EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2023
EMA/CHMP/155784/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Vemlidy

International non-proprietary name: tenofovir alafenamide

Procedure No. EMEA/H/C/004169/II/0040

Note

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
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUCtau	area under the concentration versus time curve over the dosing interval
BMD	bone mineral density
CDC	Centers for Disease Control and Prevention
CHB	chronic hepatitis B
Cmax	maximum observed concentration of drug
CSR	clinical study report
Ctau	observed drug concentration at the end of the dosing interval
EASL	European Association for the Study of the Liver
ETV	entecavir
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
Gilead	Gilead Sciences/Gilead Sciences, Inc.
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
LAM	lamivudine
LLOQ	lower limit of quantitation
M = E	missing = excluded
M = F	missing = failure
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PTM	Placebo-to-match
pol/RT	polymerase/reverse transcriptase
popPK	population pharmacokinetic
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFV	tenofovir
TFV DP	tenofovir diphosphate
ULN	upper limit of normal
US, USA	United States, United States of America

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 27 May 2022 an application for a variation.

The following changes were proposed:

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 to include treatment of chronic hepatitis B-infected children from 6 years and older and weighing at least 25 kilograms for Vemlidy, based on the interim results from Week 24 clinical study report (CSR) for Cohort 1 and Cohort 2 Group 1 and supporting modular summaries for the category 3 study GS-US-320-1092, 'A Randomised, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection'. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the MAH took the opportunity to update the wording in section 4.6 of the SmPC related to breastfeeding and pregnancies exposed to TAF, and to update the contact details of the local representative in Romania in the Package Leaflet.
An updated RMP version 8.2 has been provided.

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 EMA Decision P/0269/2021 on the agreement of a paediatric investigation plan (PIP).

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 MAH 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 MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	27 May 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	11 August 2022
PRAC Rapporteur Assessment Report	22 August 2022
CHMP Co-Rapporteur Assessment	26 August 2022
PRAC members comments	24 August 2022
PRAC Outcome	1 September 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	20 December 2022
PRAC Rapporteur Assessment Report	3 January 2023
PRAC members comments	4 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur Assessment Report	20 January 2023
Request for supplementary information (RSI)	26 January 2023
CHMP Rapporteur Assessment Report	12 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
Opinion	26 April 2023

2. Scientific discussion

2.1.1. Problem statement

Disease

Chronic hepatitis B (CHB) is a major public health care issue worldwide and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure. Following acute HBV infection, 5% to 10% of adults and up to 90% of children fail to produce an immune response adequate to clear the infection; these individuals become chronic carriers of the virus. Individuals who develop CHB are at substantial risk of cirrhosis, hepatic decompensation, and HCC, which will afflict 15% to 40% of patients with CHB in the absence of effective treatment. The World Health Organization

(WHO) estimates that 296 million people were living with CHB infection in 2019, with 1.5 million new infections each year. In 2013, an estimated 686,000 deaths were due to HBV infection, placing it among the top 20 causes of mortality worldwide.

Management

The goal of anti-HBV therapy in children, as in adults, is to improve long-term survival and quality of life by reducing disease progression to cirrhosis, decompensated liver disease, and HCC. The aim of oral antiviral treatment for CHB infection is to achieve and maintain suppression of viral replication to prevent or reduce the development of these complications.

Most children aged 2 to < 18 years have persistently normal alanine aminotransferase (ALT) values and high levels of HBV DNA, consistent with the immune-tolerant phase. However, immune activation does occur in a minority of children in whom antiviral therapy can provide benefits with regard to halting disease progression and its complications later in childhood or during young adulthood. All current guidelines suggest that antiviral therapy be considered in HBeAg positive children who have both elevated ALT and HBV DNA levels with the goal of achieving and maintaining viral suppression and producing sustained HBeAg seroconversion. Although HBeAg negative CHB is less commonly seen in children, it is generally accepted that long-term treatment is required in the absence of confirmed HBsAg seroconversion in HBeAg negative children with elevated ALT and HBV DNA levels.

Treatment options for children are similar to those for adults. Tenofovir disoproxil fumarate (TDF), a nucleotide analogue reverse transcriptase inhibitor with antiviral activity against both HBV and HIV, and entecavir (ETV), a nucleoside analogue reverse transcriptase inhibitor, are both recommended as first line treatment in all major guidelines for adults with CHB. Similarly, all major guidelines updated since approval of tenofovir alafenamide (TAF) in 2016 also list this agent as a first-line treatment in adults. While ETV is effective in HBV treatment-naive patients, including children aged 2 to < 18 years with CHB, reduced response rates are seen in patients with prior lamivudine (LAM) treatment or LAM resistance. Although TDF is approved for use in children and adolescent patients aged 2 to < 18 years with chronic HBV, bone and renal toxicities, including proximal tubulopathy and Fanconi syndrome, have been reported with TDF. The negative effects of TDF on bone metabolism, especially in adolescents and children who have not attained peak bone mass, are clinically concerning. Tenofovir alafenamide is currently only approved in adolescents (aged 12 years and older with body weight at least 35 kg) and adults.

2.1.2. About the product

Vemlidy 25 mg film coated tablets contain Tenofovir alafenamide as active substance.

TAF is a phosphonamidate prodrug of tenofovir (TFV) that is more stable in plasma than TDF, and provides higher intracellular levels of the active phosphorylated metabolite, tenofovir diphosphate (TFV-DP), to target cells (e.g., HBV-infected hepatocytes and HIV-infected lymphoid cells) with approximately 90% lower circulating levels of TFV relative to TDF at therapeutically active doses. The distinct metabolism of TAF is responsible for the improved safety profile of this novel TFV prodrug when compared with TDF. In Studies GS-US-320-0108 and GS-US-320-0110, at Weeks 48 and 96, the efficacy of TAF was non-inferior to that of TDF in participants with CHB with no documented resistance, and TAF treatment was associated with improved bone and renal safety compared with TDF.

TAF is currently approved for use in adult and adolescent patients with CHB weighing at least 35 kg in the European Union (EU) and other regions.

This application is being submitted for Vemlidy in order to expand the age range for the treatment of CHB to include use in paediatric patients at least 6 years of age and older weighing at least 25 kg.

In support of the application, results from 1 clinical study (study GS-US-320-1092) in the agreed paediatric investigation plan (PIP) has been submitted. Study GS-US-320-1092 is an ongoing double-blind, placebo-controlled, multicenter study of the safety, tolerability, PK, and antiviral activity of TAF administered once daily in treatment-naive and treatment-experienced adolescents and children with CHB. The data presented are from the interim, primary endpoint analysis for safety, efficacy, and PK, which was conducted when all participants in Cohort 1 (adolescents 12 to less than 18 years of age and weighing at least 35 kg) and Cohort 2 Group 1 (paediatric participants 6 to < 12 years of age and weighing at least 25 kg) had completed their Week 24 (i.e., primary endpoint) visit or prematurely discontinued from the study.

2.1.3. General comments on compliance with GCP

The MAH has provided a statement that study GS-US-320-1092 was conducted (largely in countries outside the European Union) under local regulatory requirements and in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical have been submitted in this application, which is considered acceptable. A full ERA was provided to support this extension of indication.

2.2.1. Ecotoxicity/environmental risk assessment

A full environmental risk assessment (ERA) has been provided in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00]. Tenofovir alafenamide is a pro-drug which is rapidly converted into the active moiety tenofovir after absorption. Consequently, the ERA was performed with tenofovir.

Table 1: Summary of main study results

Substance (INN/Invented Name): Tenofovir			
CAS-number (if available): 147127-20-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH2: -3.8 pH7: -4.3	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-3.8 to -4.3	not B
	BCF	not required	not B
Persistence	DT50	$DT_{50\ sediment,20\ °C}$ = 142.0 d $DT_{50\ sediment,12°C}$ = 303.0 d	vP
Toxicity	NOEC or CMR	NOEC ≥ 10 mg/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surfacewater}$, default	0.075	µg/L			> 0.01 threshold Y
Other concerns					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc ads soil 351 - 1091 L/kg Koc des soil 968 - 2791 L/kg KF ads sludge 6.0 - 21 L/kg KF des sludge 16 - 62 L/kg			terrestrik not triggered
Ready Biodegradability Test	OECD 301B	9% CO_2 at day 28			not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 2.0 – 3.5 d $DT_{50, sediment}$ = 28.0 - 142.0 d (303.0 d at 12 °C) $DT_{50, whole\ system}$ = 10.4 – 32.7 d >10% parent associated with sediment from Day 7; 3 significant metabolites in water and/or sediment out of which two are considered persistent			Tenofovir is considered very persistent in sediments
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition *Pseudokirchneriella subcapitata*	OECD 201	NOEC	32	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 100	mg/L	
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	≥10	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	
Phase IIb Studies					
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	≥ 290 mg/kg_{dwt} (C_{org} 2.3%) (1261 mg/kg_{dwt} normalised for 10% OC)	mg/kg	

Regarding the environmental risk assessment of tenofovir, since PECsurfacewater is above 0.01 µg/L, a Phase II assessment has been performed. Results from Phase II Tier A studies do not indicate any risks for the surfacewater, groundwater, STP and sediment compartments. Based on the log Kow value, tenofovir is not considered PBT nor vPvB. However, according to the transformation study in water/sediment systems, tenofovir has to be classified as very persistent in sediments.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical have been submitted in this application, which is considered acceptable by the Committee. A full ERA was provided to support this extension of indication; the CHMP is of the view that Vemlidy is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 2: Table of the submitted clinical trial GS-US-320-1092

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants[a]	Study Population/ Entry Criteria
Controlled clinical study pertinent to the claimed indication	GS-US-320-1092	To evaluate the PK, safety, and antiviral efficacy of TAF in children and adolescent participants with CHB infection	Phase 2 randomised, double-blind study	Participants were randomised in a 2:1 ratio to 1 of the following 2 treatment groups: TAF group: TAF 25-mg tablet once daily Placebo group: placebo-to-match TAF 25-mg tablet once daily	24 weeks of double-blind treatment[b]	Cohort 1: TAF: N = 47 Placebo: N = 23 Cohort 2 Group 1: TAF: N = 12 Placebo: N = 6	Cohort 1: 12 to < 18 years old weighing ≥ 35 kg Cohort 2 Group 1: 6 to < 12 years old weighing ≥ 25 kg

CHB = chronic hepatitis B; CSR = clinical study report; PK = pharmacokinetics; TAF = tenofovir alafenamide

a Participants in Cohort 1 were stratified based on age (12 to < 15 years and 15 to < 18 years).

b The double-blind period will be followed by the open-label extension period for up to an additional 216 weeks (through Week 240) where all participants will receive TAF 25 mg daily.

2.3.2. Pharmacokinetics

Bioanalytical method

Concentrations of TAF and TFV in human K_2EDTA plasma were determined by QPS, LLC (Newark, US) using protein precipitation (TAF) or solid phase extraction (TFV) followed by LC-MS/MS. Both methods (QPS 60-1578 for TAF and QPS 60-1368 for TFV) have already been assessed during marketing authorisation application of Vemlidy (EMEA/H/C/004169). Two further amendments have been included in method QPS 60-1368 since 2016:

- Amendment 3 (18 Feb 2021):
  - Added hemolysed and lipemic plasma tests and updated validation summary table
  - Changed the Principal Investigator and Scientific Reviewer
  - Updated Compliance Statement in Section 2
- Amendment 4 (10 Jun 2021):

- Added whole blood stability test

All study samples were analysed within the established long-term stability of 988 days at -70°C for TAF and 1092 days at -70°C for TFV.

Absorption

Study GS-US-320-1092

The steady-state PK of TAF and its major metabolite TFV were evaluated in adolescents (Cohort 1, 12 to <18 years of age weighing ≥ 35 kg) and children (Cohort 2 Group 1, Part A 6 to <12 years of age weighing ≥ 25 kg). Subjects in both cohorts were administered TAF 25 mg once daily with food. For detailed study description see section 5.4.2.

Blood samples were collected to determine the PK profile of TAF and TFV. A single PK measurement was collected from all study participants at Weeks 8, 16, and 24. PK samples (15 min to 4 h post-dose) were collected at Week 4 from subjects enrolled in Cohort 1 and at Week 12 in all subjects. For subjects who provided specific additional consent to participate in the intensive PK substudy (optional for Cohort 1 and mandatory for Cohort 2, Part A), an intensive PK evaluation at the Week 4 visit was conducted, with PK samples collected pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, and 8 h post-dose. These subjects also underwent a steady-state PK assessment of TAF and TFV at either Week 4, Week 8, Week 12, Week 16, or Week 24.

Results:

The aim of this analysis was to evaluate the PK of TAF and confirm the selected dose of 25 mg once daily. Serial PK data from 13 adolescents in Cohort 1 and 5 children in Cohort 2 were included in the analysis.

The steady-state PK parameters are presented in Table 3 for TAF and TFV.

TAF C_{max} (mean 387.7 ng/mL) occurred at 0.5 hours post-dose for subjects in Cohort 2 and was twice as high compared to C_{max} of Cohort 1 (187.8 ng/ml) at 1 h post-dose. C_{max} of TFV was comparable between cohorts (15.3 ng/ml vs. 17.4 ng/ml).

AUC_{tau} was slightly higher in Cohort 2 compared to Cohort 1 for both TAF (254.3 ng*h/ml and 312.5 ng*h/ml, respectively) and TFV (202.8 ng*h/ml and 246 ng*h/ml).

Table 3: TAF and TFV Steady-State PK Parameters (study GS-US-320-1092, PK Substudy Analysis Set)

	Mean (%CV)			
	Cohort 1 (N = 13)		Cohort 2 Group 1 (N = 5)	
PK Parameters	TAF	TFV	TAF	TFV
AUC_{tau} (ng*h/mL)	254.3 (36.4)	202.8 (27.9)	312.5 (64.8)	246.1 (23.0)
AUC_{last} (ng*h/mL)	227.0 (42.6)	96.4 (25.3)	309.4 (65.9)	111.6 (19.1)
C_{max} (ng/mL)	187.8 (45.0)	15.3 (23.5)	387.7 (96.9)	17.4 (19.6)
C_{tau} (ng/mL)	-	4.12 (39.5)	-	5.04 (35.9)
T_{max} (h)[a]	1.0 (0.50, 1.5)	1.5 (1.1, 3.0)	0.50 (0.28, 1.5)	2.0 (1.0, 2.0)
C_{last} (ng/mL)	3.83 (92.3)	10.7 (28.8)	3.92 (89.6)	11.4 (26.5)
T_{last} (h)[a]	4.0 (3.0, 5.0)	8.0 (8.0, 8.0)	3.0 (3.0, 3.9)	8.0 (8.0, 8.0)
$t_{1/2}$ (h)[a]	0.5 (0.4, 0.6)	11.8 (10.1, 13.7)	0.4 (0.4, 0.4)	13.0 (10.6, 14.0)
Vz/F (L)	87.2 (45.4)	2356.1 (34.5)	67.2 (80.0)	1820.8 (7.1)
CL/F (L/h)	112.3 (40.3)	135.5 (37.7)	102.9 (45.6)	106.5 (27.0)

%CV = percentage coefficient of variation; BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; TFV = tenofovir
a Median (Q1, Q3)
PK Substudy Analysis Set included all randomized participants who received at least 1 dose of the study drug and for whom steady-state PK parameters of any analytes of interest were available.
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ was defined as 1 ng/mL for TAF and 0.3 ng/mL for TFV.
Participants 54513, 54517, and 54519 consented to the PK substudy but later refused to have any intensive PK samples collected. As there were no postdose intensive PK samples from these 3 participants, they were excluded from PK Substudy Analysis Set.
Source: Tables 15.10.2.1 and 15.10.2.2

Population pharmacokinetic modelling

An existing TAF and TFV PopPK model using data of n=337 paediatric HIV patients was updated with data of n=59 paediatric HBV patients. For TAF n=1709 samples of HIV patients vs. n=321 samples of HBV patients were included. For TFV n=3176 samples of HIV patients were included vs. 429 samples of HBV patients.

