 TDF treated subjects with HBV infection aged from 2 to 12 years of age and to 29 subjects of the same age category having received placebo in a double blind manner for 48 weeks.

The safety profile of TDF in this study is overall similar to what was reported so far in already approved paediatric indication, i.e. in HBV-infected adolescents aged from 12 to < 18 years and in HIV-1 infected children aged from 2 to < 18 years. The main safety concerns are those, already identified for TDF, namely its impact on renal function and bone loss.

Regarding renal safety, as already seen previously with TDF, an impact of TDF on creatinine clearance is observed. A greater decrease in mean eGFR from baseline was observed at week 48 in TDF-treated patients (-8.7mL/min/1.73m^2) compared with those who received placebo (-0.09 mL/min/1.73m^2). Two TDF-treated subjects experienced eGFR below 70mL/min/1.73m^2 during the double blind period but no information has been provided by the MAH, and whether additional subjects had lesser decrease i.e. comprised between 70 and 90mL/min/1.73m^2. No serious renal AEs related to TDF have been reported in this study and no AEs of proximal renal tubulopathy were notified during the study. As a reminder, decrease was more pronounced in the youngest children in study 352 in HIV indication.

Regarding bone safety, two AEs of bone density decreased and osteopenia have been considered as related to TDF by the investigator. However, none were classified serious and none led to interruption or discontinuation to study drug. While spine and total BMD increased from baseline to week 48 in both

treatment groups, smaller percent increases were reported for TDF group compared with placebo group. TDF-treated subjects also had higher decrease in mean BMD Z-scores than placebo-treated subjects at week 48, even though these Z-score remained within normal values for this patient population throughout the study. Overall, these changes in Z-scores remain limited and of unclear significance. More worrisome is the higher cumulative incidence of decrease > 4% in spine and total body BMD reported in TDF group (18.3% and 6.7% respectively) versus placebo group (6.9% versus 0 respectively) even the difference was reported to be not statistically significant.

As previously and extensively discussed at the time of the MAA Application for the HIV-1 indication in paediatric population, these data also raise concerns on the long term impact of TDF in bone metabolism in this vulnerable population of patients of active modelling process, triggering the input of a SAG. Taking into the SAG advice, the extension of indication of Viread in HIV-1 infected children > 2 years of age was approved by the CHMP taking into account notably the fact that there is no clear correlation between BMD decrease and clinical event and that the long term bone effects may thus be considered as theoretical while there are established benefits in this population in need of treatment. In parallel the SmPC of Viread was revised to include warnings to alert physicians, notably on the uncertainties on the long term effect of bone and renal toxicity.

In September, the provision of the long term 336 week data from study 352 in HIV-1infected children was assessed at CHMP level. Data are very limited to assess long term bone safety as only few patients were evaluated but the available data were overall rather reassuring showing that decreases in BMD Z-score (spine, Total Body and Total Body Less Head) observed during the first years of therapy were not progressive over time and seemed to be stabilised. Concerns were rather raised on the evolution of patients' renal function over time, however difficulties in the interpretation of evolution of eGFR in growing children with the Schwartz formulae were acknowledged. Finally, section 4.8 was updated to provide safety information on children who achieved eGFR < 70mL/min/1.73m^2 while on long term TDF therapy.

More recently, the final results of the DUS GS-EU-174-0224 to assess physicians prescribing Viread to paediatric HBV infected patients in the EU were following the recommendations in the Viread SmPC and renal educational brochures were assessed within the type II variation II/188. Despite a low response rate, and acknowledged difficulties for interpreting and generalising study results, the final data show that a majority of physicians adhere to SmPC recommendations with regard to regular monitoring for renal and bone toxicity and consultation with specialists in case where renal or bone abnormalities are observed.

Given the above considerations, the current VIREAD SmPC and the current renal educational that have been maintained in the RMP in the perspective of this indication extension are considered sufficiently informative to alert physicians on the impact of TDF on bone and renal function and to provide appropriate recommendations for the management of these safety risks.

The final week 192 data of the current study in HBV infected children will have to be provided to further substantiate the long term renal and bone safety profile of TDF in this vulnerable population of patients.

