

CLINICAL PHARMACOLOGY REVIEW

NDA	21,356 S-57 22,557 S-13
Type of Submission	Pediatric efficacy supplement
Receipt Date	6/14/2018
PDUFA Goal Date	12/14/2018
Drug	VIREAD (tenofovir disoproxil fumarate)
Indication	Treatment of chronic hepatitis B infection
Dosage and Administration	Adults: one 300 mg tablet taken orally once daily without regard to food
Formulation	Oral tablets (150 mg, 200 mg, 250 mg, and 300 mg) Oral powder: 40 mg TDF per level scoop
Clinical Pharmacology Review Team	Simbarashe Zvada, Ph.D Chao Liu, Ph.D Su-Young Choi, Pharm.D., Ph.D

1. EXECUTIVE SUMMARY

The Applicant submitted a pediatric efficacy supplement, seeking the approval of VIREAD for the treatment of chronic hepatitis B (CHB) in pediatric patients 2 to less than 12 years of age who weigh at least 10 kg. VIREAD is currently approved for the treatment of CHB in adult patients and pediatric patients 12 years of age and older. To support the proposed indication, the Applicant submitted the clinical study report for Study GS-US-174-0144 entitled, “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”.

The primary basis for the approval is the efficacy of VIREAD, determined as HBV DNA outcomes at Week 48. Seventy seven percent of patients (46/60) achieved HBV DNA < 69 IU/mL in the TDF treated group, while 7% (2/29) of patients achieved HBV DNA < 69 IU/mL in the placebo group at Week 48. The sponsor collected intensive and sparse PK data to describe the pharmacokinetics of TFV in pediatric patients with CHB and explore the exposure-response relationships for efficacy and safety. The findings from the population pharmacokinetic analysis

and exposure-response relationships are supportive of the proposed dosing regimen, 8 mg/kg up to a maximum dose of 300 mg once daily, for the treatment of CHB in pediatric patients.

1. 1 RECOMMENDATIONS

The Office of Clinical Pharmacology has determined that the clinical pharmacology information provided in this supplemental NDA to support the approval of VIREAD 8 mg/kg once daily with a maximum daily dose of 300 mg for the treatment of CHB in pediatric patients aged 2 to < 12 years who weigh at least 10 kg.

In addition, from the clinical pharmacology perspective, the sponsor fulfilled PREA PMR 283-2 as well as the Written Request Items relevant to clinical pharmacology.

PREA PMR 283-2

Deferred pediatric studies under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 2 to < 12 years of age.

Written Request

Pharmacokinetic Endpoints:

Sparse sampling to assess PK in pediatric age groups and document similarity to HIV infected pediatric patients receiving tenofovir disoproxil fumarate and to assess adherence

2. CLINICAL PHARMACOLOGY KEY FINDINGS

Study Title: 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

Study Design: This a Phase 3, randomized, double-blind study to evaluate the antiviral efficacy, safety, and tolerability of TDF versus placebo in pediatric subjects with CHB. Approximately 100 subjects were to be randomized in a 2:1 ratio to 1 of the following treatments:

- TDF once daily by mouth for 48 weeks
 - 8 mg/kg once daily up to 300 mg, as tablets (150 mg, 200 mg, 250 mg, and 300 mg) or oral powder (40 mg/scoop)
- Placebo-to-match TDF once daily by mouth for 48 weeks

Randomization was stratified by age (< 6 years, 6 years and older) and geographic region. The interim Week 48 analysis was conducted after all randomized subjects had completed the

Week 48 study visit or had prematurely discontinued study drug. The primary efficacy endpoint was the proportion of subjects with HBV DNA 400 copies/mL (equivalent to and hereafter referred to as < 69 IU/mL) at Week 48. The key secondary efficacy endpoint was the proportion of subjects with baseline HBeAg seropositivity who achieved HBeAg seroconversion at Week 48. Other efficacy endpoints evaluated included the proportion of subjects with normal ALT, ALT normalization, HBV DNA < 69 IU/mL and normal ALT, HBV DNA < 29 IU/mL, HBeAg loss, HBsAg loss, and HBsAg seroconversion at Week 48.

Pharmacokinetic assessments

Single PK blood samples were collected at baseline/Day 1 and at each study visit thereafter. For subjects who provided additional, specific consent to participate in a PK substudy, intensive PK sampling was performed over 8 hours during a single study visit between Weeks 2 and 12. Sparse PK data were available for 58 subjects. Intensive PK data were available only for 3 subjects. Therefore, a separate NCA analysis was not performed and all available data from the study were used to develop a population PK model. Plasma samples were analyzed using a validated LC/MS/MS method.

Study Results

A total of 90 subjects were randomized in this study (60 subjects in the TDF group and 30 subjects in the Placebo group). Of these, 89 subjects received at least 1 dose of study treatment. TDF. A statistically significant proportion of subjects in the TDF group achieved the primary efficacy endpoint of HBV DNA < 69 IU/mL at Week 48 compared to the placebo group based on missing= failure approach; TDF 76.7% vs Placebo 6.9 %. The following conclusions are made based on the population PK analysis and exposure-response relationships

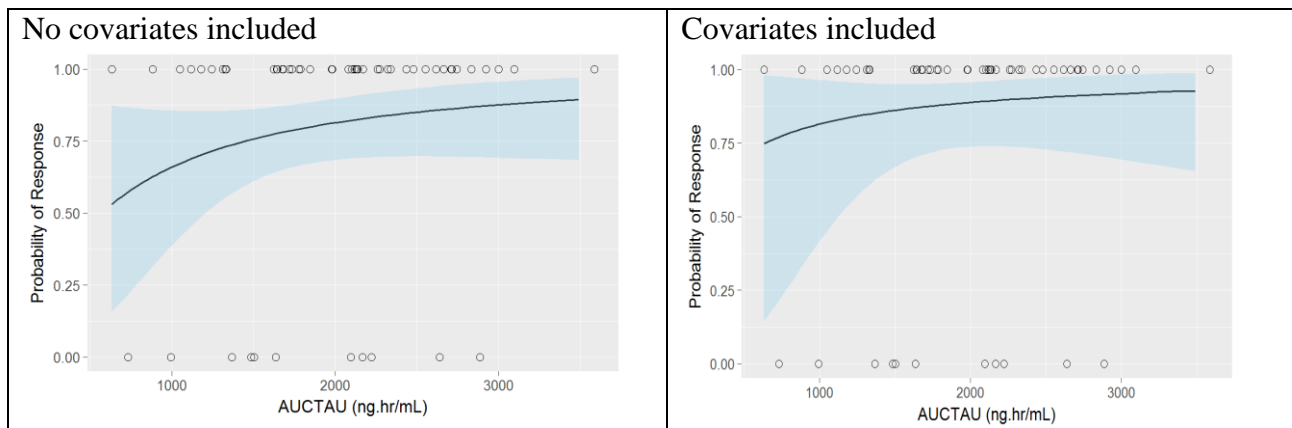
1. PK similarity between pediatric HIV patients and pediatric HBV patients

Tenofovir exposures (AUC_{tau} and C_{max}) were estimated using a population PK approach and by comparing with historical data in pediatric subjects infected with HIV who were receiving the same dose of TDF (i.e., 8 mg/kg). After accounting for drug interactions between lopinavir/ritonavir and TDF in pediatric HIV patients (32% higher TFV exposures based on the DDI study results), exposures were similar between the two populations. Since approval is being based on efficacy, not PK matching, exposures were not compared between adult patients with CHB and pediatric patients with CHB.