In studies GS-US-292-0106, GS-US-292-1515, GS-US-311-1269, GS-US-380-1474 paediatric HIV patients were treated with different fixed-dose combinations including TAF. Five Phase 2/3 studies were included in this analysis to evaluate the PK and safety of TAF and TFV. A summary of the study design, including study population, treatment, and PK sampling strategies can be found in Table 4.

The covariates to be tested included age, sex, WT, race, BSA, BMI, P-gp inhibitors, background therapy, disease status (HIV-1 vs. HBV) and renal function as described by BCL_{CRSW}. Covariates that yielded a significant decrease in −2 times the Log of the Likelihood function and resulted in a significant decrease in the Log Likelihood ratio test were retained for further analysis. A stepwise forward addition (all significant covariates at $p < 0.01$ with difference in OFV were retained) and backward elimination strategy (the least significant covariate that do not reach the $p < 0.001$ level of significance > 10.83 was dropped from the model) was then used to identify the final PopPK model.

Table 4: Study Dosing Details

Study	Study Design/Population	Treatment	Sampling (Intensive/Sparse)
GS-US-292-0106	A Phase 2/3, Open-Label Study of the Pharmacokinetics (PK), Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1–Infected, Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children	Cohorts 1 and 2 (adolescents and children [6 to < 18 years of age, weighing ≥ 25 kg]): E/C/F/TAF 150/150/200/10 mg fixed-dose combination (FDC) Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): E/C/F/TAF 90/90/120/6 mg FDC	Intensive + Sparse
GS-US-292-1515	A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1–Infected, Virologically Suppressed Adolescents	E/C/F/TAF 150/150/200/10 mg FDC	Sparse
GS-US-311-1269	A Phase 2/3, Open-Label, Multicohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1–Infected Children and Virologically Suppressed Adolescents on a 2-Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Containing Regimen	Cohort 1 (adolescents 12 to < 18 years of age, weighing ≥ 35 kg): F/TAF 200/25 mg or 200/10 mg FDC Cohort 2 Group 1 (children 6 to < 12 years of age, weighing ≥ 25 kg): F/TAF 200/25 mg Cohort 2 Group 2 (children 2 to < 12 years of age, weighing ≥ 17 to < 25 kg): F/TAF 120/15 mg	Intensive + Sparse
GS-US-380-1474	A Phase 2/3, Open-Label Study of the PK, Safety, and Antiviral Activity of the GS-9883/F/TAF) FDC in HIV-1–Infected, Virologically Suppressed Adolescents and Children	Cohorts 1 and 2 (adolescents [12 to < 18 years of age] and children [6 to < 12 years of age]): B/F/TAF 50/200/25 mg FDC Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): B/F/TAF 30/120/15 mg FDC	Intensive + Sparse
GS-US-320-1092	A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection	Cohort 1: TAF 25 mg Cohort 2 TAF 15 mg	Intensive + Sparse

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetic(s).

TAF PopPK Analysis

New data available in 59 HBV infected paediatrics patients from Study GS-US-320-1092 were used to further improve the TAF PopPK model, with particular focus on the IIV model structure. Based on the 2020 TAF PopPK analysis, a 1-compartment structural model with sequential zero-first-order absorption and first-order elimination was used as a starting point. This model included fixed allometric scaling on clearance and volume of distribution and booster effects on relative bioavailability of TAF (F1). In addition, the M3 method was implemented given the large proportion of BLQ samples. The model was found to describe well the TAF PK data across available studies and TAF regimens but was

limited in the ability to adequately quantify IIV given the reproducibility and robustness issues. First, the inclusion of a COBI/RTV booster effect on D1 showed a significant reduction in OFV (delta OFV or dOFV of −33.6 points) and further improved the characterization of TAF absorption in the presence of booster therapy.

The plasma concentrations of TAF were best described by a 1-compartment model with sequential zero- first-order absorption and first-order elimination. Effects of WT on CL/F and Vc/F were included using fixed allometric exponents of 0.75 and 1, respectively. In addition, COBI was found to affect F1 (163.6% increase). Interindividual variability was included on D1. A combined error model was used to characterise residual variability (RV), with the inclusion of interindividual variability on the proportional error term. Table 5 provides the final parameter estimates and SEs associated with the final PopPK model.

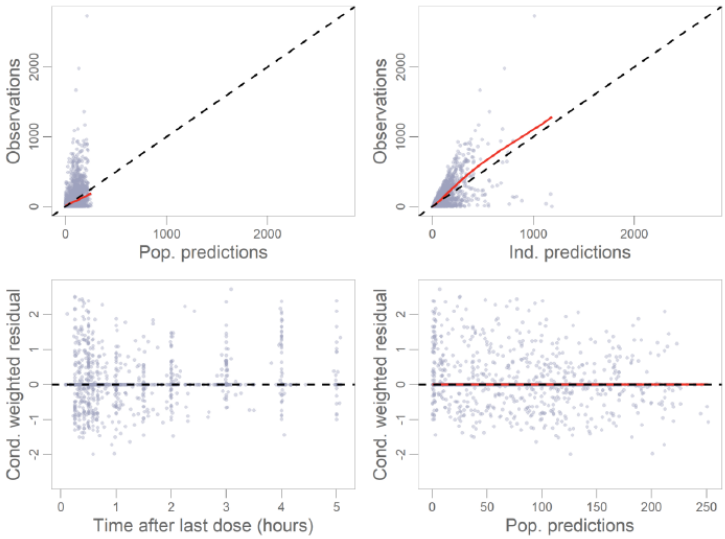
For a 38-kg paediatric patient receiving unboosted TAF, the CL/F for TAF was 112 L/h. The typical Vc/F value was 57.3 L. The ka was 1.99 h^{-1}, and D1 was 0.116 h. The $t_{1/2}$ was calculated as 0.35 h.

Standard GOF plots for the final TAF PopPK model are shown in Figure 1. The pcVPC of TAF plasma concentration-time profiles stratified by WT and booster groups are shown in Figure 2 and Figure 3.

Table 5: Summary of Parameters for Final TAF PopPK Model for Paediatric Participants

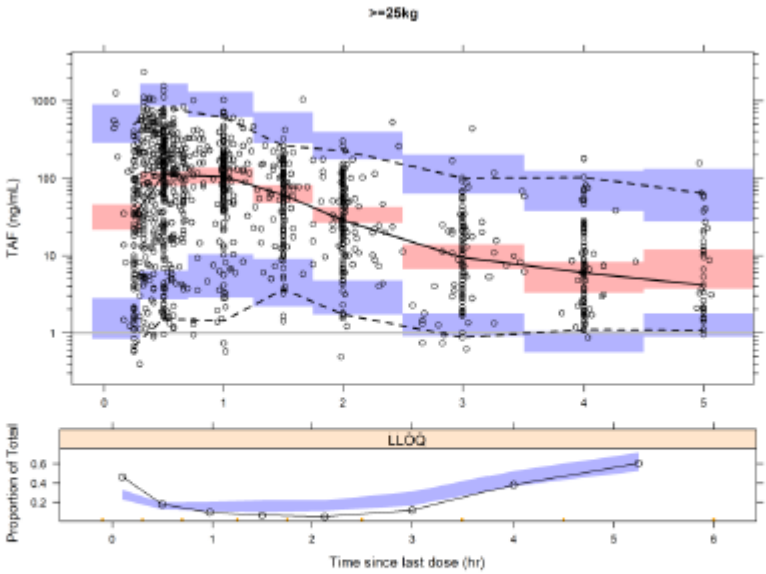
Parameter	Parameter Description	Population Estimate	Change from Typical (%)	IIV (%)
$\exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	112	–	81
$\exp(\theta_1) \times ((\frac{WT}{38})^{0.75})$	Influence of WT on CL/F, 5th %ile of WT	64	-42.9	--
	Influence of WT on CL/F, 95th %ile of WT	173	54.7	--
$\exp(\theta_2)$	Apparent central volume of distribution (non-Asian), V_c/F (L)	57.3	–	166
$\exp(\theta_1) \times ((\frac{WT}{38})^{1})$	Influence of WT on V_c/F, 5th %ile of WT	27	-52.6	--
	Influence of WT on V_c/F, 95th %ile of WT	103	78.9	--
$\exp(\theta_3)$	First order absorption rate constant, k_a (1/h)	1.99	–	–
$\exp(\theta_7)$	Duration of zero-order absorption unboosted, D1 (h)	0.116	–	–
$\exp(\theta_7) \times (1+\theta_8)$	Duration of zero-order absorption COBI or LPV/R boosted, D1 (h)	0.615	431.5	–
$1 \times (1+\theta_6)$	COBI-boosted relative bioavailability (F1)	2.9	192	–
$\exp(\theta_9)$	Lag-time (h)	0.0678	–	–
$\sqrt{\theta_4}$	Residual proportional error (%)	98	–	–
θ_5	Residual additive	0.5 [FIXED]	--	--

θ = parameter estimate; ω = standard deviation of interindividual variability; COBI = cobicistat; IIV = interindividual variability; OFV = objective function value; PK = pharmacokinetic(s); PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight
Minimum OFV = 17,895.843.
The 5th and 95th percentiles of WT are 18 and 68 kg, respectively.
Source: taf-gof-final-20211118.R



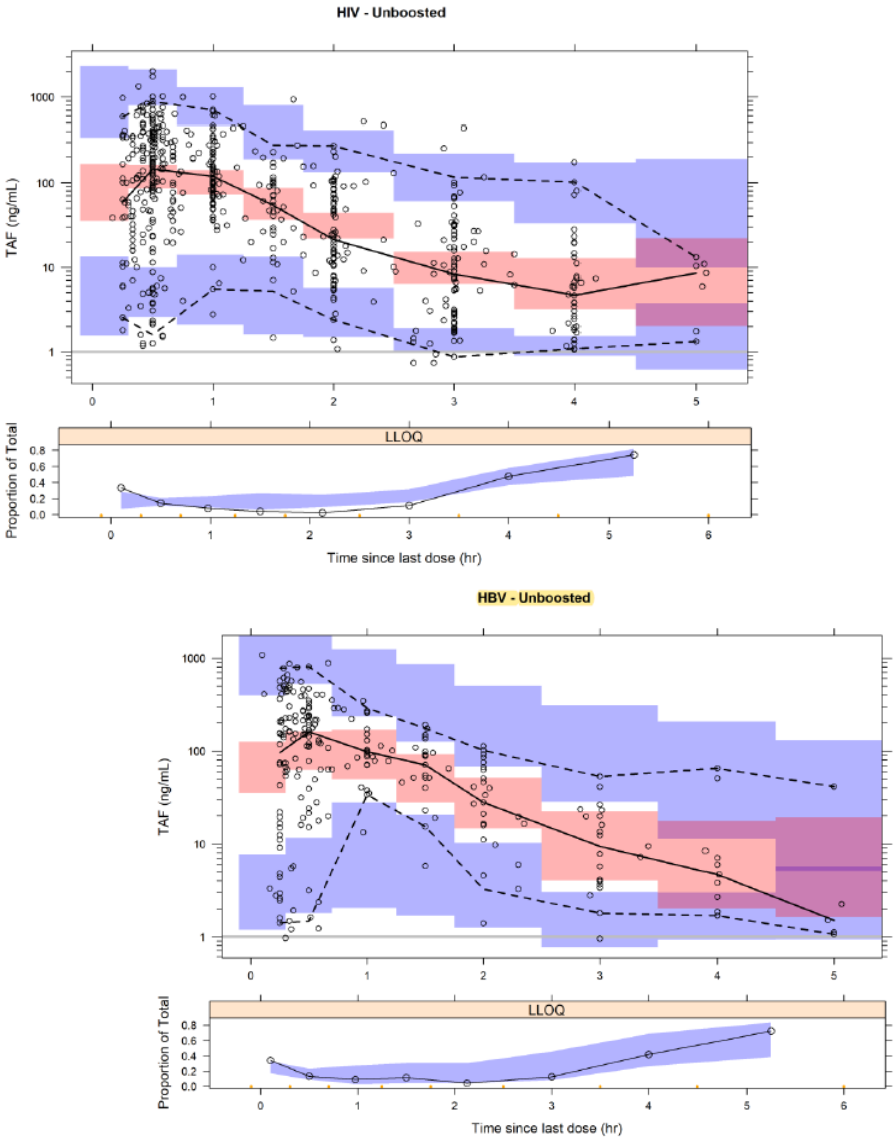
CWRES = conditional weighted residuals; Ind. = individual; Pop. = population; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide
The circles represent individual data points; the red lines represent loess smooth curves; and the dashed lines represent either the line of equality (y = x), or CWRES values of 0.
Source: taf-gof-final-20211118.R

Figure 1: Standard Goodness-of-Fit Plots for the Final TAF PopPK Model



CI = confidence interval; DV = observed concentrations; LLOQ = lower limit of quantitation; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all participants. The open black circles are the observed data. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.
Source: taf-vpc-final-20211118.R

Figure 2: pcVPC of the Final TAF PopPK Model for WT ≥25 kg



CI = confidence interval; COBI = cobicistat; DV = observed concentrations; LLOQ = lower limit of quantitation; LPV/R = lopinavir/ritonavir; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide

The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all participants. The open black circles are the observed data. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.

Source: taf-vpc-final-20211118.R

Figure 3: pcVPC of the Final TAF PopPK Model Stratified by Booster Groups (HIV Unboosted, and HBV Unboosted)

TAF steady-state exposures (AUC_{tau} and C_{max}) were simulated in paediatric patients using the Bayesian post hoc PK parameters and presented across applicable covariates in the paediatric population. The observed exposures presented in the sensitivity analysis (extrapolated range) were normalised to the baseline scenario (25 mg Unboosted TAF) for comparison purposes; this resulted in extrapolated exposures that are not representative of clinical settings. The isolated influence of statistically significant covariates on the expected steady-state exposure of TAF in paediatric patients was evaluated in a sensitivity analysis. The AUC_{tau} and C_{max} of TAF were computed for each of the scenarios based on the final PopPK model.

The sensitivity analysis showed that within paediatric patients, the effect of COBI was the most influential covariate with an increase in TAF exposures of +192%. This was followed by WT effects with

a percent change in TAF exposures ranging from approximately −40% to +91.9% (relative to the median exposures) for patients with extreme covariate values, respectively (Figure 4).