2.5.2. Conclusions on clinical safety

The safety profile of TDF in HBV infected children aged 2 to < 12 years derived from the 48 week data of study GS-US-174-0144 is overall similar to what have been previously reported in the already approved paediatric indication of TDF. Renal and bone safety remain the most salient safety issues for TDF. The long term available study results in HIV-1 infected children recently assessed at CHMP level could not allow to fully dispel the concerns as regards the uncertainties on the long term impact of TDF on renal

function and bone mineralisation in the paediatric population, due to difficulties in interpretation and low effective. This long term concern still remain.

The Viread SmPC is currently reflecting these uncertainties and provides relevant recommendations for managing the renal and bone risks. The RMP still plans renal educational brochure for paediatric population as risk minimisation measures and includes the provision of final week 192 data from study GS-US-174-0144 to further help at substantiating the long term safety impact of TDF in HBV infected children.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 24 is acceptable

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 24 with the following content:

Safety concerns

Within the procedure, Safety in Children as missing information was replaced by “long-term safety in paediatric patients (2 to <12 years of age) “

The updated table is as follows:

Important Identified Risks	Renal toxicity
	Bone events due to proximal renal tubulopathy/loss of bone mineral density
Important Potential Risks	None
Missing Information	**Long-term safety in HBV infected children aged 2 to < 12 years**
	Safety in pregnancy and lactation
	Safety in patients with renal impairment

Pharmacovigilance plan

The below study will collect information on long-term safety in HBV infected children aged 2 to < 12 years.

Category 3 - Required additional pharmacovigilance activities				
A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection GS-US-174-0144 Ongoing	To evaluate the antiviral efficacy, safety and tolerability of TDF versus placebo in pediatric patients with CHB infection	*Important identified risk*: Bone events due to proximal renal tubulopathy/ loss of BMD ***Missing information*: Long-term safety in HBV infected children aged 2 to < 12 years**	Final report	Anticipated Q4 2020

Risk minimisation measures

The additional risk minimisation activities for paediatric patients (HIV and HBV paediatric educational guides) are maintained.

The changes in the Summary Table of Pharmacovigilance and Risk Minimisation Activities are the following:

Important identified risk(s)		
Renal toxicity	Routine risk communication: SmPC sections 4.2, 4.4, 4.5 and 4.8 PL sections: 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4: Recommendations for renal function monitoring and guidance on when to interrupt or discontinue TDF SmPC section 4.4: Guidance that, for pediatric patients, a multidisciplinary approach is recommended to adequately weigh the benefit/risk balance of treatment, decide the appropriate monitoring and consider the need for supplementation	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Targeted follow-up questionnaire for renal events including tubulopathy Additional pharmacovigilance activities: Post-authorization safety study of a representative sample of HBV infected adolescent patients (GS-EU-174-1403) Drug utilization study in HBV infected pediatric patients (GS-EU-174-0224) Monitoring of reversibility of renal tubulopathy in clinical trials

	Additional risk minimization measures: **Healthcare professional educational guides for prescribers of HIV-1 or HBV infected pediatric patients**	
Missing information		
Long-term safety in HBV infected children aged 2 to < 12 years	**Routine risk communication:** **SmPC sections 4.2 and 4.4** **PL section 2**	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** **None** **Additional pharmacovigilance activities:** **Clinical study in HBV infected children aged 2 to < 12 years (GS-US-174-0144)**

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC for Viread 123 mg, 163 mg and 204 mg film-coated tablets and for Viread granules 33 mg/g have been updated to reflect the indication of CHB in paediatric patients. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have also been updated for Viread 245 mg. The Package Leaflet (PL) has been updated accordingly.

In addition, a discrepancy in the PI regarding the recommendation pertaining to pregnancy was corrected, by aligning the PL wording with that of the SmPC.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Readability testing (user consultation) for Viread 123 mg, 163 mg, 204 mg and 245 mg tablets and Viread 33 mg/g oral granules has previously been conducted using the English language version of the package leaflets by Consumation Consumer Information Design. The proposed updates to the package leaflets to extend the indication to include paediatric patients aged 2 to <12 years of age do not alter the readability of the leaflets and therefore additional testing is not considered necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Recent reports estimate that 250 to 350 million individuals were living with HBV (i.e., hepatitis B surface antigen [HBsAg] positive) in 2010, representing a worldwide prevalence of 3.6%, with considerable geographic variability. In 2013, an estimated 686,000 deaths were due to HBV infection and associated complications, placing it among the top 20 causes of mortality worldwide.