2. Exposure-response relationship for efficacy

Analyses for the exposures-response relationship for efficacy were conducted using the primary clinical endpoint, HBV DNA < 69 IU/mL at week 48. While there was an apparent exposure-response relationship (Figure 1, left), there was no clear exposure-response relationship for efficacy after adjusting for covariates effects (Figure 1, right). It is noted that lower exposures are mainly observed in the 2 to < 6 year old age groups.

Figure 1: Probability of HBV DNA < 69 IU/mL at week 48 (response) following 8 mg/kg dose in pediatrics with CHB



(Source: FDA analysis)

During review, extensive discussions were made to determine whether the lower efficacy of TDF in pediatric patients < 6 years old as compared to pediatric patients 6 years and older was due to lower exposures in younger pediatric patients; the proportions of patients who achieved HBV DNA < 69 IU/mL at 48 weeks were 54.5 % (12/22) and 89.5 % (34/38) in patients < 6 years old and patients 6 to < 12 years old, respectively. At the same time, TFV exposures were also lower by 34% in patients < 6 years old as compared to patients 6 to < 12 years old. However, based on the following observations, lower response rates in younger pediatric patients are unlikely due to lower TFV exposures.

- As demonstrated in Figure 1, there was no significant exposure-response relationship observed after adjusting for covariates. In addition, within the same age group, there was no apparent correlation between exposures and response rates (Figure 2).
- Following an information request, the Applicant provided detailed information on those 12 subjects who were treated as a “failure” in the primary analysis; most were due to withdrawal of consent or did not provide data at Week 48. Only two patients were deemed “virologic failure”.
- The overall HBV DNA decline kinetics are similar among adults, older pediatric patients, and younger pediatric patients (Figure 3). It is noted that comparison to the adult E-R cannot be made as the sponsor did not conduct E-R analysis in adults with CHB.

Figure 2: Proportion of patients with HBV DNA < 69 IU/mL at Week 48 by age

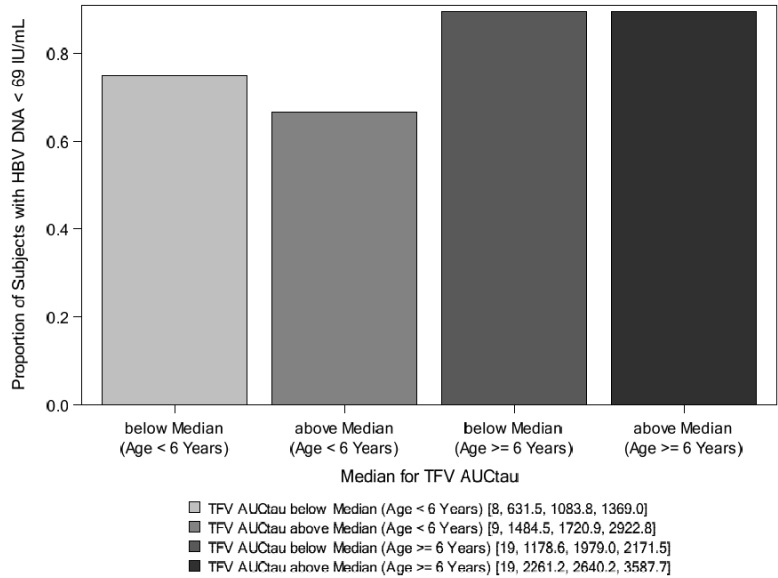
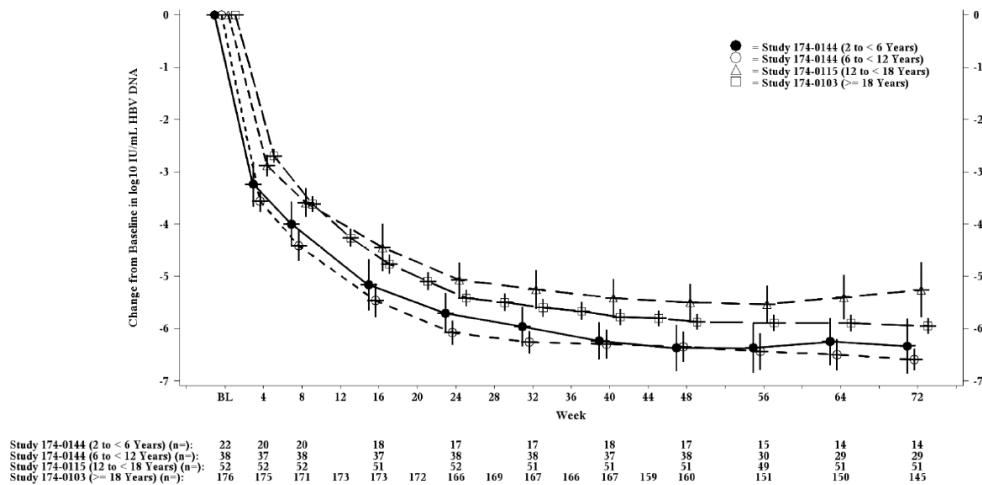


Figure 3: Mean and 95% CIs of change from baseline in log₁₀ IU/mL HBV DNA through Week 48 by age group in TDF-treated subjects



All Full Analysis Sets contains the Full Analysis Set for TDF-treated HBV pediatric subjects from study GS-US-174-0144, for HBV adolescent subjects from study GS-US-174-0115, and for HBV adult HBeAg-positive subjects from study GS-US-174-0103.

3. Exposure-response relationship for safety

The adverse event of interest for the use of TDF in pediatric patient is its effect on bone mineral density (BMD). It is known that the long-term use of TDF is associated with decreased BMD in

adults. The effects of TDF on BMD were also observed in this study. While both VIREAD and placebo treatment arms experienced an overall increase in mean lumbar spine and total body BMD over the study period, the BMD gains from baseline to Week 72 in lumbar spine and total body BMD in VIREAD-treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). The exposure-safety relationship for TFV was evaluated by determining the percent change from baseline in spine and whole-body BMD as a function of TFV exposure. The results indicated that there was no exposure-response relationship for percent change from baseline in BMD observed among patients who received 8 mg/kg TDF.

3. LABELING RECOMMENDATIONS

The following information has been added to Section 12.3.

Tenofovir exposures in HBV-infected pediatric adolescent subjects (12 years to less than 18 years of age) receiving oral once-daily doses of VIREAD 300 mg tablet and pediatric subjects 2 years to less than <12 years of age receiving VIREAD 8 mg/kg of body weight (tablet or powder) up to a maximum dose of 300 mg were comparable to exposures achieved in HIV-1 infected subjects receiving identical doses.