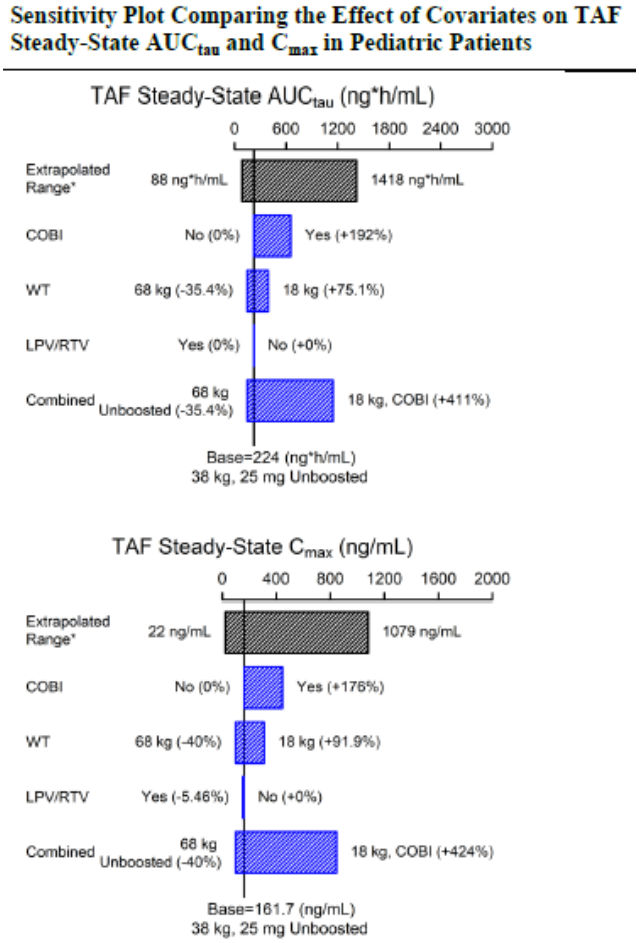
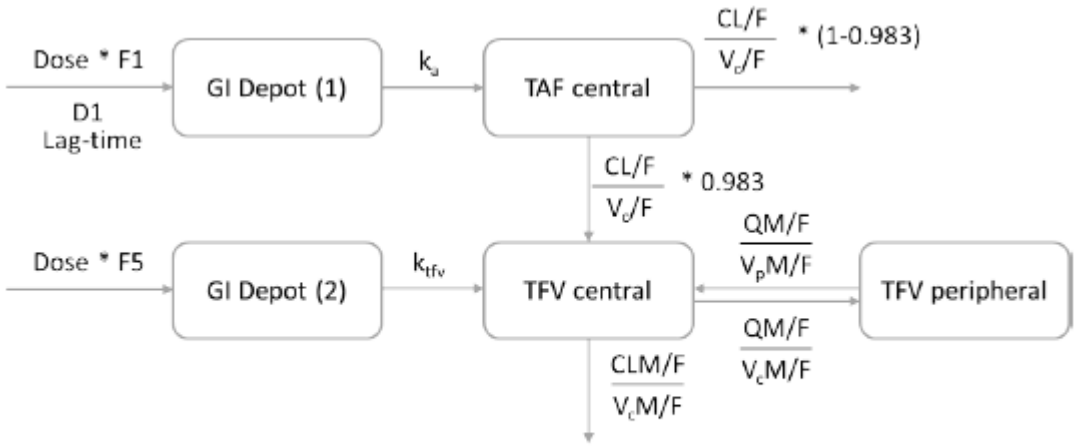


Figure 4: Sensitivity Plot Comparing the Effect of Covariates on TAF Steady-State AUC_{tau} and C_{max} in Paediatric Patients

Sequential TAF-TFV PopPK Analysis

A sequential 1-compartment TAF model and 2-compartment TFV model with first-order elimination was found to best describe the TFV paediatric data. A parallel absorption compartment with first-order process was introduced in the model to describe TFV data in the presence of the LPV/R booster. The estimated effect on TFV F was 209.5% increase. The WT effects were included on CLM/F, QM/F, VcM/F, and VpM/F using fixed allometric exponents of 0.75 and 1, for clearances and volumes of distribution, respectively. In addition, BCLCRSW was found to significantly affect CLM/F. Interindividual variability was included on CLM/F, QM/F, VcM/F, and VpM/F; and a combined proportional and additive error model was used to characterize RV (Figure 5). The final model parameter estimates for this model can be found in Table 6.

For TFV, the updated TAF PopPK model was used as input for the sequential analysis. Given the adequacy of the previously developed model to characterise TFV PK, the focus was primarily on the ability of the model to describe TFV data in the HBV infected patients. The impact of previously identified covariate effects was confirmed and repeating a full covariate analysis was not deemed necessary.



CLM/F = apparent oral clearance of TFV; k_{tfv} = first order absorption rate constant from second depot compartment; F1 = relative bioavailability of TAF; F5 = relative bioavailability for TFV; GI = gastrointestinal; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; TAF = tenofovir alafenamide; TFV = tenofovir; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

Figure 5: PopPK Model Diagram for Updated Sequential TAF-TFV Model

Table 6 provides the final parameter estimates and SEs associated with the final PopPK model. For a 38-kg paediatric patient with baseline BCL_{CRSW} of 153 mL/min/1.73 m^2, receiving unboosted, COBI-boosted, or LPV/R-boosted TAF, the CLM/F for TFV was 130 L/h. The typical VcM/F, VpM/F, and QM/F values were 2790 L, 5280 L, and 1590 L/h, respectively. The k_{tfv} was 0.138 h^{-1}. The terminal $t_{1/2}$ was calculated as 44.6 h.

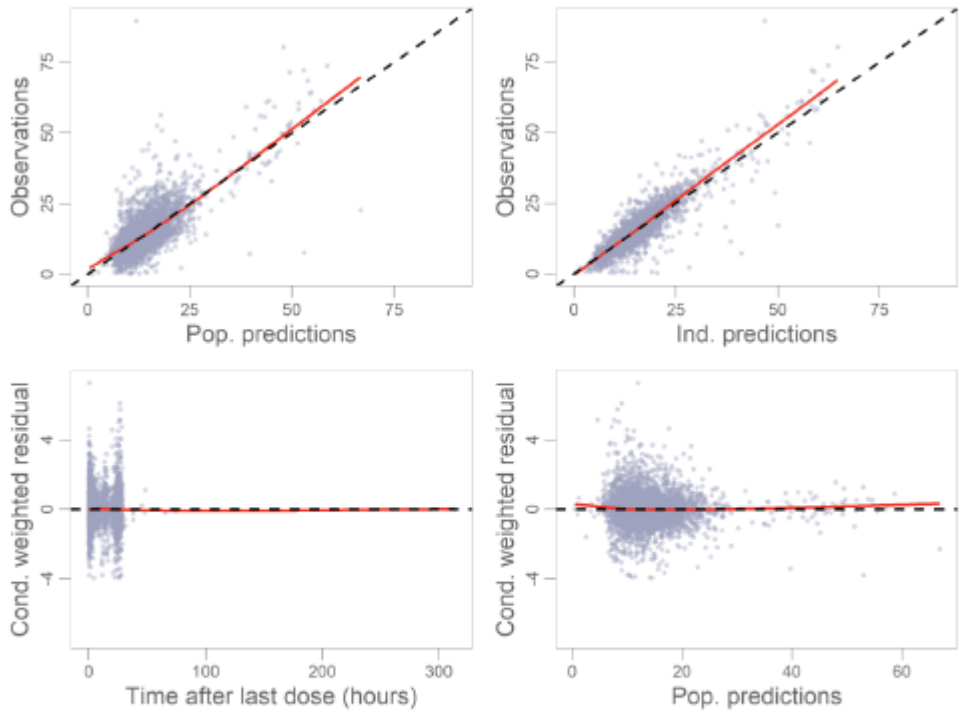
Standard GOF plots for the final TFV PopPK model are shown in Figure 6. The pcVPC of TFV plasma concentration-time profiles stratified by WT and booster groups are shown in Figure 7 and Figure 8.

Table 6: Summary of Parameters for Final TFV PopPK Model for Paediatric Participants

Parameter	Parameter Description	Population Estimate	Change from Typical (%)	IIV (%)
$\exp(\theta_1)$	Apparent oral clearance, CLM/F (L/h)	130	–	24
$\exp(\theta_1) \times ((\frac{WT}{38})^{0.75})$	Influence of WT on CLM/F, 5th %ile of WT	74	-42.9	–
	Influence of WT on CLM/F, 95th %ile of WT	201	54.7	–
$\exp(\theta_1) \times ((\frac{CLCRSW}{153})^{\theta_9})$	Influence of BCL_{CRSW} on CLM/F, 5th %ile of BCL_{CRSW}	109	-16.3	–
	Influence of BCL_{CRSW} on CLM/F, 95th %ile of BCL_{CRSW}	156	20	–
$\exp(\theta_2)$	Apparent central volume of distribution, V_cM/F (L)	2790	–	97
$\exp(\theta_1) \times ((\frac{WT}{38})^{1})$	Influence of WT on V_cM/F, 5th %ile of WT	1324	-52.6	–
	Influence of WT on V_cM/F, 95th %ile of WT	5001	78.9	–
$\exp(\theta_3)$	Apparent peripheral volume of distribution, V_pM/F (L)	5280	–	32

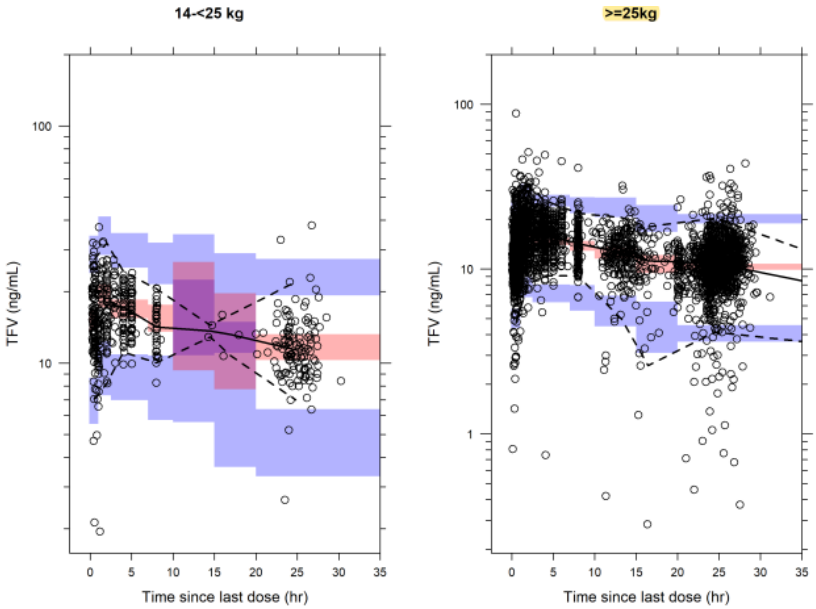
$\exp(\theta_3) \times ((\frac{WT}{38})^{1})$	Influence of WT on V_pM/F, 5th %ile of WT	2501	-52.6	–
	Influence of WT on V_pM/F, 95th %ile of WT	9448	78.9	–
$\exp(\theta_4)$	Apparent intercompartmental clearance, QM/F (L)	1590	–	40
$\exp(\theta_3) \times ((\frac{WT}{38})^{0.75})$	Influence of WT on QM/F, 5th %ile of WT	909	-42.9	–
	Influence of WT on QM/F, 95th %ile of WT	2464	54.7	–
$\exp(\theta_8)$	TFV first order absorption rate constant from second depot compartment, k_{TFV} (1/h)	0.138	–	–
$1 \times (1+\theta_7)$	LPV/r-boosted relative bioavailability	3.3	225.1	–
$\sqrt{\theta_5}$	Residual proportional error (%)	45	–	–
θ_6	Residual additive	1.3	–	–

θ = parameter estimate; CLM/F = apparent clearance of TFV; IIV = interindividual variability; k_{tfv} = first order absorption rate constant from second depot compartment; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; TFV = tenofovir; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV; WT = baseline body weight
Minimum OFV = 12862.443.
The 5th and 95th percentiles of WT are 18 and 68 kg, respectively; the 5th and 95th percentiles of BCL_{CRSW} are 114 and 207 mL/min/1.73 m², respectively.
Source: tfv-gof-final-20211124.R



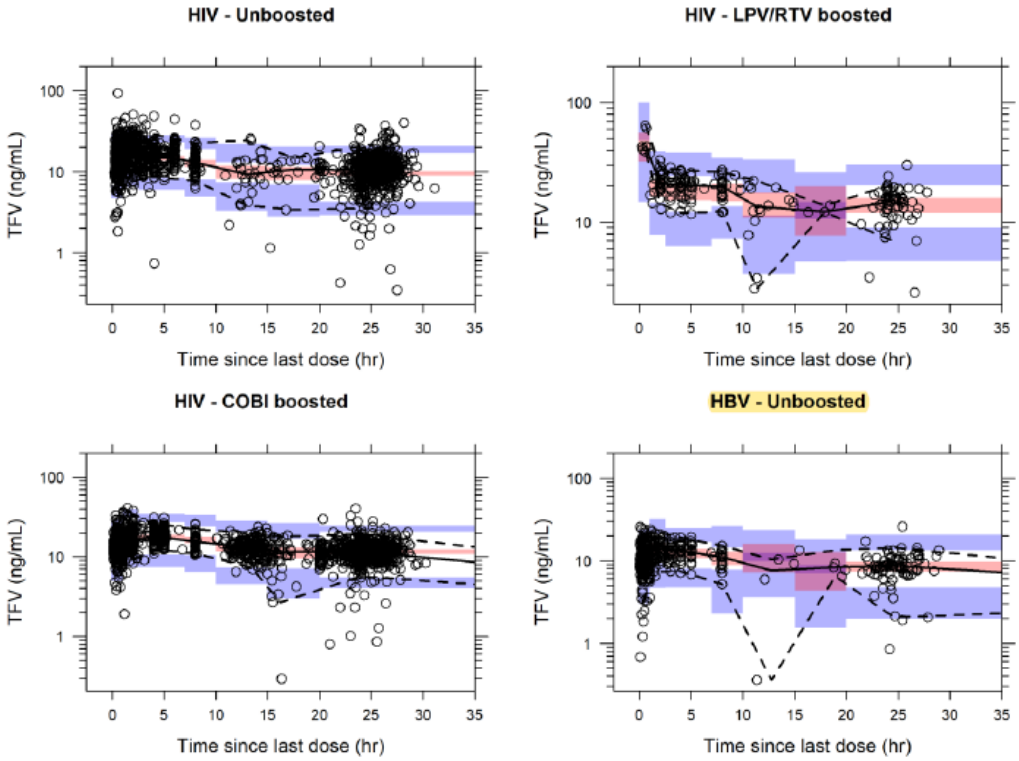
Cond. = conditional; CWRES = conditional weighted residuals; Ind. = individual; Pop. = population; PopPK = population pharmacokinetic; TFV = tenofovir
The circles represent individual data points; the red lines represent loess smooth curves; and the dashed lines represent either the line of equality (y = x), or a CWRES of 0.
Source: tfv-gof-final-20211124.R

Figure 6: Standard Goodness-of-Fit Plots for the Final TFV PopPK Model for Paediatric Participants



CI = confidence interval; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; TFV = tenofovir; WT = baseline body weight
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all participants. The open black circles are the observed data. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.
Source: tfv-vpc-final-20211124.R