Universal HBV vaccination and blood-donor screening have markedly reduced the rate of chronic infection including in Europe. However, a significant number of children are still infected each year. In Europe, prevalence remains elevated in some European areas (notably in Eastern and Southern Europe) and paediatricians are confronted with an increasing number of children adopted from higher prevalence countries.

Following acute HBV infection, the risk of developing chronic infection varies inversely with age. Chronic HBV infection occurs among about 90% of infants infected at birth, 25 to 50% of children infected at 1 to 5 years of age, and about 5 to 10% of persons infected as teens and adults.

Although most children with chronic HBV infection are asymptomatic and severe liver disease during childhood is rare, children are at risk for developing serious complications later in life, notably cirrhosis and HCC. In addition, HBV carriers can transmit the disease for many years.

Chronic HBV infection is characterised by different phases of infection:

1) the immune tolerant phase, with markedly elevated levels of HBV DNA, detectable HBsAg and HBV e antigen (HBeAg), and normal or low levels of alanine aminotransferase (ALT);

2) the immune active phase, characterised by elevated levels of HBV DNA with persistently elevated ALT, an indicator of ongoing liver damage;

3) the inactive HBsAg carrier phase, with undetectable or low levels of HBV DNA and the presence of anti-HBe antibodies; and

4) the reactivation phase, characterised by HBeAg seronegativity (and anti-HBe seropositivity) but with elevated HBV DNA levels and abnormal ALT.

Management of CHB in children and adolescents is evolving and optimal treatment is not well established. The current consensus is that no treatment is indicated for HBV-infected children in the immune tolerant or inactive HBsAg carrier phases (AASLD 2018, EASL 2017). However, treatment may be warranted for children in the immune active or reactivation phases to suppress viral replication and prevent complications and poor clinical outcomes, including cirrhosis, decompensated liver disease, and HCC. Indeed, studies in adults suggest that a prolonged period of time in the immune active phase is associated with an increased risk of cirrhosis and HCC.

As mentioned in the ESPGHAN clinical practice guidelines (Sokal et al. J of Heatology 2013), for all patients, the ideal end point of treatment is sustained HBsAg clearance, as it stops disease progression and reduces the risk of HCC, although it occurs in a minority of treated subjects. When HBsAg seroclearance is not achieved, sustained off-therapy suppression of viral replication (undetectable HBV DNA levels with a sensitive real time polymerase chain reaction assay), associated with durable anti-HBe seroconversion in originally HBeAg-positive patients, is a good end point, being associated with improved prognosis, including decreased risk of HCC. In the absence of off-therapy viral suppression, undetectable HBV DNA under long-term antiviral therapy (maintained virological response) is the next desirable end point. Reduction of viremia levels leads to decreased liver inflammation and subsequent normalisation of ALT levels, reducing the risk of disease progression.

3.1.1. Available therapies and unmet medical need

Currently, there are two main treatment options for CHB patients: treatment with oral antiviral agents or with IFNa, currently pegylated interferon alfa-2a. The rationale for a PegIFNa based approach is to induce long-term immunological control with a finite duration treatment (EASL 2017); however, pegIFN is associated with important safety and tolerability issues. Entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are potent inhibitors of HBV replication with a high barrier to resistance, and these 3 agents are recommended as preferred monotherapies for CHB in adults regardless of the severity of liver disease (EASL 2017).

Entecavir, TDF and TAF as well as peginterferon alfa-2a are currently approved for use in CHB-infected adolescents in Europe. In children, only entecavir is approved for paediatric patients (from 2 years of age) and Pegasys (from 3 years of age). A study is ongoing with TAF in paediatric patients <12 y.o.

Thus, TDF represents a new treatment option for children 2 to < 12 years old. Given its potent antiviral activity in CHB, including patients with resistance to other oral antivirals, such as LAM and ETV, TDF would become a standard of care (with entecavir) for the treatment of chronic hepatitis B in children in need for treatment. To be noted that entecavir is only approved for use in nucleoside naive children while TDF could be use also in treatment-experienced children.