4 Population Pharmacokinetic/Pharmacodynamic Analyses

4.1 Population Pharmacokinetic Analyses

The Applicant performed a population PK analysis to evaluate if the proposed dosing regimen of 8 mg/kg of TDF is adequate for the treatment of CHB in children 2 to <12 years of age. This 8 mg/kg once daily dose was approved for pediatric patients 2 to <12 years of age infected with HIV. To carry out the population PK analysis, the Applicant used PK data from Phase 3 study (GS-US-174-0144) conducted in pediatric subjects 2 to <12 years of age with CHB infection who were naïve to TDF. The study design of GS-US-174-0144 is summarized in Table 1.

Table 1: Summary of GS-US-174-0144 study design

Type of Study	Study Number	Study Objective	Design	Study and Control Drug Regimens ^a	Duration of Treatment	Number of Subjects ^b	Study Population/Entry Criteria	Study Status; Type of Report
Controlled Clinical Study Pertinent to the Claimed Indication	GS-US-174-0144	To evaluate safety and tolerability of TDF versus placebo in 2 to < 12 year old subjects with CHB	Phase 3, randomized, double-blind study	TDF once daily by mouth for 48 weeks Placebo-to-Match TDF once daily by mouth for 48 weeks.	48 to 72 weeks of double-blind treatment	TDF: 60 subjects Placebo-to-Match TDF: 29 subjects	2 to < 12 year old subjects with CHB ^c	Study ongoing; Week 48 Interim CSR

CHB = chronic hepatitis B virus; TDF = tenofovir disoproxil fumarate

a TDF and placebo-to-match TDF were administered as weight-based doses of 150, 200, 250, or 300 mg tablets or 40 mg powder

b Subjects in the Full Analysis Set who completed 48 weeks of double-blind treatment or prematurely discontinued study drug.

c One subject in the Placebo group who was < 12 years old at screening had turned 12 years old by the time of randomization.

A total of 89 CHB subjects aged 2 to 12 years received ≥ 48 weeks of double-blind treatment with TDF 8 mg/kg (n = 60) or placebo (n = 29). Randomization was stratified by age at baseline (< 6 years, ≥ 6 years) and region (North America/Europe, Asia). Demographic and baseline characteristics were similar for the TDF and placebo treatment groups. The median age of subjects was 6 years (range: 2 to 12 years, and the majority of subjects were male (56.2%), Asian (65.2% [including 15.7% Indian]), and not Hispanic or Latino (100.0%). Overall, median (first quartile [Q1], third quartile [Q3]) baseline HBV DNA was 8.2 (7.8, 8.7) log₁₀ IU/mL. The majority of subjects (95.5%) were HBeAg positive at baseline, and the median (Q1, Q3) baseline HBsAg was 4.49 (3.97, 4.72) log₁₀ IU/mL. Overall, 83.1% and 86.5% of subjects had baseline ALT > 1.5 ULN based on central laboratory criteria and the AASLD criterion, respectively. A total of 75.3% of subjects were naïve 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. Only 58 subjects who had TDF PK were included in the population PK analysis. The intensive PK sampling occurred at study visits at Weeks 2 or 12. A single PK blood sample was collected for all subjects at study visits from Weeks 4 through 48 for TFV. All PK samples available were included in these analyses.

- **Dose selection rationale**

The efficacy and safety of TDF was evaluated in GS-US-174-0144 study in pediatric subjects 2 to <12 years of age with CHB infection who were naïve to TDF. The recommended oral dose of TDF in HIV-infected children is 8 mg/kg of body weight, to a maximum of 300 mg/day (≥ 35 kg). As there is no expectation of differences in tenofovir (TFV) pharmacokinetics in HIV-infected subjects and subjects with CHB, and adult doses for CHB and HIV are the same, an 8 mg/kg dose was chosen for an evaluation in this study. Matching with the prescribing information for VIREAD in pediatric subjects with HIV, all pediatric subjects with CHB weighing ≥ 17 kg who could swallow tablets received tenofovir DF tablet (150, 200, 250, or 300 mg tablet or placebo based on body weight). Pediatric subjects weighing < 17 kg and subjects weighing ≥ 17 kg who were unable to swallow a tablet received TDF oral powder.

- **Methods**

Applicant conducted population PK analysis using NONMEM for TFV using data from study GS-US-174-0144. Study data from GS-US-174-0144 for TFV was generated in .csv format and used for the analysis. Additional modifications, using Microsoft Excel and R, were made as deemed necessary to create NONMEM specific data file structures for the tested models. The population PK base model was developed by the applicant based on the previously established adult HIV Population PK model, which is a two-compartment model with first order absorption and elimination. The model was further characterized with first order absorption (K_a), and first order elimination from the central compartment and parameterized with apparent oral clearance (CL/F), apparent central volume (V_c/F), apparent inter-compartmental clearance (Q/F), apparent peripheral volume (V_p/F), and first-order absorption rate constant (K_a), with inter-individual variability (IIV) terms on apparent CL/F, V_c/F , and V_p/F . IOV was sequentially evaluated on each PK parameter (CL/F, V_c/F , V_p/F), and was included on CL/F based on statistically significant change in OFV ($p < 0.05$). The effects of baseline demographic covariates (age, body weight (WT), body mass index (BMI), sex, race, ethnicity, geographical region), pathophysiological covariates such as body surface adjusted creatinine clearance (BCLCRSW, derived by the Schwartz equation), disease related covariates (HBVGT, HBeAg) and FAST and FORM on TFV CL/F, V_c/F and V_p/F were assessed graphically followed by linear regression (continuous covariates) and ANOVA testing (categorical covariates). Individual specific random effects (ETA) for CL/F, V_c/F , and V_p/F were plotted versus the covariates to identify potential relationships. Model diagnostics included prediction corrected VPC (pcVPC).

- **Results**

TFV plasma concentrations were best described by a 2-compartment model with first order absorption, linear elimination, inter-individual variability term on CL/F, V_c/F and V_p/F , IOV on CL/F, and a combined error model

Table 2: Parameter estimates from the final population PK model of TFV

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
$\omega_{\text{CL/F}}$	IIV of CL/F (%)	23.1	21.6	15.5	27.0
$\omega_{\text{Vc/F}}$	IIV of V_c/F (%)	111	122	65.9	186
$\omega_{\text{Vp/F}}$	IIV of V_p/F (%)	133	134	85.8	169
ω_{IOVCL}	IOV of CL/F (%)	14.1	10.5	2.11	19.0
ω_{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