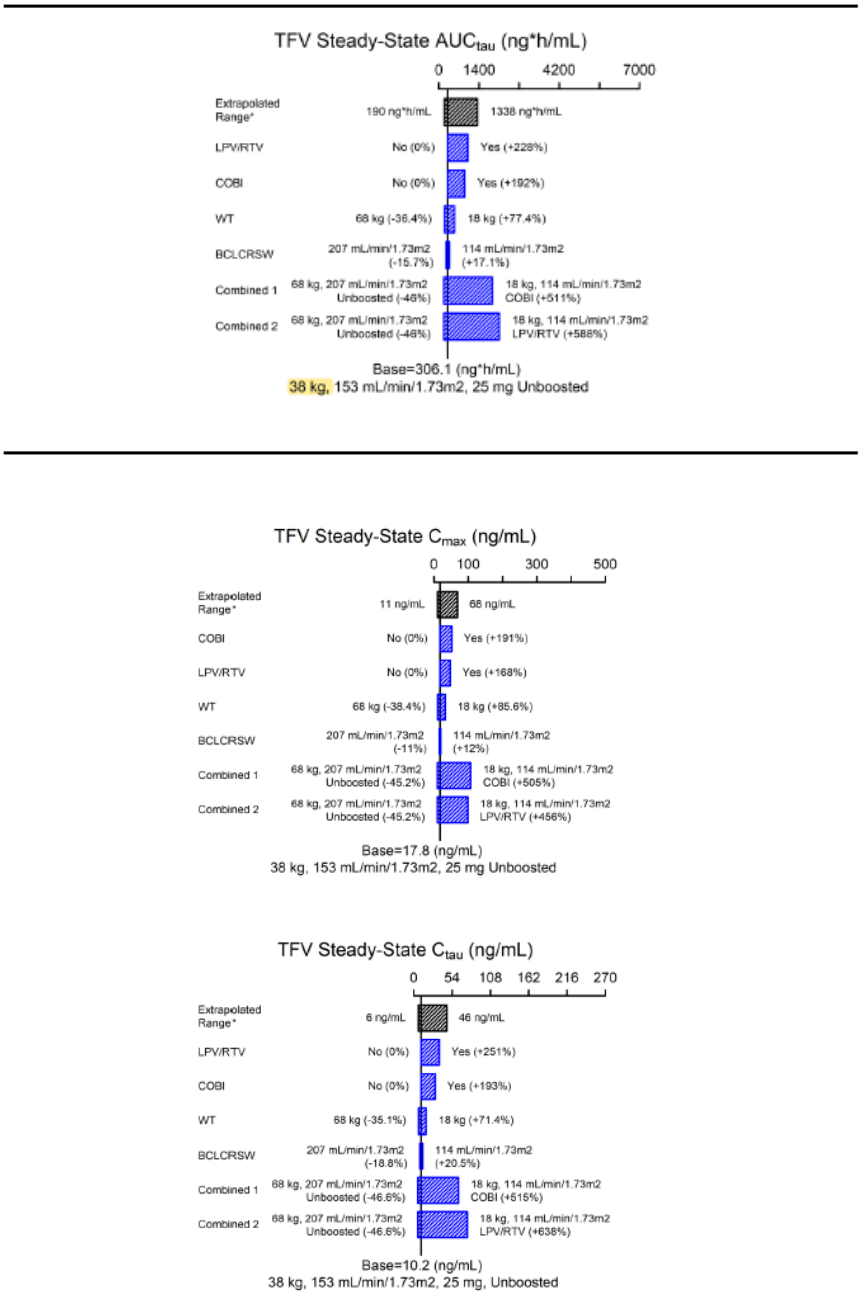
Figure 7: pcVPC of the Final TFV PopPK Model Stratified by WT (14 to < 25 kg, and ≥ 25 kg) – with Data Points



CI = confidence interval; COBI = cobicistat; DV = observed concentrations; LPV/R = lopinavir/ritonavir; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; TFV = tenofovir
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all participants. The open black circles are the observed data. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.
Source: tfv-vpc-final-20211124.R

Figure 8: pcVPC of the Final TFV PopPK Model Stratified by Booster Groups with Data Points

In sensitivity analyses TFV exposures (AUC_{tau} and C_{max} and C_{tau}) were simulated using the Bayesian post hoc PK parameters and presented across applicable covariates in the form of tornado plots (Figure 9).



COBI = cobicistat; BCL_{CRSW} = creatinine clearance derived by Schwartz equation; LPV = lopinavir/ritonavir; TFV = tenofovir; WT = baseline body weight

* The observed exposures are normalized to the baseline scenario for comparison purposes. This results in extrapolated exposures that are not representative of clinical settings.

Base, as represented by the black vertical line and values, refers to the median post hoc AUC_{tau} of TFV. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire pediatric population. Each blue shaded bar represents the influence of single or combined covariates on the steady-state exposure. The label at the left end of the bar represents the covariate(s) being evaluated. The upper and lower values for each covariate capture 90% of the plausible range in the population. The length of each bar describes the potential impact of that covariate(s) on TFV exposure at steady state, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The covariates are listed in descending order of influence. The plot for AUC_{tau} is shown in the upper panel, the plot for C_{max} is shown in the middle panel, and C_{tau} is shown in the lower panel.

Source: tfv-gof-final-20211124.R

Figure 9: Sensitivity Plot Comparing the Effect of Covariates on TFV Steady-State AUC_{tau}, C_{max}, and C_{tau} in Paediatric Patients

Discussion:

The population PK model used for justification of the 25 mg dose in paediatric HBV patients (≥6 years and ≥25 kg) is based on data from n=396 paediatric patients in total, from which n=59 were HBV patients and 337 were HIV patients. Plasma concentrations of n=12 paediatric patients of the intended patient population (≥6 – <12 years and ≥25 kg – 35 kg; HBV infection) were included, from which only n=5 had intensive PK sampling (for quantification of TAF and TFV). Mean weight in these n=12 patients was 37.9 kg. For HIV patients more subjects with lower weights were included.

Firstly, an updated PopPK model for TAF was submitted describing TAF PK as a 1-compartment model with lag-time and sequential zero- and first-order absorption and first-order elimination. Allometric exponents were fixed to 0.75 and 1 for weight effects on CL/F and Vc/F, respectively. Comedication with cobistat affected F1 (192% increase) and COBI and LPV/r were found to influence D1 (slower absorption). Interindividual variability was included on CL/F and Vc/F.

Secondly, a combined sequential model for TAF and TFV was developed using post hoc PK parameters of the final TAF PopPK model as input. A two-compartment TFV model with first-order elimination was found to best describe the TFV PK data. A parallel absorption compartment with first-order process was introduced in the model to describe TFV data in the presence of the LPV/r booster (225.1% increase) in HIV patients. Weight effects were included on CLM/F, QM/F, VcM/F, and VpM/F using fixed allometric exponents of 0.75 and 1, for CL and V. In addition, the magnitude of the BCL_{CRSW} effect on CLM/F was confirmed in the updated analysis. Interindividual variability was included on CLM/F, QM/F, VcM/F, and VpM/F. It was stated that the impact of previously identified covariate effects was confirmed and repeating a full covariate analysis was not deemed necessary. Patient status (HIV or HBV patient) was not found to be a significant covariate in the paediatric PopPK model whereas it was found to be a significant covariate on volume in the adult PopPK model (which also combined HIV and HBV data). This is probably due to lack of sufficient data in the paediatric population to show a significant difference. Since indication did not influence clearance values, it is considered acceptable not to include this covariate since it will not influence maintenance dosing.

Only few data are available in paediatric HBV patients and the proposed dose (25 mg as in adults) for paediatric HBV patients ≥ 6 years of age and with a body weight between 25 and 35 kg is mainly based on the PopPK model. In order to evaluate whether the model is qualified for the intended purpose, the following issues were adequately addressed by the MAH, at the request of the CHMP:

- The requested GOF plots have been provided and are considered acceptable by the CHMP.

- The requested plots have also been provided for TAF and TFV. The CHMP is of the view that pcVPCs show that, overall, observed concentrations are well captured by the model, with only a slight underprediction around C_{max} for HIV-COBI boosted patients. The issue was therefore considered resolved by the Committee.

Section 5.2 of the SmPC was amended accordingly, introducing pharmacokinetics data of tenofovir alafenamide and its metabolite tenofovir in paediatric patients aged 6 to < 18 years and adults as compared to that in adolescents and adults.

2.3.3. Pharmacodynamics

PK/PD analyses, i.e., exposure-response relationships for efficacy and safety and maximum increase from baseline in serum creatinine (sCR) at week 24, were evaluated using PK parameters derived from popPK modelling. Please see section below.

Clinical Virology

Resistance surveillance was conducted. For further information, please refer to clinical efficacy section.

2.3.4. PK/PD modelling

N/A

2.3.5. Discussion on clinical pharmacology

Extrapolation concept and extrapolation plan were discussed during the procedure. In general, it is expected that a similar exposure (AUC_{tau} and C_{max}) is demonstrated between paediatric CHB patients 6 to < 12 years of age weighing at least 25 kg and adults based on PK data and popPK model to allow for an extrapolation of efficacy and safety data from adults to the paediatric population. The MAH was requested to address this concern. The CHMP considered that the related data provided by the Company indicated that the popPK model reasonably well captured the observed TFV concentrations in paediatric HBV patients. AUC and C_{max} values in younger patients were comparable to those in adults. Hence, extrapolation of efficacy and safety data from adults to children 6 to < 12 years of age and weighing at least 25 kg was generally considered acceptable by the CHMP.

However, C_{tau} was clearly lower in younger HBV patients compared to adults with HBV. The clinical impact on the lower trough concentrations with regard to efficacy and resistance development in younger HBV patients was discussed also based on available data from adolescents (e.g., literature data) for which Vemlidy is already approved but in which C_{trough} is even lower than in HBV patients aged 6-12 years according to the submitted popPK data. The MAH submitted the required updated analysis of the exposure in paediatric patients as compared to adults. Particularly for C_{trough}, a considerable proportion of paediatric patients had lower exposures as compared to adults. The underlying reason of this finding was unclear, in particular as flat dosing of 25 mg QD was used for paediatric and adult participants, which raised the question if the presented data on TAF and TFV exposure in paediatric CHB patients were correct. According to the MAH's position, the efficacy response rate was not dependent upon the C_{trough} concentration. The CHMP was in agreement with the above-mentioned approach.

Section 4.2 of the SmPC was amended accordingly, reading as follows:

Posology

Adults and paediatric patients at least 6 years of age and older weighing at least 25 kg: one tablet once daily

2.3.6. Conclusions on clinical pharmacology

The CHMP is of the view that the PopPK model is qualified to confirm the 25 mg dose in the intended age group, based on extrapolation of the adult's efficacy and safety data. The PK/PopPK data are therefore considered sufficient to justify the 25 mg dose for the treatment of children 6 to <12 years of age weighing ≥ 25 kg. Section 4.2 of the SmPC was amended accordingly.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No additional dose response studies have been submitted.

2.4.2. Main study

Title of Study

GS-US-320-1092, 'A Randomised, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection'

Methods

Study GS-US-320-1092 is an ongoing double-blind, placebo-controlled, multicenter study of the safety, tolerability, PK, and antiviral activity of TAF administered once daily in treatment-naive and treatment-experienced adolescents and children with CHB. Participants were randomised to receive either blinded TAF 25 mg tablets or placebo tablets once daily through Week 24, and the primary efficacy endpoint was the percentage of participants who achieved HBV DNA < 20 IU/mL at Week 24. Following double blind treatment for 24 weeks, all participants were eligible to roll over to receive open label TAF for up to an additional 216 weeks (through Week 240).

The data presented are from the interim, primary endpoint analysis for safety, efficacy, and PK, which was conducted when all participants in Cohort 1 (adolescents 12 to less than 18 years of age and weighing at least 35 kg) and Cohort 2 Group 1 (paediatric participants 6 to < 12 years of age and weighing at least 25 kg) had completed their Week 24 (i.e., primary endpoint) visit or prematurely discontinued from the study.

Figure 10 and Figure 11 show the study schemes for Cohort 1 and Cohort 2, respectively.

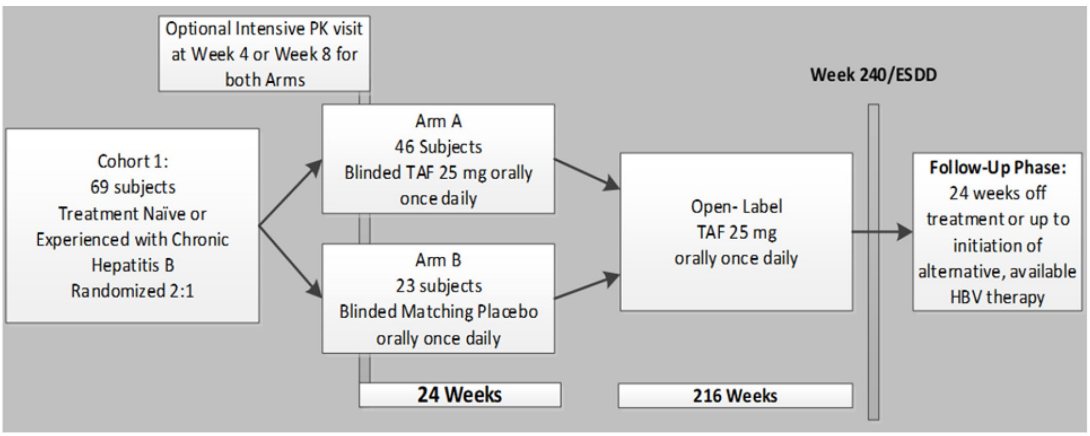


Figure 10: Study scheme for Cohort 1

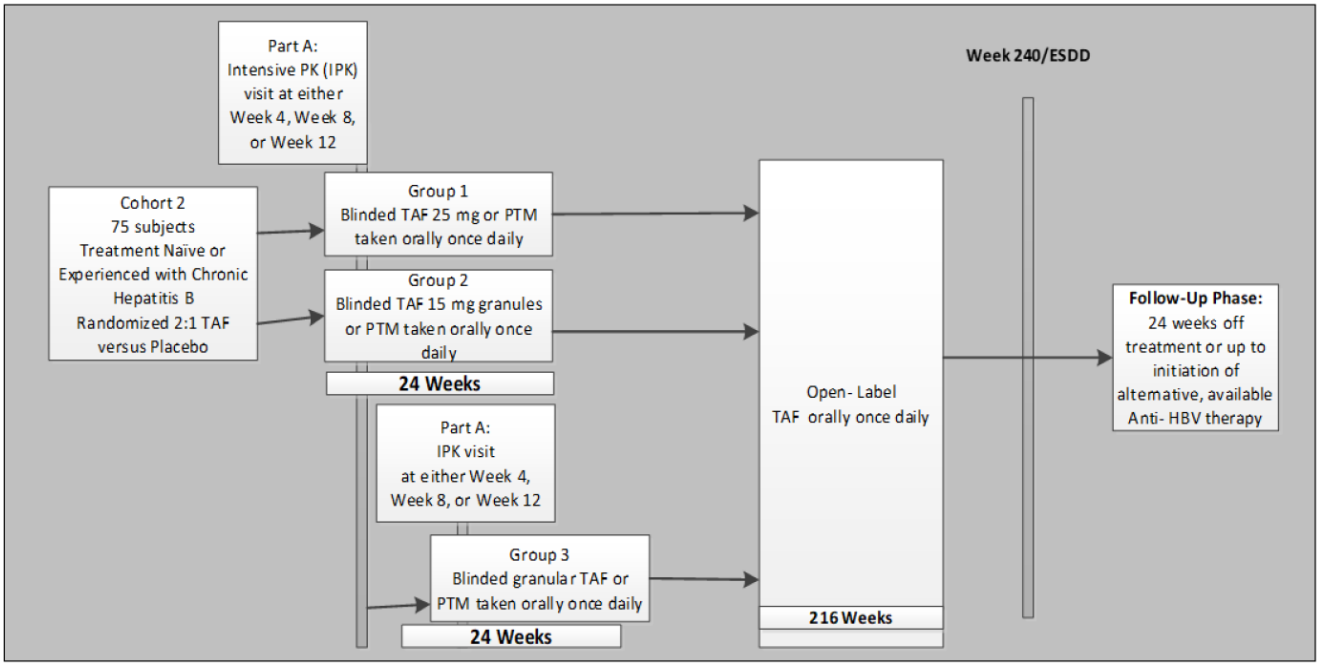


Figure 11: Study scheme for Cohort 2

Study participants

Cohort 1: At least 69 male and female adolescent participants (12 to < 18 years of age weighing ≥ 35 kg) were planned to be enrolled and randomised to receive either the blinded TAF 25 mg tablet or placebo-to-match (PTM) tablet once daily through Week 24. Randomisation was stratified by age (12 to < 15 and 15 to < 18 years of age).