3.1.2. Main clinical studies

The application relies on the submission of the 48 weeks results of study GS-US-174-0144. The dose used in this study was the dose previously approved for use in HIV-infected children.

This study is an ongoing Phase 3, randomised, double-blind, multicentre study that is evaluating the antiviral efficacy, safety and tolerability of TDF versus Placebo in paediatric patients aged 2 to <12 years with chronic hepatitis B infection.

The study was initiated in December 2012 and was primarily conducted in Asia and North America/Europe (the EU centres being in Romania and Bulgaria). At the time of the study initiation, entecavir was not yet approved in children and the study was designed as a placebo controlled study. The study therefore compared TDF and placebo over 48 weeks, at which time children from the placebo arm could switch to open-label TDF (until Week 192).

3.2. Favourable effects

As expected, a striking superiority of TDF over placebo was demonstrated on the primary endpoint (proportion of patients with HBV DNA <69 IU/ml, equivalent to <400 copies/ml at Week 48): 76.7% vs 6.9%; p<0.001.

Biochemical response was also significantly higher in the TDF arm: 65.5% vs 14.8% at Week 48 by central laboratory criteria, p < 0.001; 51.7% vs 17.9% by AASLD criterion, p = 0.002.

Similarly to adults, TDF seems to have a high genetic barrier in children as no patients had TDF resistance-associated mutation through week 48 in this study.

3.3. Uncertainties and limitations about favourable effects

To select a paediatric population with immune-active disease, children should have ALT>1.5 ULN at screening. The cut-off was chosen based on recommendation from US experts panel and ESPGHAN guidelines. However, while US and EU experts recommends ALT should be persistently elevated (>1.5 ULN on at least 2 occasions over 6 months), children were eligible in the study if ALT were >1.5 ULN at screening without confirmation required. Therefore, whether all paediatric patients included in this study were in active immune phase is questionable, all the more there was no biopsy requirement in this study.

Contrarily to the study in HBV-infected adolescent, for which 85% of patients had prior exposure to anti-HBV agents, the majority of children were treatment naïve in this study. Of note, a significantly higher proportion of patients having received prior HBV treatment in the Placebo group (41.4% versus 16.7% in the Viread group). Moreover, all but 4 children had HBeAg+ disease. Although sample size were small, treatment response to TDF did not differ according to prior treatment status or HBeAg status in this study. The MAH applies for an unqualified (large) indication, which is acceptable when considering the efficacy of tenofovir in adults is regarded as established in both HBeAg+ and HBeAg- disease and prior exposure to anti-HBV agents did not impact response to TDF in adults and adolescents.

The primary objective of the study is to confirm the antiviral efficacy of Viread in children as a surrogate of the clinical benefit of the drug. The association between viral suppression and reduction of the risk of progression of liver disease is less documented in paediatric patients. Nevertheless, durable suppression of viral replication is acknowledged to be an appropriate marker in children.

As previously raised for adolescents and for adults, the superior virological potency of TDF did not translate into a superior rate of HBeAg seroconversion. As a matter of fact, the rate of HBeAg seroconversion was similar in the TDF and the placebo arm at W48, and was around 25%. This implies there is a need for long-term treatment for a majority of children.

A similar very low proportion of patients (3%) achieved HBsAg loss and no patients achieved HBs seroconversion.

Patients with high ALT level (>2N) at baseline had notably greater rate of response as compared to patients who had ALT <2 N at baseline. The difference is no longer observed when cut-off for ALT is 1.5 N. Response rate was higher in children aged >6 y.o as compared to younger children (15/22, 68% versus 34/38, 89.5%; updated analysis). While treatment response in subgroups combining ALT and age categories were provided, those results are difficult to interpret given the small sample size and no clear trend can be retrieved from those data.

A finding for a numerically lower response rate in genotype D, most common in Europe, as compared to other genotypes (54% versus 75-100%) was also found.

3.4. Unfavourable effects

Safety data derived from this study pertains to 60 TDF treated subjects with HBV infection aged from 2 to 12 years of age and to 29 subjects of the same age category having received placebo in a double blind manner for 48 weeks.