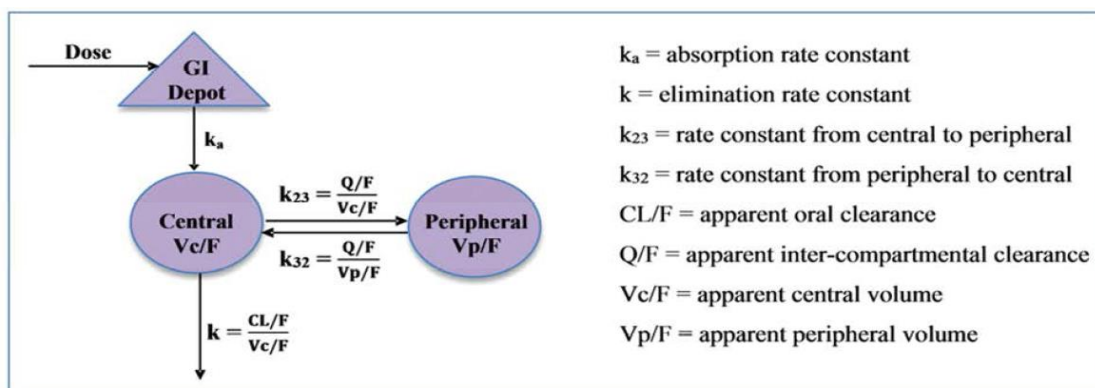
Figure 4). The parameter estimates for the final Population PK model done by the Applicant are provided in **Error! Reference source not found.** For a typical CHB pediatric subject with BCLCRSW of 167 mL/min/1.73m² weighing 21 kg, estimated TFV CL/F was 75.3 L/hr. Subjects corresponding to the 5th and 95th percentile of body weight (12.7 kg and 38.2 kg, respectively) demonstrated a -22 % and 34 % difference in CL/F as compared to the typical 21 kg subject. Similarly, subjects corresponding to the 5th and 95th percentile of BCLCRSW (134 mL/min/1.73m² and 210 mL/min/1.73m², respectively) demonstrated a -10 % and 11 % difference in CL/F compared to the typical subject with BCLCRSW of 167 mL/min/1.73m². The absorption rate constant (K_a) decreased by 38 % with powder compared to the tablet formulation. The typical apparent V_c/F was 211 L, Q/F was 105 L/hr and V_p/F was 7290 L. Interindividual variability was 23.1 % for CL/F, 111 % for V_c/F and 133% for V_p/F . The median and range of individual Bayesian post hoc CL/F, V_c/F , and K_a estimates for all subjects were

78.3 L/hr (5th and 95th percentile range: 43.3 to 110 L/hr), 209L (5th and 95th percentile range: 103 to 657 L), and 0.313 hr⁻¹ (5th and 95th percentile range: 0.195 to 0.313 hr⁻¹).

Table 2: Parameter estimates from the final population PK model of TFV

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

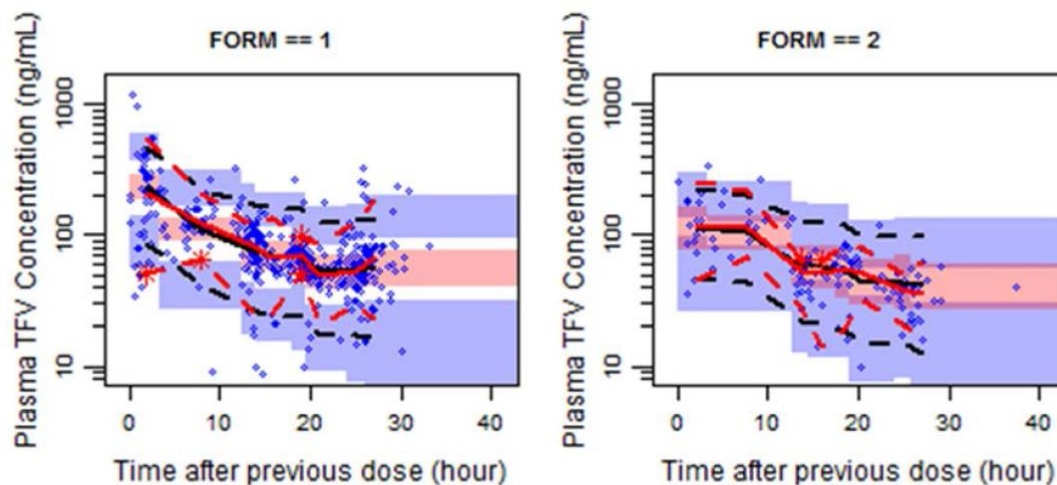
Figure 4: Illustration of TFV final model structure



- **Model diagnostics**

The pcVPC evaluated the ability of the model to reproduce the distribution of the data. pcVPC simulations of TFV after administration of 8mg/kg TDF once daily were performed as a validation of the final Population PK model. The Applicant used a total of 500 replicates of the trials were simulated using the observed covariates for each individual, the final Population PK model parameter estimates, the estimated subject specific random effects, and the residual error. The pcVPC of TFV plasma concentration-time profiles are shown in Figure 5. The pcVPC plots show that the final TFV Population PK model could adequately predict the central tendency and variability of the plasma TFV concentrations in CHB pediatric subjects

Figure 5: pcVPC of the final TFV model stratified by formulation



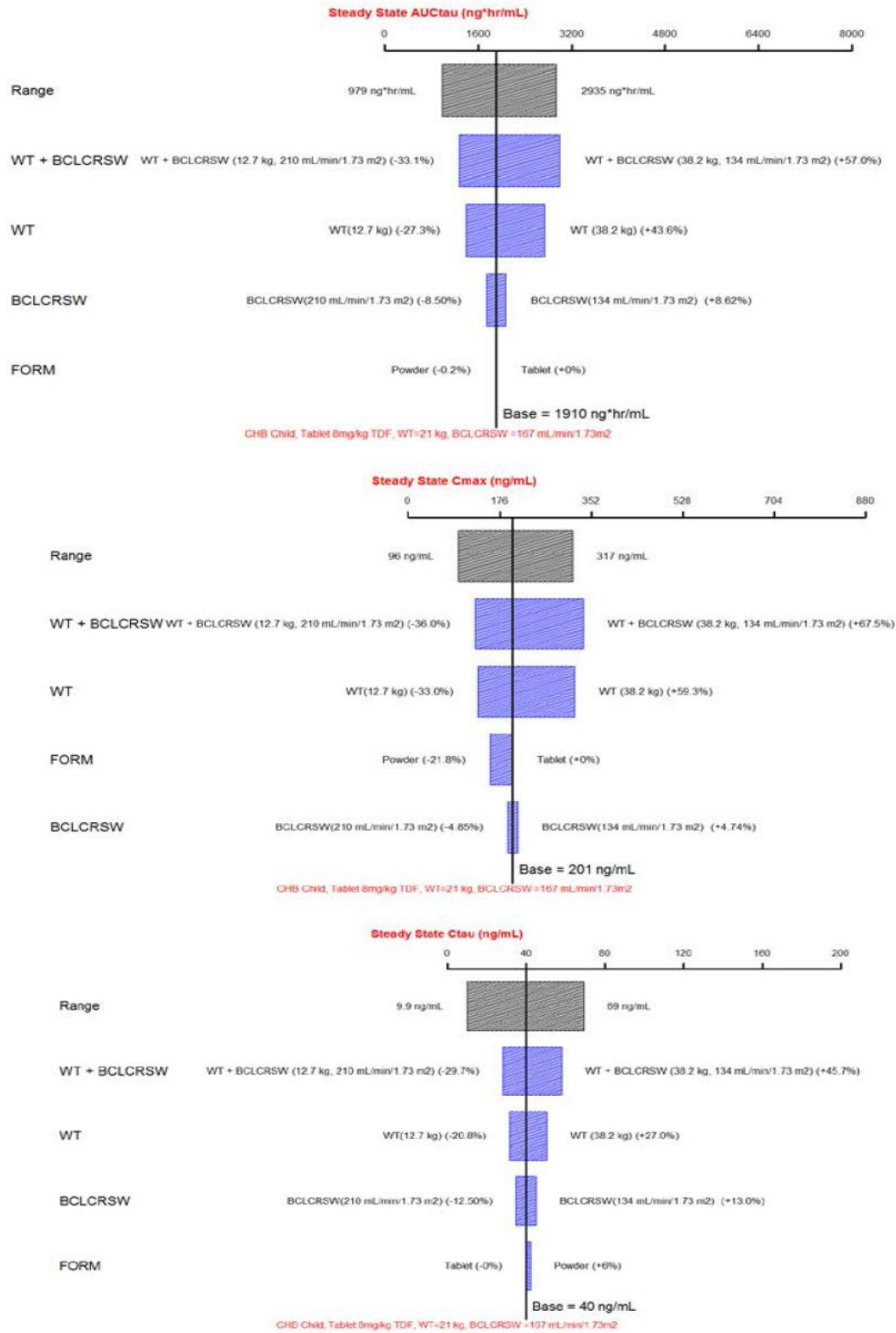
FORM=1 is tablet, FORM=2 is powder formulation. pcVPC plots show the observed concentrations (points), median (solid red lines) and spread (5th to 95th percentile, dashed red line) of the observed concentrations, and median (solid black lines) and spread (5th to 95th percentile, dashed black lines) of 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 5th and 95th percentiles.