Cohort 2: At least 75 children were planned to be enrolled in Cohort 2 of the study. Cohort 2 is divided into 3 dose groups (Groups 1, 2, and 3) by age and weight, with enrolment into each dose group divided into 2 parts: Part A (mandatory intensive PK to confirm the dose) and Part B (identical to part A in design but no intensive PK sampling).

The duration of double-blind treatment for both cohorts was 24 weeks. After completing the double-blind phase, all Cohort 1 and Cohort 2 Group 1 participants were eligible to roll over to receive open-label TAF 25 mg once daily for up to an additional 216 weeks (total planned duration of study treatment is 240 weeks). The interim analysis was performed when all participants in Cohort 1 and Cohort 2 Group 1 had completed their Week 24 visit or prematurely discontinued from the study.

Inclusion criteria:

1) Males and nonpregnant, nonlactating females

2) Age at screening: 12 to < 18 years (Cohort 1) and 6 to < 12 years (Cohort 2 Group 1) old

3) Weight at screening as follows:

Cohort (Group)	Age Range	Weight
Cohort 1	12 years to < 18 years	>= 35 kg
Cohort 2 (Group 1)	**6 years to < 12 years**	**>= 25kg**

4) Willing and able to provide written informed consent/assent (child and parent/legal guardian)

5) Documented evidence of CHB (e.g., HBsAg positive for ≥ 6 months)

6) HBeAg positive, or HBeAg negative, chronic HBV infection with all of the following:

- Screening HBV DNA ≥ 2×10^4 IU/mL
- Screening serum ALT > 45 U/L (> 1.5 × ULN: 30 U/L) and ≤ 10 × ULN (by central laboratory range)

7) Treatment-naive (defined as < 12 weeks of oral antiviral treatment with any oral nucleos(t)ide analogue) OR treatment-experienced participants (defined as participants meeting all entry criteria [including HBV DNA and serum ALT criteria] and > 12 weeks of oral antiviral treatment with any oral nucleos(t)ide analogue) were eligible for enrolment. All participants taking oral antiviral treatment were required to have discontinued oral nucleos(t)ide therapy ≥ 16 weeks prior to screening to avoid ALT flare if randomised to the placebo arm.

8) Any previous treatment with IFN (pegylated or non-pegylated) must have ended at least 24 weeks prior to the baseline visit.

9) Estimated CLcr ≥ 80 mL/min/1.73m2 (using the Schwartz formula; = k × L/sCR) (k = proportionality constant; L = height in centimeters; and sCR = serum creatinine [mg/dL])

10) Normal electrocardiogram (ECG) (or if abnormal, determined by the investigator not to be clinically significant)

11) Had to be willing and able to comply with all study requirements

Exclusion Criteria:

1) Pregnant females, females who were breastfeeding or who believed they may wish to become pregnant during the course of the study

2) Males and females of reproductive potential who were unwilling to use an "effective," protocol-specified method(s) of contraception during the study, as specified in Appendix 5 of the study protocol (Appendix 16.1.1).

3) Coinfection with HCV, HIV, or hepatitis delta virus (HDV)

4) Evidence of HCC (Note: if screening alpha fetoprotein [AFP] is ≤ 50 ng/mL no imaging study was needed; however, if the screening AFP is > 50 ng/mL an imaging study was required)

5) Any history of, or current evidence of, clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage)

6) Abnormal hematological and biochemical parameters, including:

a) Hemoglobin < 10 g/dL

b) Absolute neutrophil count < 1500/mm3

c) Platelets ≤ 100,000/mm3

d) Aspartate aminotransferase (AST) or ALT > 10 × ULN (by central laboratory range)

e) Total bilirubin > 2.5 × ULN

f) Albumin < 3.0 g/dL

g) International normalised ratio (INR) > 1.5 × ULN (unless on stable anticoagulant regimen)

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

8) Has received a solid organ or bone marrow transplant

9) Currently receiving therapy with immunomodulators (e.g., corticosteroids) or immunosuppressants

10) Significant renal, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator

11) Malignancy within the 5 years prior to screening. Participants under evaluation for possible malignancy were not eligible.

12) Known hypersensitivity to study drugs, metabolites, or formulation excipients

13) Current alcohol or substance abuse judged by the investigator to potentially interfere with participant compliance

14) Participants on prohibited concomitant medications (Section 5.4 of the protocol [Appendix 16.1.1]). Participants on prohibited medications, otherwise eligible, were required to undergo a washout period of at least 28 days prior to the baseline visit.

15) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements.

Prior and Concomitant Therapy:

Concomitant/previous medications taken within 30 days of screening, up to and including the date of the visit 4 weeks after discontinuation of study drug, were recorded.

The following medications were prohibited during the screening period and for a minimum of 28 days prior to the Day 1 visit through the end of treatment:

- Investigational agents or devices for any indication
- Nephrotoxic agents (e.g., aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine)
- Probenecid
- Agents that reduce renal function or compete for active tubular secretion with TFV (e.g., cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir)
- Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use]), immunosuppressant, or immunomodulating agents
- Bisphosphonates
- Medications excluded due to the potential for drug-drug interaction with TAF listed in Section 5.4 of the protocol (Appendix 16.1.1)

In jurisdictions in which TAF has been approved, the local prescribing information for TAF dose recommendations with concomitant medications was consulted.

Treatments

Regimen:

Paediatric participants (children and adolescent) with CHB aged 6 years old and above weighing at least 25 kg were treated with the approved adult dose of TAF, i.e., 25 mg tablet once daily or placebo.

Duration:

The duration of the double blind phase was 24 weeks. After completing the double-blind phase, all participants were eligible to roll over to receive open label TAF 25 mg once daily for up to an additional 216 weeks.

Justification of dose and duration of treatment:

For adolescent participants (12 to < 18 years) with CHB weighing ≥ 35 kg, the already approved dose of TAF 25 mg was proposed for evaluation.

Children 6 to < 12 years old weighing ≥ 25 kg also received the adult/adolescent dose of TAF (25 mg). This dose was based on allometric scaling of adult exposures from the Genvoya and Biktarvy development programs for TAF, and from the TAF development program in participants with CHB for TFV exposures, considering correlations between body weight and clearance capacity (liver volume/size for TAF, and renal capacity for TFV).

Objectives

Primary objectives

Cohort 1 (adolescents 12 to < 18 years of age, ≥ 35 kg):

- To evaluate the safety, tolerability, and antiviral activity (HBV DNA < 20 IU/mL) of TAF 25 mg once daily versus placebo at Week 24 in adolescent participants with CHB

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

Part A:

- To evaluate the steady-state pharmacokinetics (PK) of TAF and TAF-metabolite, TFV, and confirm the dose of TAF given once daily in children with CHB

Part B:

- To evaluate the safety, efficacy, and tolerability of TAF given once daily at Week 24 in children with CHB
- To evaluate the antiviral activity (HBV DNA < 20 IU/mL) of TAF given once daily versus placebo at Week 24 in children with CHB

Secondary objectives

- To evaluate the open-label safety and tolerability of TAF given once daily at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the antiviral activity (HBV DNA < 20 IU/mL) of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB

- To evaluate the serologic response (loss of hepatitis B e antigen [HBeAg] and seroconversion to antibody against hepatitis B e antigen [anti-HBe], and loss of hepatitis B surface antigen (HBsAg) and seroconversion to antibody against hepatitis B surface antigens [anti-HBs]) of TAF versus placebo at Week 24, and of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the biochemical response (alanine aminotransferase [ALT] normalization) of TAF versus placebo at Week 24, and of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the change in fibrosis as assessed by FibroTest® of TAF versus placebo at Week 24, and of open-label TAF at Weeks 48, 96, and 240 in adolescents and children with CHB
- To evaluate the palatability and acceptability of TAF at baseline and at Weeks 4, 24, and 36 in adolescents and children with CHB
- To evaluate the incidence of drug resistance mutations associated with TAF at Weeks 24, 48, 96, and 240 in adolescents and children with CHB
- To evaluate the steady-state PK of TAF and TFV following administration of TAF 25 mg once daily in adolescents with CHB

Outcomes/endpoints

The primary efficacy endpoint for Study GS-US-320-1092 was the proportion of participants with plasma HBV DNA < 20 IU/mL at Week 24. The primary cut-off of HBV DNA was < 20 IU/mL to reflect the current HBV DNA assay LLOQ.

An endpoint of HBV DNA suppression is widely recognised as a useful marker for the assessment of antiviral activity in patients with CHB, is a standard measurement for evaluating the antiviral activity of a drug in adult and paediatric patients with CHB, and was the basis for Vemlidy approval in adults (i.e., proportion with HBV DNA < 29 IU/mL at Week 48).

Secondary efficacy endpoints included additional analysis of HBV DNA and analyses of ALT, noninvasive changes in liver fibrosis (i.e., serum FibroTest), HBeAg and HBsAg serology, virological resistance, and acceptability/palatability analysis.

Sample size

Approximately 144 participants were planned to be enrolled with a randomization ratio 2:1 to TAF or matching placebo in 2 cohorts.

Cohort 1 was planned to enrol at least 69 adolescent participants. This sample size was expected to provide 91% power to detect a 32% difference in the proportion of participants with HBV DNA < lower limit of quantitation (LLOQ) at Week 24 based on a 2-sided Fisher's exact test at a significance level of 0.05. This calculation assumed a response rate of 3% in the placebo arm and 35% in the TAF arm. The assumptions were derived from the TAF adult study, GS-US-320-0110 (HBeAg positive participants), based on the proportion of participants in the TAF arm with HBV DNA <LLOQ using a missing = failure (M = F) approach.

Cohort 2 in children enrolled approximately 75 participants into 2 parts. A minimum of 27 participants were enrolled in Part A, including 6 participants (6 to < 12 years and ≥ 25 kg), 9 participants (6 to <12 years and ≥17 kg to < 25 kg), and 12 participants (2 to < 6 years and < 17 kg). With a 2:1

randomization ratio, 4, 6, and 8 participants were expected to be randomized to receive active TAF in this study Cohort, respectively. Comparing with population PK data for TAF in 539 participants derived from E/C/F/TAF HIV Studies GS-US-292-0104 and GS-US-292-0111, the sample sizes were expected to provide 39%, 51%, and 61% power, respectively, to conclude equivalence of TAF AUC_{tau} in children age 2 to < 12 years in each dosing group versus adult participants, assuming the expected geometric mean ratio is 1, equivalency lower boundary is 70%, one-sided test performed at an alpha level of 0.05, and the SD of AUC_{tau} is 0.52 ng•h/mL (natural-log scale). The samples sizes in this study was considered to provide sufficient assessment of the analysis given that PK data for TAF in children living with HIV (6 to <12 years weighing ≥ 25 kg) is already available, which was used to further support dose confirmation in this group.

The sample size of at least 75 participants in Cohort 2 was expected to provide 91% power to detect a 32% difference in the proportion of participants with HBV DNA < LLOQ at Week 24 based on a 2-sided Fisher's exact test at a significance level of 0.05. This calculation assumed a response rate of 3% in the placebo arm and 35% in the TAF arm. The assumptions are derived from the TAF adult study, GS-US-320-0110 (HBeAg positive participants), based on the proportion of participants in the TAF arm with HBV DNA < LLOQ using a M = F approach.

Cohort 2, Group 1 participants were combined with Cohort 1 participants to provide a summary of available efficacy, safety, and PK results for all participants under treatment with TAF 25 mg. Cohort 2, Groups 2 and 3 will be summarized separately in a future analysis and will enrol approximately 63 participants to ensure sufficient statistical power.

Randomisation

A centralised randomisation procedure via an interactive web response system (IWRS) was used for this study, whereby study treatment was assigned to participants according to the randomisation schedule. A unique participant number was provided during randomisation. Eligible participants (n = 150) were randomised 2:1 to receive either blinded TAF or placebo for 24 weeks. Participants in Cohort 1 were stratified based on age (12 to < 15 years and 15 to < 18 years). Cohort 2 consisted of 3 groups with Group 1 including participants 6 to < 12 years of age weighing ≥ 25 kg, Group 2 including participants 6 to <12 years of age weighing ≥17 kg to < 25 kg and Group 3 including participants 2 to < 6 years of age weighing < 17 kg.

Blinding (masking)

The Clinical Pharmacology team was unblinded when there was a need to review the PK data in adolescent participants and children for dose selection and dose confirmation. Unblinded information was kept confidential.

Before the study was formally unblinded at the Week 24 analysis, HBV DNA results were blinded to investigators, participants, and Gilead personnel involved in the clinical conduct of the study from baseline to Week 36. The only exception was in the case of ALT flare, considering a situation of medical need, when serial HBV DNA values from baseline through time of event was made available to the investigator. Additionally, Gilead Global Patient Safety (GLPS) was provided with unblinding information upon request for expedited reporting of suspected unexpected serious adverse reactions.

The study was unblinded to a limited number of Gilead study team personnel at the time of the primary end point analysis at Week 24 for Cohort 1 and Cohort 2 Group 1 once all participants in Cohort 1 and Cohort 2 Group 1 completed the Week 24 visit or prematurely discontinued prior to Week 24.

Statistical methods

The primary efficacy analysis was conducted after the last randomised participant reached Week 24 or discontinued study drug prematurely. The primary efficacy analysis used the Full Analysis Set (FAS), which included all participants who were randomised into the study and received at least 1 dose of study drug. The purpose of the primary efficacy end point analysis was to evaluate the difference between treatment with TAF and placebo in the proportion of participants with HBV DNA < 20 IU/mL (by missing equals failure [M = F] analysis) at Week 24.

A P value testing the superiority of TAF over placebo for the proportion of HBV DNA < 20 IU/mL was calculated using the stratified Cochran-Mantel-Haenszel (CMH) test. The analysis of the proportion of participants with plasma HBV DNA < 20 IU/mL at Week 24 was repeated within each subgroup.

The analyses for the secondary efficacy end points were conducted using the FAS, unless otherwise specified.

Results

Participant flow

Table 7: Disposition of participants (all screened participants)

	Cohort 1		Cohort 2 Group 1		Total		
	TAF 25mg	Placebo	TAF 25mg	Placebo	TAF 25mg	Placebo	Overall
Screened							161
Screen failure participants who were not randomized							73
Participants who met all eligibility criteria and were not randomized							3
COVID-19 resulted in temporary halt of enrollment							1
Withdrew consent							2
Randomized Analysis Set	47	23	12	6	59	29	88
Safety Analysis Set	47	23	12	6	59	29	88
Full Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Per Protocol Analysis Set	44 (93.6%)	23 (100.0%)	11 (91.7%)	5 (83.3%)	55 (93.2%)	28 (96.6%)	83 (94.3%)
Double-Blind Phase							
Completed Double-Blind drug	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Continuing	0	0	0	0	0	0	0
Prematurely discontinued	0	0	0	0	0	0	0

COVID-19 = coronavirus disease 2019; TAF = tenofovir alafenamide
Denominator for percentages was the Safety Analysis Set.
Source: Table 15.8.1.4

Recruitment

A total of 161 participants were screened for this study; 73 participants failed screening, including 3 participants who met all eligibility criteria but were not randomised due to COVID-19 resulting in

temporary halt of enrolment (1 participant) or withdrawal of consent (2 participants). Of the 161 participants screened, 88 were randomised (Cohort 1 TAF 47 participants, placebo 23 participants; Cohort 2 Group 1 TAF 12 participants, placebo 6 participants). The 88 participants were randomised and treated at 36 study centers in the following countries/regions: 1 in Belgium, 2 in Hong Kong, 12 in India, 1 in New Zealand, 5 in Romania, 17 in Russia, 8 in South Korea, 8 in Taiwan, and 34 in the US. All participants who were randomised received study drug or placebo and were included in the Full Analysis Set (59 TAF participants; 29 placebo participants).