The safety profile of TDF in this study is overall similar to what was reported so far in already approved paediatric indication, i.e in HBV-infected adolescents aged from 12 to < 18 years and in HIV-1 infected children aged from 2 to < 18 years. The main safety concerns are those, already identified for TDF, namely its impact on renal function and bone loss.

Regarding renal safety, as already seen previously with TDF, an impact of TDF on creatinine clearance is observed. A greater decrease in mean eGFR from baseline was observed at week 48 in TDF-treated patients (-8.7mL/min/1.73m^2) compared with those who received placebo (-0.09 mL/min/1.73m^2). The magnitude of the decrease in TDF-treated children was more pronounced in the youngest children the decrease in renal function with TDF therapy was more pronounced in the youngest category (-17.97 mL/min /1.73m^2 for subjects between 2 and 6 years of age versus -5.60 mL/min/1.73m^2 for subjects between 6 and 12 years of age at week 48). Similar differential was previously reported in the study 352 in HIV infected children. Three TDF-treated subjects experienced eGFR below 70mL/min/1.73m^2 during the double blind period but the decrease in eGFR in these patients was transient and not associated with laboratory abnormalities that could speak in favour of tubular damage. No serious renal AEs related to TDF have been reported in this study and no AEs of proximal renal tubulopathy were notified during the study nor infraclinical PRT.

Regarding bone safety, two AEs of bone density decreased and osteopenia have been considered as related to TDF by the investigator. However, none were classified serious and none led to interruption or discontinuation to study drug. While spine and total BMD increased from baseline to week 48 in both treatment groups, smaller percent increases were consistently reported for TDF group compared with placebo group whatever the age category (2 to <6 years or 6 to < 12 years). For both spine and whole body BMD the magnitude of the mean percentage increases in the TDF and Placebo groups was greater in the younger compared with the older age group.

TDF-treated subjects also had higher decrease in mean BMD Z-scores than placebo-treated subjects at week 48, even though these Z-score remained within normal values for this patient population throughout the study. Overall, these changes in Z-scores remain limited and of unclear significance. More worrisome is the higher cumulative incidence of decrease > 4% in spine and total body BMD reported in TDF group (18.3% and 6.7% respectively) versus placebo group (6.9% versus 0 respectively) even the difference was reported to be not statistically significant.

3.5. Uncertainties and limitations about unfavourable effects

Renal and bone safety remain the most salient safety issues for TDF. The long term available study results in HIV-1 infected children recently assessed at CHMP level could not allow to fully dispel the concerns as regards the uncertainties on the long term impact of TDF on renal function and bone mineralisation in the paediatric population, due to difficulties in interpretation and low effective. The potential long-term toxicities of Viread in paediatric patients are not known.

Finally, unnecessary early therapy with nucleoside analog can result in development of resistance, thereby limiting treatment option later in life.

3.6. Benefit-risk assessment and discussion

Although most children with chronic HBV infection are asymptomatic and severe liver disease during childhood is rare, it is acknowledged that some children are at risk for developing serious complications later in life, notably cirrhosis and HCC. Thus, current clinical guidelines consider that no treatment is indicated for HBV-infected children in the immune tolerant or inactive HBsAg carrier phases but treatment may be warranted for children in the immune active or reactivation phases to suppress viral replication and prevent complications and poor clinical outcomes, including cirrhosis, decompensated liver disease, and HCC.

This approach has already been discussed and agreed upon at the time of the approval of entecavir in paediatric patients from 2 to <18 years of age. Considering that entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are recommended as preferred monotherapies for CHB in adults, there is no obvious reason that this will not be the case in paediatric patients. To be noted that use of TAF in paediatric patients <12 y.o. is currently explored in an ongoing study.

Moreover, while entecavir is only approved for use in nucleoside naive children, TDF could be use also in treatment-experienced children given its antiviral activity is maintained in patients with resistance to other oral antivirals, such as LAM and ETV.

The MAH has shown the exposure of HBV-infected children with the 8mg/kg dose was similar to the exposure previously reported in HIV paediatric population of the same age receiving the same dose of TDF. Moreover, the formulation proposed to be used in HBV-infected children are the same than those already approved for use in HIV-infected children, i.e. low-strength Viread tablets (123 mg; 163 mg; 204 mg) and Viread 33mg/kg granules.