- **Sensitivity analysis**

The Applicant performed sensitivity analysis to evaluate the impact of covariates on estimated post-hoc TFV exposure in pediatrics with CHB. The final population PK model included covariates of WT and BCLCRSW on CL/F, and formulation on Ka. The isolated influence of selected covariates on the expected steady state exposure of TFV following administration of TDF in pediatric CHB subjects was evaluated in a sensitivity analysis. The steady state area under the plasma concentration versus time curve (AUC_{τ}), maximum concentration (C_{max}), and concentration at the end of the dosing interval (C_{τ}) of TFV were computed for each of the scenarios based on the final Population PK model. The sensitivity analysis results are shown in Figure 6. The sensitivity analysis demonstrated minimal effects of BCLCRSW (8% on AUC_{τ} , 5% on C_{max} and 13% on C_{τ} change from typical value) and formulation (FORM) (no change on

AUC_{tau}, 22% on C_{max} and 6 % on C_{tau} change from typical value). WT had larger impact (-27 to +44% on AUC_{tau}, -33% to +59% on C_{max}, and -21% to +27% on C_{tau} between the 5th and 95th percentile body weight) on steady-state TFV exposures.

Figure 6: Sensitivity plot comparing the effect of covariates on TFV steady state AUC_{tau} , C_{max} and C_{tau} in CHB infected pediatric subjects



- Impact of body weight (WT) on TFV exposure

The Applicant identified WT as a statistically significant covariate on TFV CL/F in the final model parameters. As shown summarized in **Table 3**, in pediatric CHB subjects between 10.5 to 51.1 kg, TFV exposures showed the increasing trend between the lowest and highest body weight quartiles. The Applicant concluded the difference is not clinically meaningful.

Table 3: Impact of WT on mean (%CV) steady-state TFV exposure in pediatric subjects

Characteristics	WT Quartiles			
	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 on TFV exposure

As summarized in Table 4, In pediatric subjects across the range of BCLCRSW values (114 to 237 mL/min/1.73m²), TFV exposures demonstrated approximately ≤4 0% difference between the lowest and highest eGFR quartiles. The Applicant concluded that such difference was not considered clinically significant. It should be noted that there was no subject with significant renal impairment in the trial.

Table 4: Impact of BCLCRSW on mean (%CV) steady-state TFV exposure in pediatric subjects

Characteristics	BCLCRSW Quartiles			
	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 formulation (FORM) on TFV exposure

The impact of FORM on TFV exposure is presented in Table 5. Pediatric subjects with CHB who received the tablet formulation had higher ($\leq 50\%$) AUC_{τ} , C_{\max} and C_{τ} compared with subjects who received the powder formulation. The Applicant concluded that the difference in exposures is reflective of the effect of body weight, which explains the majority of variability in TFV exposures as shown in sensitivity analysis plot in Figure 6.

Table 5: Impact of formulation 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_{τ} (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_{τ} (ng/mL)	44.5 (40.6)	31.1 (46.8)	35.9 (50.4)

^aSubjects who switched formulations during the 48 Week treatment of TDF.

- **Comparison to TFV PK in pediatric HIV patients**

TFV exposures in pediatric CHB subject 2 to < 12 years old receiving TDF 8 mg/kg were compared with those from pediatric 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). LPV/r, an inhibitor of P-gp and BCRP, has been shown to moderately increase mean TFV concentrations (32%). After accounting for this drug interaction, TFC exposures were similar for the pediatric CHB and HIV patients.

Table 6. Comparisons of TFV PK parameters for pediatric CHB patients vs. pediatric HIV patients

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.

• **Applicant’s conclusions:**

- The Population PK model for TFV adequately described the observed exposures in pediatric CHB patients (2 to <12 year old) receiving TDF 8mg/kg powder or tablet daily (study GS-US-174-0144).
- The TFV exposure estimates can be used for additional demographic exposure summaries, subgroup analyses, and exposure-response analyses, as applicable.
- No clinically relevant differences in TFV exposures (AUC_{tau} or C_{max}) were observed in the pediatric CHB population compared with pediatric HIV subjects 2 to < 12 years old

Reviewer’s comments: Applicant’s population PK analysis reasonably described the PK of TFV in CHB patients from 2 to 12 years old. The submitted final population PK model was reproducible and FDA reviewer agreed that it was appropriate to use exposure derived from this model to perform exposure-response analysis. Although exposures were lower in younger pediatric patients (less than 6 years) as compared to older pediatric patients (6 years and older), no dose adjustment is needed based on the totality of evidences including efficacy data and exposure-response analysis.

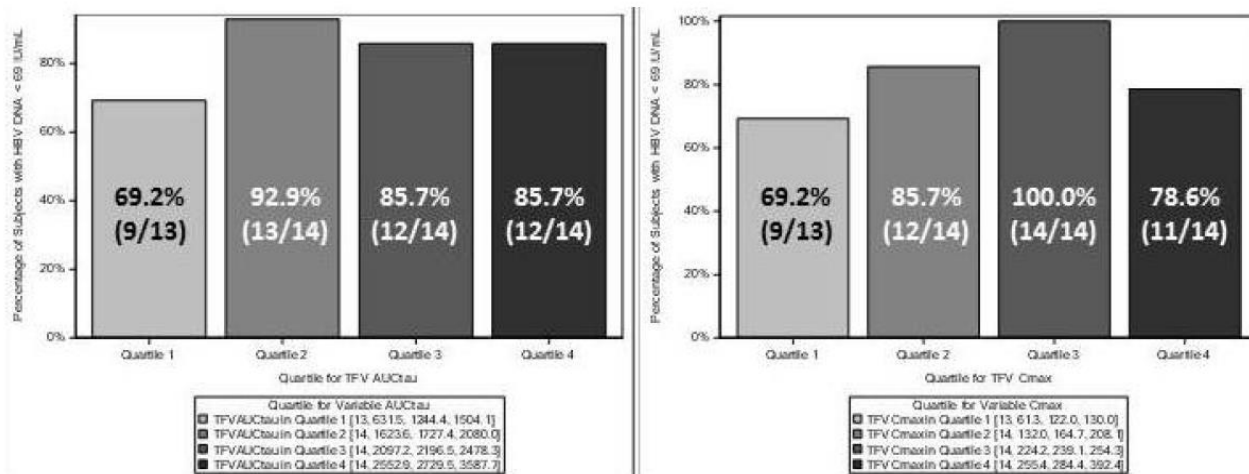
4.2 Exposure-response (E-R) analysis

Exposure-efficacy analysis

The applicant analyzed exposure-efficacy relationship for TFV which was evaluated by determining the proportion of subjects who achieved the primary (HBV DNA < 69 IU/mL at Week 48) and secondary (normalized ALT at Week 48) efficacy endpoints as a function of TFV exposure quartiles (AUC_{τ} and C_{\max}). The analyses also determined the proportion of subjects stratified by age (< 6 years and \geq 6 years) who achieved these efficacy endpoints as a function of median TFV exposures for that age group (ie, above or below the age group median).