All 88 participants who were randomised completed the double-blind study treatment. No participant discontinued study drug or the study during the double blind phase.

Conduct of the study

Key dates

Table 8 lists the key dates relevant to the conduct of the study.

Table 8: Key dates of study GS-US-320-1092

Event	Date
First participant screened	22 November 2016
First participant enrolled/randomized	10 August 2017
Last participant enrolled/randomized	22 December 2020
Last participant last visit for the primary end point	07 June 2021
Last participant last visit for this interim Week 24 CSR	12 August 2021
Database finalization	16 August 2021
Treatment unblinding	16 August 2021

Changes in the protocol:

The protocol was amended 5 times during the course of Study GS-US-320-1092, as indicated in the following Table 9:

Table 9: Protocol amendments

Protocol/Amendment	Date
Original	29 March 2016
Amendment 1	30 May 2016
Amendment 2	13 October 2017
Amendment 3	30 October 2017
Amendment 4	06 February 2018
Amendment 5	03 September 2021
Coronavirus Outbreak Crisis Management Plan	05 October 2020

Protocol deviations:

Due to disruption in study conduct as a result of the COVID-19 pandemic, some efficacy and/or safety assessments were not conducted and the handling of these protocol deviations is described in the SAP. A summary of participants who missed study visit(s) or had virtual study visit(s) due to restrictions related to the COVID-19 pandemic is provided. None of these missed or virtual study visits affected the overall quality or interpretation of the study data.

Table 10 provides a categorical summary of important protocol deviations that occurred during the study up to the data cut-off date. Protocol deviations were documented during routine monitoring visits and reviewed by the study team prior to study unblinding.

A total of 106 important protocol deviations occurred in 53 participants during the study, of which 65 occurred in 35 participants in the TAF group and 41 occurred in 17 participants in the placebo group.

In addition, 2 unintended unblinding events occurred with 9 investigators and 3 Gilead personnel, respectively, during the conduct of the study.

None of these important protocol deviations affected the overall quality or interpretation of the study data.

Table 10: Important protocol deviations (Randomised Analysis Set)

	Cohort 1		Cohort 2 Group 1		Total	
Protocol Deviation Category	**TAF 25 mg (N = 47)**	**Placebo (N = 23)**	**TAF 2 5mg (N = 12)**	**Placebo (N = 6)**	**TAF 25 mg (N = 59)**	**Placebo (N = 29)**
Participants with at least 1 important protocol deviation	28 (59.6%)	15 (65.2%)	7 (58.3%)	2 (33.3%)	35 (59.3%)	17 (58.6%)
Off-schedule procedure	16 (34.0%)	12 (52.2%)	6 (50.0%)	1 (16.7%)	22 (37.3%)	13 (44.8%)
Wrong treatment or incorrect dose	9 (19.1%)	6 (26.1%)	0	0	9 (15.3%)	6 (20.7%)
Other treatment compliance issue	9 (19.1%)	3 (13.0%)	1 (8.3%)	0	10 (16.9%)	3 (10.3%)
Missing data	3 (6.4%)	4 (17.4%)	1 (8.3%)	1 (16.7%)	4 (6.8%)	5 (17.2%)
Excluded concomitant medication	2 (4.3%)	0	0	0	2 (3.4%)	0
Other	0	2 (8.7%)	0	0	0	2 (6.9%)
Eligibility criteria	1 (2.1%)	0	0	0	1 (1.7%)	0
Informed consent	1 (2.1%)	0	0	0	1 (1.7%)	0

TAF = tenofovir alafenamide
Participants with multiple protocol deviations were counted only once in each protocol deviation category.
Source: Table 15.8.2

Baseline data

Demographic and baseline characteristics were generally similar between the TAF and placebo groups, with no statistically significant differences between the groups at baseline.

Demographic and baseline characteristics are summarized in Table 11. The median age in Cohort 1 was 15 years (range: 12 to 17 years) in both TAF and placebo groups and Cohort 2 Group 1 was 10 years (range: 7 to 11 years) in the TAF group and 8 years (range: 7 to 9 years) in the placebo group. The median (Q1, Q3) weight for participants in Cohort 1 was 54.6 kg (46.2, 61.1) for the TAF group and 55.8 kg (50.4, 64.3) for the placebo group, and for participants in Cohort 2 Group 1 was 37.1 kg (30.7, 43.7) for the TAF group and 32.2 kg (25.6, 34.5) for the placebo group. The majority of participants were Asian (65.9%); 25.0% and 5.7% of the participants, respectively, were White and Black or African American. The majority of participants were from Europe or North America (64.8%).

Table 11: Demographic and baseline characteristics (Safety Analysis Set)

	Cohort 1		Cohort 2 Group 1		Total		
	TAF 25 mg (N = 47)	**Placebo (N = 23)**	**TAF 25 mg (N = 12)**	**Placebo (N = 6)**	**TAF 25 mg (N = 59)**	**Placebo (N = 29)**	**Overall (N = 88)**
Age (years)							
N	47	23	12	6	59	29	88

	Cohort 1		Cohort 2 Group 1		Total		
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	Overall (N = 88)
Mean (SD)	15 (1.9)	15 (1.5)	10 (1.3)	8 (0.8)	14 (2.7)	13 (3.0)	14 (2.8)
Median	15	15	10	8	14	14	14
Q1, Q3	13, 17	14, 16	10, 11	8, 9	12, 16	12, 16	12, 16
Min, max	12, 17	12, 17	7, 11	7, 9	7, 17	7, 17	7, 17
Sex at birth							
Female	20 (42.6%)	7 (30.4%)	5 (41.7%)	5 (83.3%)	25 (42.4%)	12 (41.4%)	37 (42.0%)
Male	27 (57.4%)	16 (69.6%)	7 (58.3%)	1 (16.7%)	34 (57.6%)	17 (58.6%)	51 (58.0%)
Race							
Asian	33 (70.2%)	18 (78.3%)	4 (33.3%)	3 (50.0%)	37 (62.7%)	21 (72.4%)	58 (65.9%)
Black or African American	2 (4.3%)	2 (8.7%)	1 (8.3%)	0	3 (5.1%)	2 (6.9%)	5 (5.7%)
Native Hawaiian Or Other Pacific Islander	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)
Other	2 (4.3%)	0	0	0	2 (3.4%)	0	2 (2.3%)
White	9 (19.1%)	3 (13.0%)	7 (58.3%)	3 (50.0%)	16 (27.1%)	6 (20.7%)	22 (25.0%)
Ethnicity							
Hispanic or Latino	2 (4.3%)	0	0	0	2 (3.4%)	0	2 (2.3%)
Not Hispanic or Latino	44 (93.6%)	22 (95.7%)	12 (100.0%)	6 (100.0%)	56 (94.9%)	28 (96.6%)	84 (95.5%)
Not permitted	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Region							
Asia	17 (36.2%)	11 (47.8%)	1 (8.3%)	2 (33.3%)	18 (30.5%)	13 (44.8%)	31 (35.2%)
Europe or North America	30 (63.8%)	12 (52.2%)	11 (91.7%)	4 (66.7%)	41 (69.5%)	16 (55.2%)	57 (64.8%)
Weight (kg)							
N	47	23	12	6	59	29	88
Mean (SD)	54.0 (10.74)	56.5 (10.96)	37.9 (7.96)	30.8 (4.97)	50.7 (12.09)	51.2 (14.53)	50.9 (12.86)
Median	54.6	55.8	37.1	32.2	52.2	52.0	52.1
Q1, Q3	46.2, 61.1	50.4, 64.3	30.7, 43.7	25.6, 34.5	42.1, 57.5	36.5, 59.5	41.8, 59.0
Min, max	36.3, 87.5	35.0, 78.5	29.0, 54.1	24.0, 36.5	29.0, 87.5	24.0, 78.5	24.0, 87.5
Height (cm)							
N	47	23	12	6	59	29	88
Mean (SD)	161.8 (9.74)	164.6 (9.95)	141.4 (9.14)	136.8 (5.11)	157.6 (12.63)	158.8 (14.62)	158.0 (13.25)
Median	160.5	166.5	140.2	136.4	156.4	161.3	159.9
Q1, Q3	153.4, 171.1	159.9, 172.0	135.5, 148.6	133.0, 141.0	150.5, 169.0	147.5, 170.5	148.7, 169.5
Min, max	143.0, 183.0	144.8, 179.5	125.0, 155.0	130.0, 144.0	125.0, 183.0	130.0, 179.5	125.0, 183.0
Body mass index (kg/m^2)							
N	47	23	12	6	59	29	88
Mean (SD)	20.5 (2.89)	20.7 (2.57)	18.8 (2.70)	16.4 (2.16)	20.2 (2.91)	19.8 (3.02)	20.0 (2.93)
Median	20.4	20.3	18.2	16.4	20.1	19.7	20.0
Q1, Q3	18.7, 22.1	19.7, 22.1	16.6, 21.0	15.1, 17.4	18.0, 21.8	17.3, 21.4	17.8, 21.7
Min, max	15.5, 29.4	16.0, 27.3	15.8, 24.3	13.6, 19.7	15.5, 29.4	13.6, 27.3	13.6, 29.4

max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide
Denominator for percentages was the Safety Analysis Set.
P values were based on 2-sided Wilcoxon rank sum test for continuous data or Cochran-Mantel-Haenszel test for categorical data.
P value for race used the categories: Asian and non-Asian.

No significant differences were observed between the TAF and placebo groups.
Body Mass Index (kg/m^2) = [Weight (kg)/Height (cm)^2] × 10,000.
Age (in years) was calculated from the date of the first dose of study drug.
Source: GS-US-320-1092 Week 24 Interim CSR, Table 15.8.3.1

Baseline disease characteristics are summarised in Table 12. Overall, baseline disease characteristics were similar for the 2 treatment groups, except baseline proteinuria tox grade. The median (Q1, Q3) baseline HBV DNA value was 8.1 (7.8, 8.6) $\log_{10}$ IU/mL, and median (Q1, Q3) HBsAg was 4.5 (4.2, 4.9) $\log_{10}$ IU/mL. Moreover, 68.2% participants had HBV DNA ≥ 8 $\log_{10}$ IU/mL, characteristic of the paediatric population.

Nearly all participants (98.9%) were HBeAg positive at baseline, and all (100%) participants were HBsAg positive at baseline. One participant in the TAF group in Cohort 1 was HBeAg negative and HBeAb positive at baseline (also at screening).

By HBV genotype assessment at baseline, genotype D was most commonly seen (43.9%), followed by genotypes C (24.4%) and B (23.2%).

Overall, 64.8% of participants had baseline ALT > 1.5 × ULN based on central laboratory criteria, and the median (Q1, Q3) baseline estimated glomerular filtration rate (eGFR) by the Schwartz formula was 153.5 (138.0, 170.5) mL/min/1.73 m^2.

For 71.6% of participants, a response of 'No' was given for 'Previous hepatitis B medication', with 78.4% of participants naive to prior HBV treatment, and participants who had received prior HBV treatment primarily treated with interferon alpha (IFN-α) and/or lamivudine (LAM).

The baseline demographic and disease characteristics are representative of the diversity of paediatric patients with CHB.

Notably, Cohort 2 Group 1 had a numerically higher proportion of participants with genotype D HBV infection as well as high baseline viral load (i.e., HBV DNA ≥ 8 $\log_{10}$ IU/mL), and a lower mean (SD) ALT at baseline compared to participants in Cohort 1.

Table 12: Baseline disease characteristics (Safety Analysis Set)

	Cohort 1		Cohort 2 Group 1		Total			Total TAF 25 mg vs Total Placebo
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	Overall (N = 88)	*P* Value
HBV DNA ($\log_{10}$ IU/mL)								
N	47	23	12	6	59	29	88	0.3310
Mean (SD)	7.9 (1.13)	8.1 (0.80)	8.0 (1.09)	8.3 (0.28)	7.9 (1.12)	8.1 (0.72)	8.0 (1.01)	
Median	8.1	8.3	8.1	8.3	8.1	8.3	8.1	
Q1, Q3	7.4, 8.6	7.6, 8.6	7.9, 8.6	8.1, 8.5	7.7, 8.6	7.9, 8.6	7.8, 8.6	
Min, max	2.5, 9.2	5.4, 9.2	5.0, 9.2	7.8, 8.6	2.5, 9.2	5.4, 9.2	2.5, 9.2	
HBV DNA ($\log_{10}$ IU/mL) category								
< 8 $\log_{10}$ IU/mL	17 (36.2%)	7 (30.4%)	3 (25.0%)	1 (16.7%)	20 (33.9%)	8 (27.6%)	28 (31.8%)	0.5524
≥ 8 $\log_{10}$ IU/mL	30 (63.8%)	16 (69.6%)	9 (75.0%)	5 (83.3%)	39 (66.1%)	21 (72.4%)	60 (68.2%)	
HBsAg ($\log_{10}$ IU/mL)								
N	47	23	12	6	59	29	88	0.1134
Mean (SD)	4.4 (0.50)	4.5 (0.57)	4.4 (0.84)	4.7 (0.49)	4.4 (0.58)	4.6 (0.55)	4.5 (0.57)	
Median	4.5	4.6	4.5	4.7	4.5	4.7	4.5	
Q1, Q3	4.2, 4.9	4.2, 5.1	4.3, 4.9	4.7, 5.1	4.2, 4.9	4.4, 5.1	4.2, 4.9	
Min, max	3.3, 5.1	2.9, 5.1	2.0, 5.1	3.8, 5.1	2.0, 5.1	2.9, 5.1	2.0, 5.1	
HBsAg status								
Positive	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)	N/A
HBeAg status								
Negative	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)	0.4832
Positive	46 (97.9%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	58 (98.3%)	29 (100.0%)	87 (98.9%)	