Viread has been shown to supress viral replication in paediatric patients in study GS-US-174-0144 (n=60 receiving Viread). Even though the association between viral suppression and reduction of the risk of progression of liver disease is less documented in paediatric patients, the clinical benefit of durable suppression of viral replication has been shown in adults.

The majority of children in this study were treatment naïve (83%) and all but 4 children had HBeAg+ disease. The MAH nevertheless applies for an unqualified (large) indication, which is acceptable when considering the efficacy of tenofovir in adults is regarded as established in both HBeAg+ and HBeAg- disease and prior exposure to anti-HBV agents did not impact response to TDF in adults and adolescents.

The salient aspects of the safety profile of Viread remain the renal and bone safety, which may be of particular concern for the vulnerable population of paediatric patients in active modelling process. This issue has already been extensively discussed during the approval of Viread in HIV-infected children with involvement of a SAG. Even though the uncertainties on the long term impact of TDF on renal function and bone mineralisation in the paediatric population could not be dispel, it was concluded that in absence of a clear correlation between BMD decrease and clinical event, the long term bone effects may be considered as theoretical while there are established benefits in this population in need of treatment. The SmPC of Viread has been reinforced with warning to alert physicians on the impact of TDF on bone and renal function and to provide appropriate recommendations for the management of these safety risks. Moreover, there is a specific renal educational dedicated to paediatric patients.

The same approach can apply for HBV-infected paediatric patients.

Overall, the CHMP is of the view that the attention should be paid that the indication and warning in the SmPC should prevent going beyond a population in immediate need for treatment. This is all the more important that, unnecessary early therapy with nucleoside analog can result in development of resistance, thereby limiting treatment option later in life. In line with the CHMP proposal, the indication now selects for a paediatric population with immune active disease and a warning was added in the SmPC to encourage the prescribers to cautiously weigh the benefit and risks when deciding to initiate treatment in paediatric patients from 2 years of age. It was agreed at the CHMP level to make optional the requirement for histological evidence in the indication, acknowledging biopsy is not universally performed and considering section 4.4 will call for a particular weighing of the decision to treat.

The CHMP considers essential that the relatively rare cases of children with need for HBV treatment are managed and monitored for bone and renal toxicity at specialised centres.

4. Recommendations

Outcome

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	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication based on results from interim Week 48 clinical study report (CSR) for Study GS-US-174-0144; a 'Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection', resulting in the following changes:

1) Viread 123 mg, 163 mg and 204 mg film coated tablets: new chronic hepatitis B (CHB) indication to include treatment of CHB in paediatric patients aged 6 to < 12 years, update of Sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC.

2) Viread 245 mg film-coated tablets, update of Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC.

3) Viread granules 33 mg/g: extension of the existing CHB indication to include treatment of CHB in paediatric patients aged 2 to < 12 years, update of Sections 4.1, 4.2, 4.4, 5.1 and 5.2 of the SmPC.

The Package Leaflet has been updated accordingly for all formulations.

In addition, a discrepancy in the PI regarding the recommendation pertaining to pregnancy was corrected, by aligning the PL wording with that of the SmPC.

The Marketing authorisation holder (MAH) submitted a revised RMP version 24.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

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

- HIV paediatric educational brochure
- HBV paediatric educational brochure

The HIV and HBV paediatric educational brochures 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. Interrupting treatment with Viread should also be considered in case of progressive decline of renal function when no other cause has been identified.
- 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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0262/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication based on results from interim Week 48 clinical study report (CSR) for Study GS-US-174-0144; a 'Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection', resulting in the following changes:

1) Viread 123 mg, 163 mg and 204 mg film coated tablets: new chronic hepatitis B (CHB) indication to include treatment of CHB in paediatric patients aged 6 to < 12 years, update of Sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC.

2) Viread 245 mg film-coated tablets, update of Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC.

3) Viread granules 33 mg/g: extension of the existing CHB indication to include treatment of CHB in paediatric patients aged 2 to < 12 years, update of Sections 4.1, 4.2, 4.4, 5.1 and 5.2 of the SmPC.

The Package Leaflet has been updated accordingly for all formulations.

In addition, a discrepancy in the PI regarding the recommendation pertaining to pregnancy was corrected, by aligning the PL wording with that of the SmPC.

Summary

Please refer to the Scientific Discussion – Viread-191.