Figure 7 displays the proportion of pediatric CHB subjects who achieved the primary efficacy endpoint by quartiles for TFV AUC_{τ} (left panel) and C_{\max} (right panel). The applicant concluded that the 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_{τ} , $p = 0.14$ 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. Further the Applicant conducted another stratification for proportion of CHB subjects with HBV DNA < 69 IU/mL at Week 48 by age (Figure 8). 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 exposure median in this age group ($p = 1.00$ TFV AUC_{τ} , $p = 0.62$ for TFV C_{\max}). Similarly, for subjects in the \geq 6 to 12 years old group, the differences in response rates for subjects with TFV exposures above or below exposure median of this age group were not statistically significant ($p = 1.00$ for TFV AUC_{τ} , $p = 0.60$ for TFV C_{\max}).

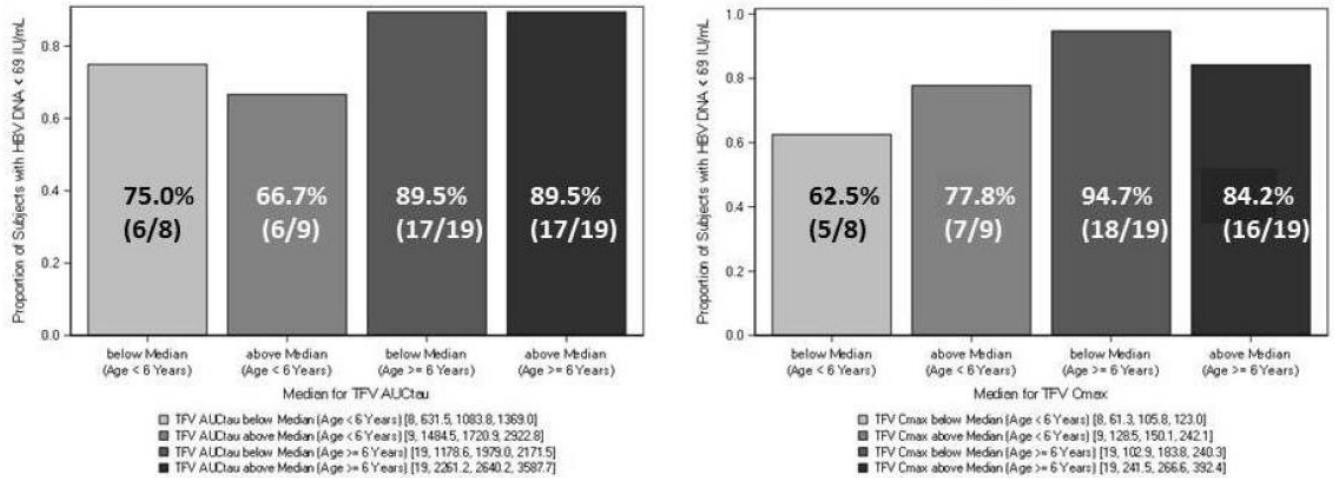
Figure 7: Proportion of pediatric CHB subjects with HBV DNA < 69 IU/mL at Week 48 by TFV AUC_{τ} and C_{\max} quartiles



Analysis were based on an M = E approach.

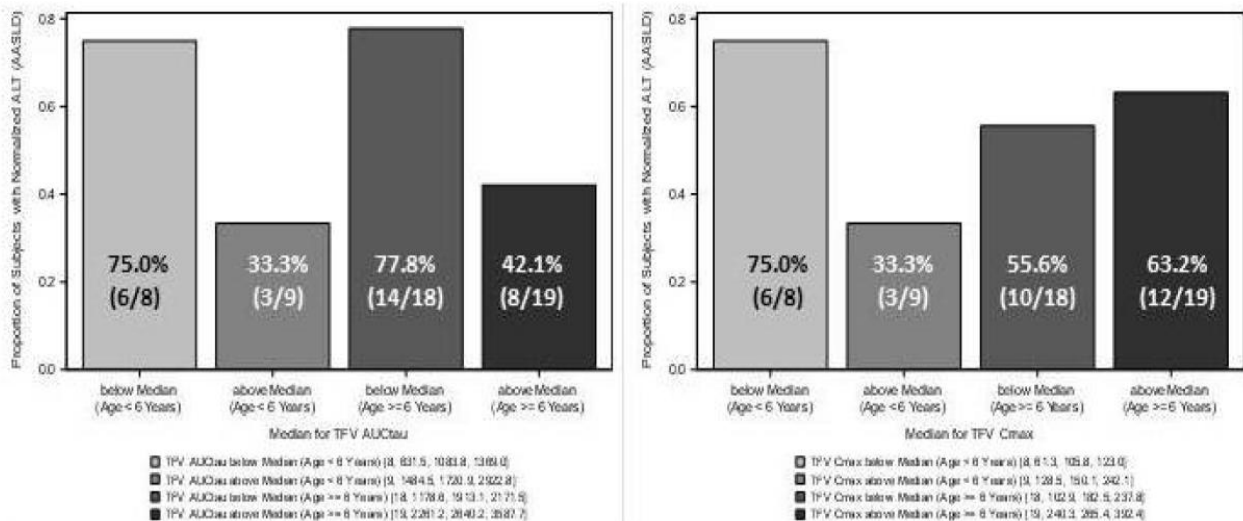
The numbers presented in brackets are the sample size, minimal, median, and maximal values of the TFV PK parameter.

Figure 8: 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)



The Applicant conducted E-R analysis for normalized ALT at Week 48, and the plots are shown in Figure 9. For the proportion of pediatric CHB subjects with ALT normalization at Week 48 by age group (2 to < 6 years and 6 to < 12 years), the response rates were numerically higher with subjects with lower TFV AUC_{tau} and C_{max}.

Figure 9: 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)



Analysis were based on an M = E approach.