HBeAb status								
Positive	1 (100.0%)	0	0	0	1 (100.0%)	0	1 (100.0%)	N/A
Years positive for HBV								
N	47	23	12	6	59	29	88	0.1758
Mean (SD)	7 (5.4)	6 (5.1)	6 (3.9)	5 (3.3)	7 (5.1)	6 (4.7)	7 (5.0)	
Median	7	4	6	7	6	5	6	
Q1, Q3	2, 13	1, 10	2, 10	1, 7	2, 12	1, 8	2, 11	
Min, max	1, 18	1, 15	1, 12	1, 8	1, 18	1, 15	1, 18	
HBV genotype								
Genotype A	4 (9.3%)	1 (4.8%)	1 (8.3%)	0	5 (9.1%)	1 (3.7%)	6 (7.3%)	0.7980
Genotype B	10 (23.3%)	5 (23.8%)	3 (25.0%)	1 (16.7%)	13 (23.6%)	6 (22.2%)	19 (23.2%)	
Genotype C	11 (25.6%)	7 (33.3%)	1 (8.3%)	1 (16.7%)	12 (21.8%)	8 (29.6%)	20 (24.4%)	
Genotype D	17 (39.5%)	8 (38.1%)	7 (58.3%)	4 (66.7%)	24 (43.6%)	12 (44.4%)	36 (43.9%)	
Mixed genotype detected	1 (2.3%)	0	0	0	1 (1.8%)	0	1 (1.2%)	
ALT (U/L)								
N	47	23	12	6	59	29	88	0.6348
Mean (SD)	112 (134.4)	110 (110.5)	85 (69.0)	96 (94.0)	106 (123.9)	107 (105.9)	107 (117.6)	
Median	68	76	59	60	65	66	66	
Q1, Q3	50, 109	56, 91	46, 112	50, 75	50, 109	54, 89	52, 103	
Min, max	19, 793	20, 502	22, 274	43, 286	19, 793	20, 502	19, 793	
ALT level based on central lab range								
≤ 1.5 × ULN	18 (38.3%)	5 (21.7%)	6 (50.0%)	2 (33.3%)	24 (40.7%)	7 (24.1%)	31 (35.2%)	0.5026
> 1.5 × ULN-5 × ULN	23 (48.9%)	15 (65.2%)	5 (41.7%)	3 (50.0%)	28 (47.5%)	18 (62.1%)	46 (52.3%)	
> 5 × ULN-10 × ULN	4 (8.5%)	2 (8.7%)	1 (8.3%)	1 (16.7%)	5 (8.5%)	3 (10.3%)	8 (9.1%)	
> 10 × ULN	2 (4.3%)	1 (4.3%)	0	0	2 (3.4%)	1 (3.4%)	3 (3.4%)	
ALT level based on AASLD range								
≤ 1.5 × ULN	8 (17.0%)	2 (8.7%)	3 (25.0%)	1 (16.7%)	11 (18.6%)	3 (10.3%)	14 (15.9%)	0.7533
>1.5 × ULN-5 × ULN	32 (68.1%)	17 (73.9%)	8 (66.7%)	4 (66.7%)	40 (67.8%)	21 (72.4%)	61 (69.3%)	
> 5 × ULN-10 × ULN	3 (6.4%)	2 (8.7%)	1 (8.3%)	1 (16.7%)	4 (6.8%)	3 (10.3%)	7 (8.0%)	
> 10 × ULN	4 (8.5%)	2 (8.7%)	0	0	4 (6.8%)	2 (6.9%)	6 (6.8%)	
Baseline fibrosis score category								
0.00-0.48	43 (95.6%)	21 (95.5%)	11 (91.7%)	6 (100.0%)	54 (94.7%)	27 (96.4%)	81 (95.3%)	0.7308
0.49-0.74	2 (4.4%)	1 (4.5%)	1 (8.3%)	0	3 (5.3%)	1 (3.6%)	4 (4.7%)	
Previous hepatitis B medication exposure								
No	32 (68.1%)	20 (87.0%)	7 (58.3%)	4 (66.7%)	39 (66.1%)	24 (82.8%)	63 (71.6%)	0.1054
Yes	15 (31.9%)	3 (13.0%)	5 (41.7%)	2 (33.3%)	20 (33.9%)	5 (17.2%)	25 (28.4%)	
Previous oral antiviral treatment status								
Treatment-experienced	11 (23.4%)	3 (13.0%)	3 (25.0%)	2 (33.3%)	14 (23.7%)	5 (17.2%)	19 (21.6%)	0.4894
Treatment-naive	36 (76.6%)	20 (87.0%)	9 (75.0%)	4 (66.7%)	45 (76.3%)	24 (82.8%)	69 (78.4%)	

Corrected BMD for spine (g/cm^2)								
N	42	21	12	6	54	27	81	0.8490
Mean (SD)	1.0 (0.18)	1.0 (0.17)	0.7 (0.13)	0.7 (0.10)	0.9 (0.20)	0.9 (0.19)	0.9 (0.19)	
Median	1.0	1.0	0.7	0.7	0.9	0.9	0.9	
Q1, Q3	0.8, 1.1	0.9, 1.0	0.7, 0.8	0.7, 0.8	0.8, 1.1	0.8, 1.0	0.8, 1.1	
Min, max	0.6, 1.4	0.6, 1.4	0.5, 1.0	0.6, 0.9	0.5, 1.4	0.6, 1.4	0.5, 1.4	
Corrected BMD for whole body (g/cm^2)								
N	44	21	12	6	56	27	83	0.9380
Mean (SD)	0.9 (0.10)	0.9 (0.12)	0.7 (0.07)	0.7 (0.07)	0.9 (0.12)	0.9 (0.15)	0.9 (0.13)	
Median	0.9	0.9	0.7	0.7	0.9	0.9	0.9	
Q1, Q3	0.8, 1.0	0.9, 1.0	0.7, 0.7	0.6, 0.7	0.8, 1.0	0.8, 1.0	0.8, 1.0	
Min, max	0.7, 1.1	0.7, 1.2	0.6, 0.9	0.6, 0.8	0.6, 1.1	0.6, 1.2	0.6, 1.2	
Corrected Z-scores for spine								
N	42	21	12	6	54	27	81	0.6923
Mean (SD)	−0.1 (1.03)	0.0 (1.18)	0.2 (1.08)	0.7 (0.93)	-0.1 (1.04)	0.1 (1.15)	0.0 (1.08)	
Median	−0.3	−0.2	0.4	0.5	−0.2	−0.1	−0.1	
Q1, Q3	−0.7, 0.6	−0.7, 0.3	−0.6, 0.8	−0.1, 1.3	−0.7, 0.7	−0.7, 1.0	−0.7, 0.7	
Min, max	−2.6, 1.6	−1.5, 3.3	−1.6, 1.8	−0.3, 2.0	−2.6, 1.8	−1.5, 3.3	−2.6, 3.3	
Corrected Z-scores for whole body								
N	44	21	11	5	55	26	81	0.8515
Mean (SD)	−0.4 (0.82)	−0.3 (1.04)	−0.2 (1.03)	0.4 (1.41)	−0.3 (0.86)	−0.2 (1.13)	−0.3 (0.95)	
Median	−0.4	−0.6	−0.3	0.8	−0.3	−0.6	−0.4	
Q1, Q3	−0.8, 0.1	−1.1, 0.6	−1.0, 0.5	−0.7, 1.3	−0.8, 0.2	−1.1, 0.6	−0.8, 0.4	
Min, max	−2.4, 1.4	−2.3, 1.8	−2.2, 1.4	−1.3, 2.1	−2.4, 1.4	−2.3, 2.1	−2.4, 2.1	
Estimated GFR by the Schwartz formula (mL/min/1.73 m^2)								
N	47	23	12	6	59	29	88	0.8071
Mean (SD)	154.8 (30.37)	157.5 (32.49)	154.6 (21.10)	167.0 (24.67)	154.8 (28.57)	159.4 (30.88)	156.3 (29.26)	
Median	154.0	145.0	153.5	173.0	154.0	149.0	153.5	
Q1, Q3	137.0, 169.0	142.0, 175.0	142.0, 168.5	152.0, 189.0	137.0, 169.0	143.0, 180.0	138.0, 170.5	
Min, max	85.0, 270.0	119.0, 254.0	122.0, 193.0	126.0, 189.0	85.0, 270.0	119.0, 254.0	85.0, 270.0	
Fasting serum creatinine (mg/dL)								
N	47	21	12	6	59	27	86	0.9480
Mean (SD)	0.7 (0.13)	0.7 (0.15)	0.5 (0.09)	0.5 (0.07)	0.6 (0.14)	0.7 (0.17)	0.7 (0.15)	
Median	0.7	0.7	0.5	0.4	0.6	0.6	0.6	
Q1, Q3	0.6, 0.8	0.6, 0.8	0.4, 0.6	0.4, 0.5	0.5, 0.8	0.5, 0.8	0.5, 0.8	
Min, max	0.4, 1.0	0.4, 1.0	0.4, 0.7	0.4, 0.6	0.4, 1.0	0.4, 1.0	0.4, 1.0	
Baseline proteinuria tox grade								
Grade 0	43 (91.5%)	15 (65.2%)	12 (100.0%)	6 (100.0%)	55 (93.2%)	21 (72.4%)	76 (86.4%)	0.0099
Grade 1	3 (6.4%)	8 (34.8%)	0	0	3 (5.1%)	8 (27.6%)	11 (12.5%)	
Grade 2	1 (2.1%)	0	0	0	1 (1.7%)	0	1 (1.1%)	

AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; BMD = bone mineral density; GFR = glomerular filtration rate; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; max = maximum; min = minimum; N/A = not applicable; Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; tox = toxicity; ULN = upper limit of normal; vs = versus
P values were based on 2-sided Wilcoxon rank sum test for continuous data or Cochran-Mantel-Haenszel test for categorical data.
ULN for central lab was defined as 34 U/L for females aged 2 or older or males aged 1 to 9 years old and 43 U/L for males aged older than 9 years.
ULN for the American Association for the Study of Liver Diseases (AASLD) was defined as 30 U/L for pediatric participants.
Bone mineral density measurements and corresponding Z-scores were corrected for longitudinal changes in the scanner calibration.
HBeAb was a reflex test performed if HBeAg was negative.
Source: GS-US-320-1092 Week 24 Interim CSR, Table 15.8.3.2

Numbers analysed

The analysis sets used for data evaluation are shown in Table 13. Overall, 88 participants (TAF 59 participants; placebo 29 participants) who were randomised and received at least 1 dose of treatment were included in the Safety Analysis Set and the FAS for the Week 24 analysis. Of these, Cohort 1 comprised 47 participants in the TAF group and 23 participants in the placebo group and Cohort 2 Group 1 comprised 12 participants in the TAF group and 6 participants in the placebo group.

In total, 5 participants (TAF 4 participants; placebo 1 participant) were excluded from the Week 24 Per-Protocol Analysis Set. 3 participants were excluded because of less than 80% adherence to the study drug in the double-blind phase, 1 participant was excluded because of premature discontinuation and/or missing HBV DNA assessment at Week 24 and 1 participant was excluded for receiving ongoing therapy with a prohibited drug listed in the study protocol.

The primary analysis set for efficacy analysis was the FAS, defined as all randomised participants who received at least 1 dose of study drug.

Table 13: Analysis sets (Randomised Analysis Sets)

	Cohort 1		Cohort 2 Group 1		Total		
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	Overall (N = 88)
Randomized Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Safety Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Full Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Per Protocol Analysis Set	44 (93.6%)	23 (100.0%)	11 (91.7%)	5 (83.3%)	55 (93.2%)	28 (96.6%)	83 (94.3%)
Spine DXA Analysis Set	42 (89.4%)	21 (91.3%)	12 (100.0%)	6 (100.0%)	54 (91.5%)	27 (93.1%)	81 (92.0%)
Whole Body DXA Analysis Set	44 (93.6%)	21 (91.3%)	12 (100.0%)	6 (100.0%)	56 (94.9%)	27 (93.1%)	83 (94.3%)
PK Analysis Set	46 (97.9%)	0	12 (100.0%)	0	58 (98.3%)	0	58 (65.9%)
PK Substudy Analysis Set	13 (27.7%)	0	5 (41.7%)	0	18 (30.5%)	0	18 (20.5%)
Serologically evaluable FAS for HBeAg loss/seroconversion	46 (97.9%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	58 (98.3%)	29 (100.0%)	87 (98.9%)
Serologically evaluable FAS for HBsAg loss/seroconversion	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)

DXA = dual-energy x-ray absorptiometry; FAS = Full Analysis Set; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; PK = pharmacokinetic(s); TAF = tenofovir alafenamide
Denominator for percentages was the Randomized Analysis Set.
Source: Table 15.8.5

Outcomes and estimation

Primary efficacy endpoint

The results of the analysis of the primary efficacy endpoint, i.e. the percentage of participants with plasma HBV DNA < 20 IU/mL at Week 24, are presented by treatment group (TAF and placebo) in the Full Analysis Set (FAS) in Table 14. The percentage of participants with plasma HBV DNA < 20 IU/mL at Week 24 was significantly greater in the TAF group (18.6% [11/59 participants]; 95% CI: 9.7% to 30.9%) compared with the placebo group (0% [0/29 participants]; 95% CI: 0.0% to 11.9%) (P = 0.0137). The difference in proportion between the TAF and placebo groups was 18.5% (95% CI: 5.4% to 31.6%). Additionally, 8 participants (13.6%) in the TAF group and no participant in the placebo group had HBV DNA between 20 to < 69 IU/mL by Week 24.

Similar results were observed when the primary efficacy endpoint analysis was repeated using the missing = excluded (M = E) approach (TAF: 19.0% [11/58 participants]; placebo: 0% [0/27 participants]; P = 0.0150) and for the PP Analysis Set using the missing = failure (M = F) approach (TAF: 18.2% [10/55 participants]; placebo: 0.0% [0/28 participants]; P = 0.0163).

Overall, the results demonstrate a superior antiviral response with TAF treatment compared with placebo for the primary efficacy endpoint of proportion with HBV DNA < 20 IU/mL at Week 24.

Table 14: Proportion of participants with HBV DNA < 20 IU/mL at week 24 (Missing = Failure) (Full Analysis Set)

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo	
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	*P* Value	Prop Diff (95% CI)
HBV DNA at Week 24								
< 20 IU/mL	10/47 (21.3%)	0/23	1/12 (8.3%)	0/6	11/59 (18.6%)	0/29	0.0137	18.5% (5.4% to 31.6%)
95% CI	10.7% to 35.7%	0.0% to 14.8%	0.2% to 38.5%	0.0% to 45.9%	9.7% to 30.9%	0.0% to 11.9%		
< 20 Not Detected	2/47 (4.3%)	0/23	0/12	0/6	2/59 (3.4%)	0/29		
< 20 Detected	8/47 (17.0%)	0/23	1/12 (8.3%)	0/6	9/59 (15.3%)	0/29		
≥ 20 IU/mL	37/47 (78.7%)	23/23 (100.0%)	11/12 (91.7%)	6/6 (100.0%)	48/59 (81.4%)	29/29 (100.0%)		
20 to < 69 IU/mL	6/47 (12.8%)	0/23	2/12 (16.7%)	0/6	8/59 (13.6%)	0/29		
≥ 69 IU/mL	30/47 (63.8%)	22/23 (95.7%)	9/12 (75.0%)	5/6 (83.3%)	39/59 (66.1%)	27/29 (93.1%)		
Missing	1/47 (2.1%)	1/23 (4.3%)	0/12	1/6 (16.7%)	1/59 (1.7%)	2/29 (6.9%)		

CI = confidence interval; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; Prop Diff = difference in proportions; TAF = tenofovir alafenamide; vs = versus
Denominator for percentages was the Full Analysis Set.
P values were based on a 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.
95% CIs were calculated using the Clopper-Pearson method.
Source: m2.7.3, Table 4

Subgroup Analysis

The consistency in antiviral treatment response was explored by evaluating the proportions of participants achieving the primary efficacy endpoint of plasma HBV DNA < 20 IU/mL at Week 24 by pre-specified subgroups.

Overall, the proportions of participants achieving HBV DNA < 20 IU/mL were statistically significantly higher in the TAF group than the placebo group for those with baseline ALT > 1.5 × ULN (TAF 20.8%; placebo 0.0%; *P* = 0.0117 [AASLD] and TAF 28.6%; placebo 0.0%; *P* = 0.0062 [central laboratory]), baseline HBV DNA levels < 8 $\log_{10}$ IU/mL at Week 24 (TAF 45.0%; placebo 0.0%; *P* = 0.0278), and participants who were treatment-naive at baseline (TAF 20.0%; placebo 0.0%; *P* = 0.0149). In addition, there were statistically significant treatment effects noted for participants who were Asian (TAF 24.3%; placebo 0.0%; *P* = 0.0123), enrolled in sites in North America/Europe (TAF 22.0%; placebo 0.0%; *P* = 0.0431), and with genotype B or C infection (TAF 36.0%; placebo 0.0%; *P* = 0.0130). The differences were not statistically significant for the following subgroups: age at baseline (6 to < 12 years; 12 to < 15 years; 15 to < 18 years), baseline ALT ≤ 1.5 x ULN (by both central laboratory and AASLD criteria), race (non-Asian), region (Asia), sex (male; female), baseline HBV DNA ≥ 8 log10 IU/mL, treatment-experienced, or other genotype (i.e., non-genotype B or C). The limited numbers of participants in some of these subgroups likely contributed to the lack of difference between TAF and placebo.