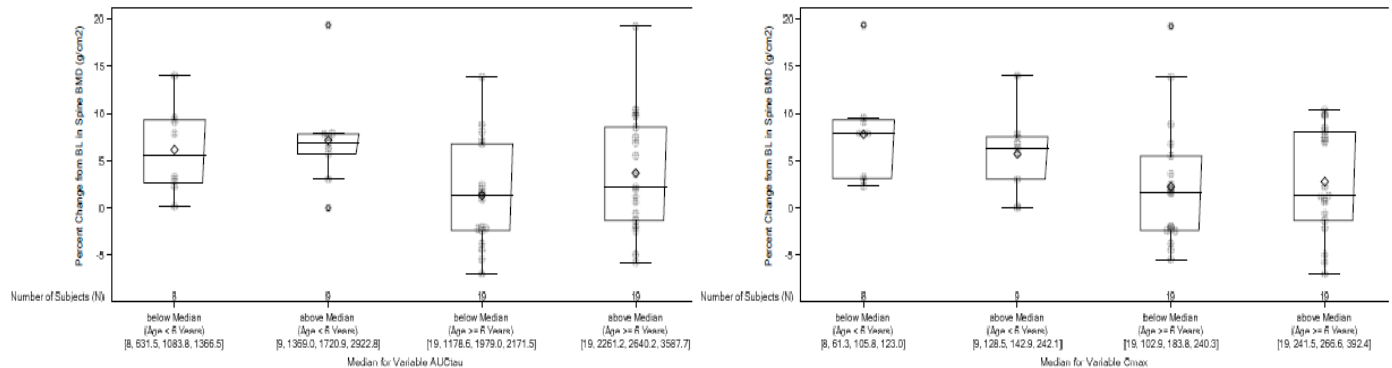
The numbers presented in brackets are the sample size, minimal, median, and maximal values of the TFV PK parameter.

Exposure -safety analysis

The Applicant conducted an exposure safety analysis for the percent change from baseline in spine and whole-body bone mineral density (BMD) as a function of TFV exposure quartiles (AUC_{τ} and C_{\max}). Further analyses evaluated the relationship at different age groups (< 6 years and ≥ 6 years).

The Applicant observed that for both age groups, the percent changes from baseline in spine BMD were numerically similar for subjects with TFV AUC_{τ} and C_{\max} above or below the age group median (Figure 10). For whole body BMD, the percent changes from baseline in whole BMD were numerically similar for subjects with TFV AUC_{τ} and C_{\max} above or below the age group median (Figure 11). Overall, there was no difference in percent change from baseline in spine and whole-body bone mineral density between exposure subpopulations. No data from the placebo arm were included in this analysis.

Figure 10: Mean (SD) percent change from baseline in spine BMD by age Group (TFV AUC_{τ} and C_{\max} above and below the age group median)

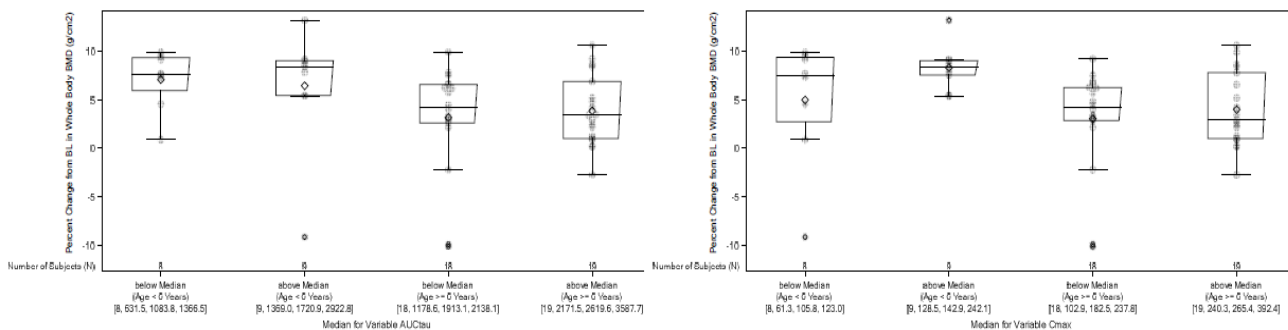


Analysis were based on an M = E approach.

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 $1.5 \times$ the interquartile range.

Numbers in brackets below each plot are sample size, minimum, median, and maximum values for TFV AUC_{τ} 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 $1.5 \times$ 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.

Applicant's conclusions:

- Exposure-efficacy relationships between TFV exposures (across quartiles, as well as above or below age group medians) versus the primary efficacy endpoint (HBV DNA < 69 IU/mL at Week 48) and a secondary efficacy endpoint (normalized ALT at Week 48) were examined for pediatric CHB subjects 2 to < 12 years old with evaluable PK data who participated in Study GS-US-174-0144. Overall there was no evident E-R relationship for efficacy.
- The effect of TFV exposure (AUC_{tau} or C_{max}) on safety was assessed as the percent changes from baseline in spine and whole body BMD at Week 48 as a function of TFV exposure (across quartiles, as well as above or below age group median, stratified by age subgroups). Results demonstrated a lack of association between TFV exposures and percent changes from baseline in spine and whole-body BMD, with TDF dose of 8 mg/kg.
- Overall, these results support the appropriateness of TDF 8 mg/kg for use in the pediatric CHB population 2 to < 12 years of age

Reviewer's comments: Applicant's E-R analysis is reasonable. In terms of E-R for safety, the applicant did not include placebo data in the analysis. Given it's known effects of TFV on BMD, the lack of apparent association between bone mineral density either in spine or whole body and the TFV exposure with 8 mg/kg TFN may suggest a saturable effect on BMD reduction under the therapeutic dosing regimen. The reviewer conducted an independent E-R analysis to assess the applicant's findings and conclusions.

4.3 Reviewer's Analysis

Independent analysis objective

The objective of analysis is to verify the Applicant's population PK model and conduct exposure response analysis using multiple regression models.

- **Data sets**

The data sets used in the analyses are listed in Table 6.

Table 6: Analysis Datasets for FDA Reviewer's Analysis

Study Number	Name	Link to EDR
	Population PK dataset: tfv.xpt	\\CDSESUB1\evsprod\NDA021356\0778\m5\datasets\pop-pk-viread-hbv-peds\analysis\legacy\datasets
	Population PK/PD dataset: adpkpd.xpt	\\CDSESUB1\evsprod\NDA021356\0778\m5\datasets\pk-pd\analysis\adam\datasets

- **Software**

NONMEM 7 and R were used for the reviewer's analysis.

- **Method**

The reviewer explored the Applicant's final population PK model by evaluating the diagnostic plot. After it was confirmed, the Applicant's final PPK model was used to obtain AUC_{τ} which was used for exposure response analysis for both efficacy and safety. R software was used for E-R analysis. The E-R relationship for disease response (DNA < 69 IU/mL at week 48) was analyzed by logistic regression after adjusting for covariates such as age, baseline weight, baseline viral load. In addition, change in viral load from baseline at Week 48 was analyzed by linear regression. In E-R analysis for safety, percentage changes from baseline BMD for spine or whole-body were employed as the endpoint.

- **Results**

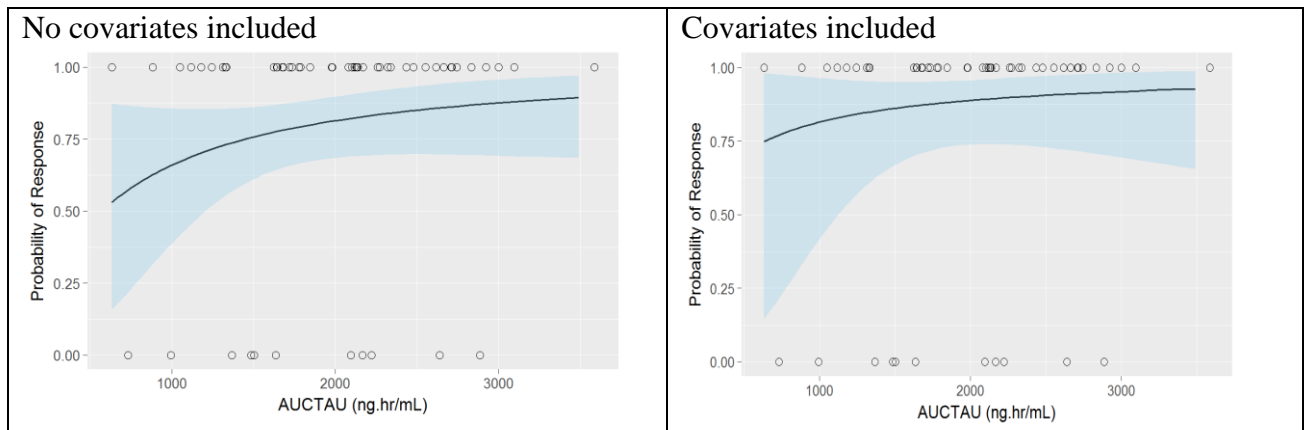
Population PK analysis

The reviewer tested the effect of body weight on volumes of distribution and intercompartmental clearance, but the body weight effect was not significant. The reviewer then adopted the exposure metrics derived from the applicant's final population PK model for E-R analysis.

Exposure-efficacy analysis

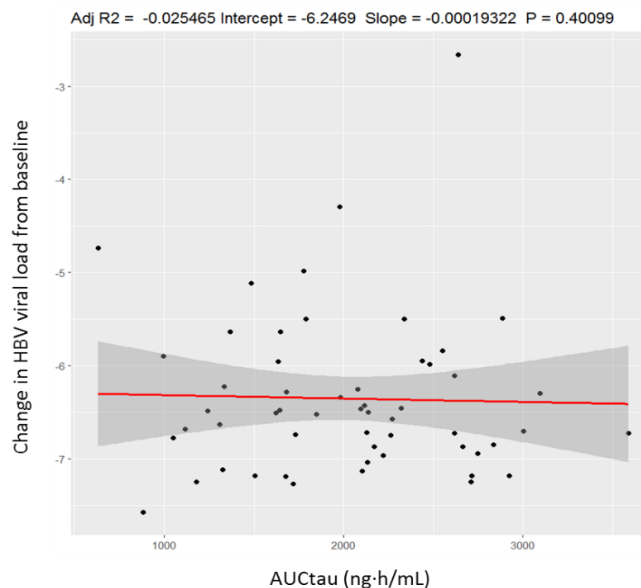
The results for the E-R analysis are shown in Figure 12. On the left panel are the results of logistic regression without accounting for covariates while on the right is after accounting for covariates. After adjusting for age, baseline weight, baseline viral load, the analysis did not show a significant relationship between tenofovir exposure and disease response (HBV DNA < 69 IU/mL at week 48). Also, there was no evident exposure-viral load relationship as shown in Figure 13.

Figure 12: Probability of HBV DNA < 69 IU/mL at week 48 (response) following 8 mg/kg dose in pediatric CHB patients



(Source: FDA reviewer's analysis)

Figure 13: TFV exposure-response relationship for changes in HBV viral load from baseline

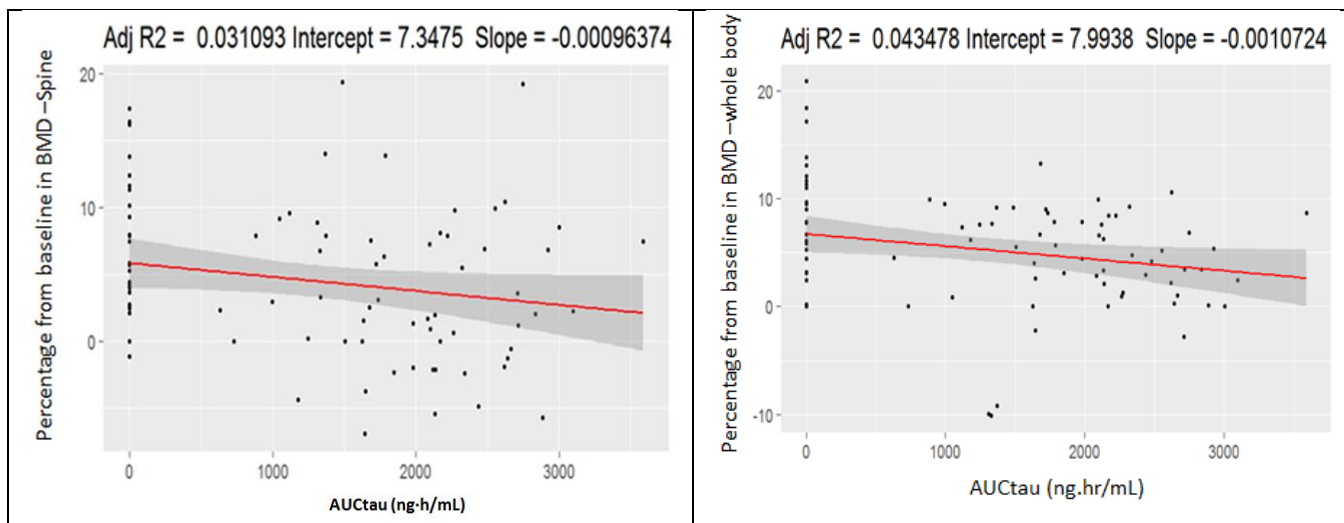


(Source: FDA reviewer's analysis)

Exposure-safety analysis

The results for exposure-safety analysis using percentage changes from baseline in spine and whole body BMD are summarized in Figure 14. The placebo arm was included in the analysis.

Figure 14: Multiple linear regression for safety indicators at week 48 (response) following 8 mg/kg dose in pediatrics with CHB



(Source: FDA reviewer's analysis)

Reviewer's conclusions:

The reviewer tested effect of body weight, through allometric scaling, on volumes of distribution and intercompartmental clearance, but the effect was not statistically significant. The final model from the Applicant was used to obtain exposure indices which were used to conduct ER analysis for efficacy and safety. The major findings based on reviewer's analysis are:

- The Applicant's population PK model was reproducible.
- There is no apparent relationship between TFV exposures and changes in HBV DNA from baseline at week 48 or HBV DNA < 69 IU/mL at week 48 after adjusting covariates such as age, body weight, baseline viral load.
- BMD in TDF treated patients was numerically lower than that in placebo treated patients. However, there is no apparent relationship between bone mineral density either in spine or whole body within the exposure range under 8 mg/kg TDF in pediatrics with CHB, suggesting a saturable effect on BMD reduction with the therapeutic dosing regimen.

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

/s/

SIMBARASHE P ZVADA
11/21/2018

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