The subgroup with high baseline viral load (≥ 8 $\log_{10}$ IU/mL), representing the majority of participants in the study (68.2%), showed a lower response with TAF treatment overall (HBV DNA < 20 IU/mL: TAF 5.1%, placebo 0.0%; HBV DNA 20 to < 69 IU/mL: TAF 12.8%, placebo 0.0%; *P* = 0.3228). Given this, the impact of baseline viral load was further assessed within the 2 treatment cohorts (Cohort 1 and Cohort 2 Group 1 for TAF and placebo). Of note, participants in Cohort 2 Group 1 had a numerically

higher proportion with baseline HBV DNA levels ≥ 8 log_{10} IU/mL compared to participants in Cohort 1 (Cohort 1 [TAF 63.8%, placebo 69.6%], Cohort 2 Group 1 [TAF 75.0%, placebo 83.3%]). No participant with baseline HBV DNA levels ≥ 8 log_{10} IU/mL in Cohort 2 Group 1 had yet achieved plasma HBV DNA < 20 IU/mL by Week 24.

In Study GS-US-320-1092, the highest proportion of enrolled participants were those with HBV genotype D (43.9%) infection; notably, in comparison to overall results, TAF participants in Cohort 2 Group 1 showed an even higher proportion with genotype D at baseline compared to TAF participants in Cohort 1 (Cohort 1 [39.5%] vs Cohort 2 Group 1 [58.3%]). Genotype D has been previously shown to impact the rate of viral suppression in adults. In order to further explore this imbalance, an ad hoc analysis of treatment responses by baseline HBV genotype was performed for genotypes A through D using an M = F approach. A numerically lower response rate with TAF treatment was observed in participants with HBV genotype D infection. No participant with genotype D had achieved plasma HBV DNA < 20 IU/mL by Week 24; however, there were 3 participants (12.5%) in the TAF group with genotype D with HBV DNA between 20 to < 69 IU/mL (Cohort 1: 1/17 [5.9%]; Cohort 2 Group 1: 2/7 [28.6%]). Similar results were observed when the primary efficacy endpoint analysis for participants with genotype D was repeated using the M = E approach (no participant with HBV DNA < 20 IU/mL; 20 to < 69 IU/mL: TAF: 3/24 [12.5%]; placebo: 0/10 [0.0%]). Previous subgroup analyses in adults in Studies GS-US-320-0108 and GS-US-320-0110 had identified lower response rates (proportion of participants with HBV DNA < 29 IU/mL at Week 48) in participants with genotype D infection compared to other genotypes with both TAF and TDF treatment.

Taken together, these additional analyses support that the lower response rates observed with TAF treatment in this study in comparison to results in the Phase 3 study in HBeAg positive adults (GS-US-320-0110) are likely due to higher proportions of participants in Study GS-US-320-1092 with both high baseline HBV DNA levels (≥ 8 log_{10} IU/mL), as well as a higher proportion of participants with HBV genotype D infection. As seen in adults, a longer duration of treatment is likely required in order to see more participants achieve full viral suppression (i.e., HBV DNA < 20 IU/mL).

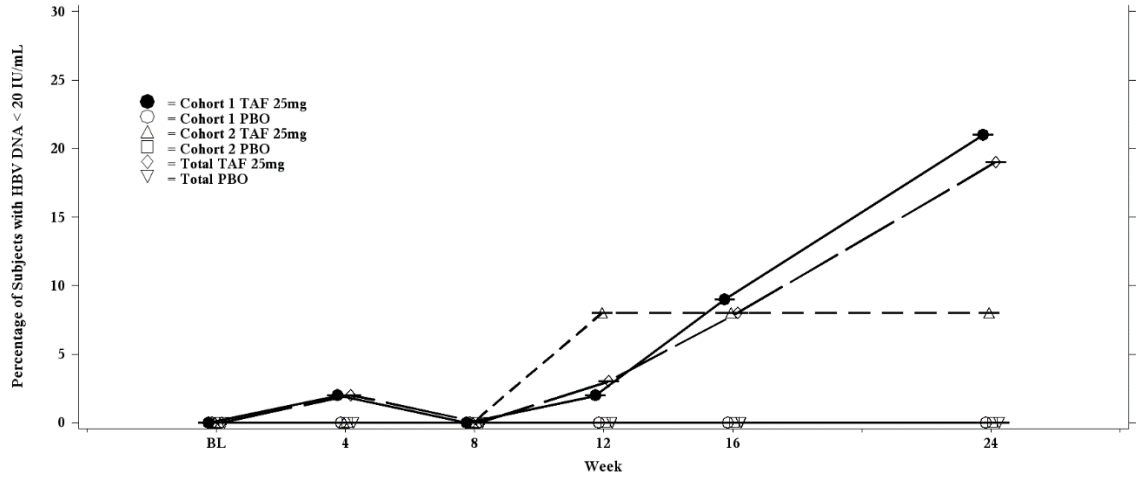
Secondary efficacy endpoints

Secondary efficacy endpoints of Study GS-US-320-1092 included additional analysis of HBV DNA and analyses of ALT, noninvasive changes in liver fibrosis (i.e., serum FibroTest), HBeAg and HBsAg serology, virological resistance, and acceptability/palatability analysis.

Virologic Suppression

Proportion of participants with plasma HBV DNA < 20 IU/mL over 24 weeks

Figure 12 presents the proportion of participants with plasma HBV DNA < 20 IU/mL over 24 weeks by treatment group (TAF and placebo) for the FAS using the M = F approach for missing data. Overall, a consistent increase in the number of participants with HBV DNA < 20 IU/mL was observed in the TAF group after Week 8, while no change was observed in the placebo group over the 24-week period. Of the participants with plasma HBV DNA < 20 IU/mL at Week 24, HBV DNA was not detected in 2 participants (3.4%) in the TAF group.



Cohort 1 TAF 25mg (n=):	47	47	47	47	47	47
Cohort 1 PBO (n=):	23	23	23	23	23	23
Cohort 2 TAF 25mg (n=):	12	12	12	12	12	12
Cohort 2 PBO (n=):	6	6	6	6	6	6
Total TAF 25mg (n=):	59	59	59	59	59	59
Total PBO (n=):	29	29	29	29	29	29

BL = baseline; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; PBO = placebo; TAF = tenofovir alafenamide
Source: GS-US-320-1092 Week 24 Interim CSR, Figure 15.11.5.1

Figure 12: Proportion of participants with HBV DNA < 20 IU/mL by visit (Missing = Failure) (Full Analysis Set)

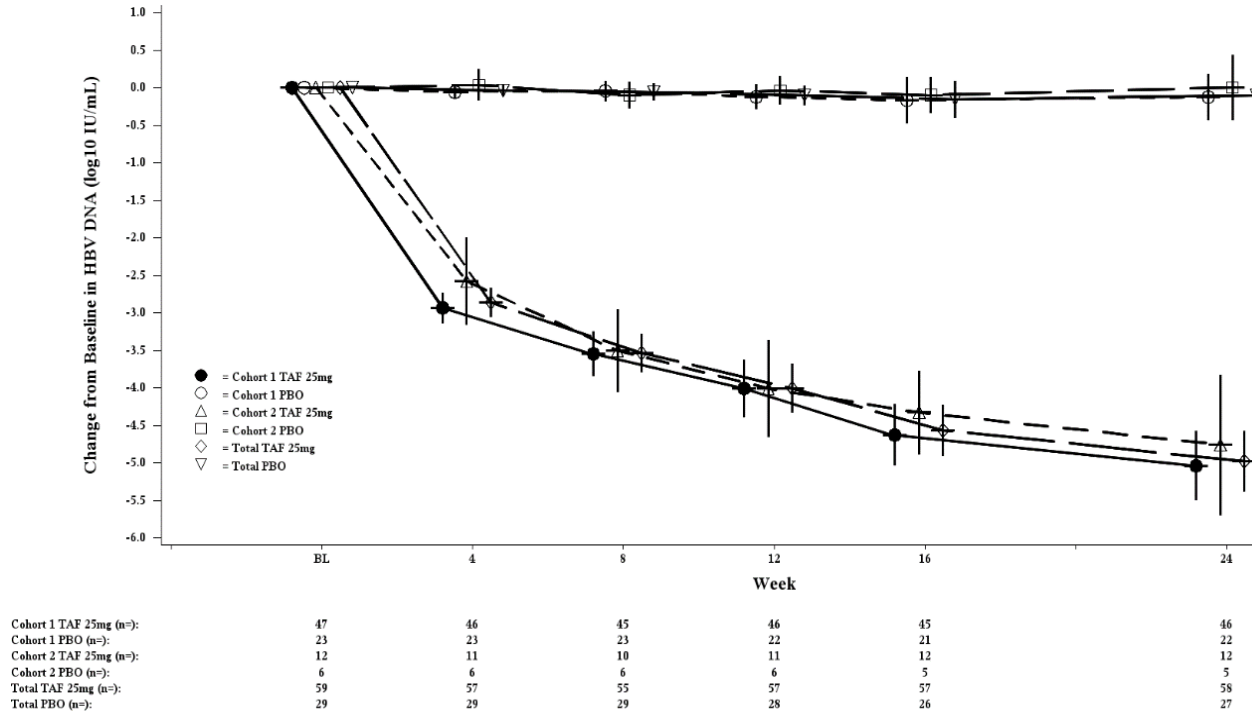
Change from baseline in HBV DNA levels

Figure 13 presents the change in HBV DNA (log10 IU/mL) by visit. Significant decreases in HBV DNA in the TAF group compared with the placebo group were observed from baseline at all measured time points ($P < 0.0001$ from Week 4 to Week 24).

The mean (SD) change at Week 24 overall and in individual cohorts was as follows:

- Total: TAF −4.98 (1.520) $\log_{10}$ IU/mL versus placebo −0.10 (0.636) $\log_{10}$ IU/mL ($P < 0.0001$)
- Cohort 1: TAF −5.04 (1.544) $\log_{10}$ IU/mL versus placebo −0.13 (0.689) $\log_{10}$ IU/mL
- Cohort 2 Group 1: TAF −4.76 (1.466) $\log_{10}$ IU/mL versus placebo 0.00 (0.346) $\log_{10}$ IU/mL

Taken together, these results indicate progressively improving rates of viral suppression over 24 weeks with TAF treatment compared with no change in those receiving placebo.



BL = baseline; CI = confidence interval; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; PBO = placebo; TAF = tenofovir alafenamide
HBV DNA values below the lower limit of quantification were imputed as 19 IU/mL.
Source: GS-US-320-1092 Week 24 Interim CSR, Figure 15.11.9

Figure 13: Mean and 95% CIs of change from baseline in HBV DNA (log10 IU/mL) by visit (Full Analysis Set)

Biochemical Analyses

ALT normalisation

The proportion of participants with baseline abnormal ALT that had achieved normalised ALT (i.e., ALT > ULN at baseline but within the normal range at the postbaseline visit) by Week 24 is presented in Table 15. Overall, a consistently higher percentage of participants in the TAF group compared with the placebo group achieved ALT normalisation (central laboratory criteria: TAF 67.3% versus, placebo 3.7%; P < 0.0001; AASLD criteria: TAF 44.6%, placebo 0.0%; P < 0.0001).

The percentage of participants achieving ALT normalisation was also consistently higher in the TAF group compared with the placebo group (assessed by both central laboratory criteria and AASLD criteria) in both Cohort 1 (central laboratory criteria: TAF 66.7% versus placebo 4.8%; AASLD criteria: TAF 43.5%, placebo 0.0%) and Cohort 2 Group 1 (central laboratory criteria: TAF 70.0% versus placebo 0.0%; AASLD criteria: TAF 50.0% versus placebo 0.0%).

The results obtained using the M = E method were generally similar to those obtained using the M = F method.

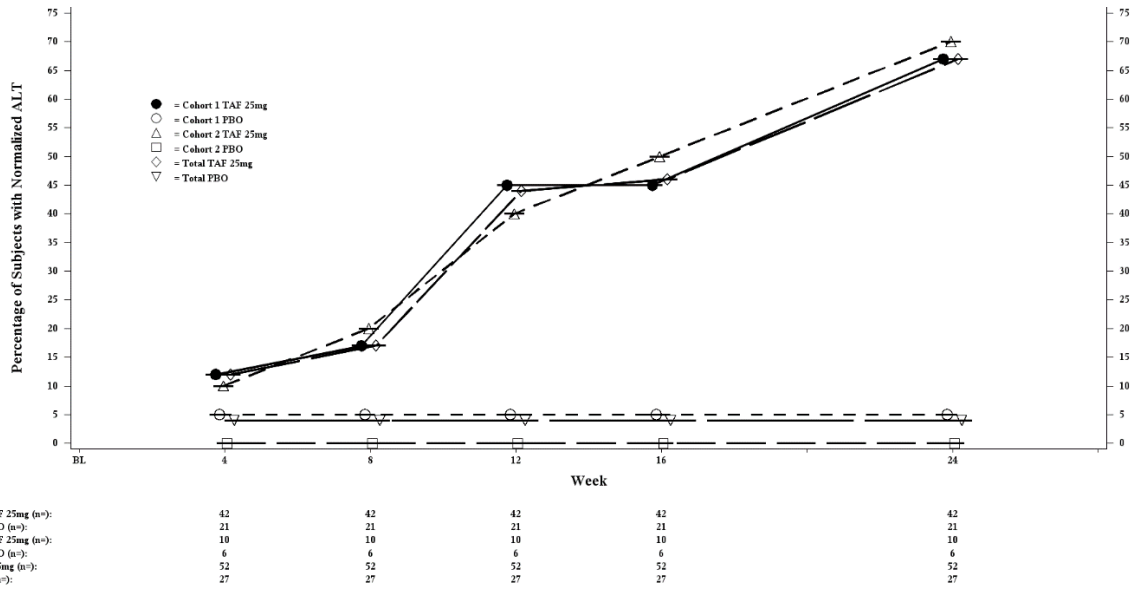
Table 15: Proportion of participants with normalised ALT at week 24 (Missing = Failure) (Full **Analysis Set With Baseline Abnormal ALT)**

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	*P* Value
Normalised ALT (Central Laboratory)							
Week 24, M = F	28/42 (66.7%)	1/21 (4.8%)	7/10 (70.0%)	0/6	35/52 (67.3%)	1/27 (3.7%)	< 0.0001
Normalised ALT (AASLD)							
Week 24, M = F	20/46 (43.5%)	0/22	5/10 (50.0%)	0/6	25/56 (44.6%)	0/28	< 0.0001

AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; M = F = missing = failure; TAF = tenofovir alafenamide; ULN = upper limit of normal; vs = versus
Denominator for percentages was the Full Analysis Set including only participants who had abnormal ALT (ALT > ULN) at baseline.
P values were based on a 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline.
Central laboratory normalised ALT was defined as ≤ 34 U/L for females aged 2 or older or males aged 1 to 9 years and ≤ 43 U/L for males aged older than 9 years.
AASLD normalised ALT was defined as ≤ 30 U/L for males and females based on the range for paediatric participants.
Source: GS-US-320-1092 Week 24 Interim CSR, Tables 15.9.10.1.1, 15.9.10.1.2

Figure 14 and Figure 15 display the proportion of participants with ALT normalisation by visit during double-blind study treatment according to central laboratory and AASLD criteria, respectively. The proportion of participants with ALT normalisation progressively increased in TAF-treated participants and was statistically greater for the TAF group compared with the placebo group at all assessments from Week 12 to Week 24 by central laboratory and AASLD criteria.

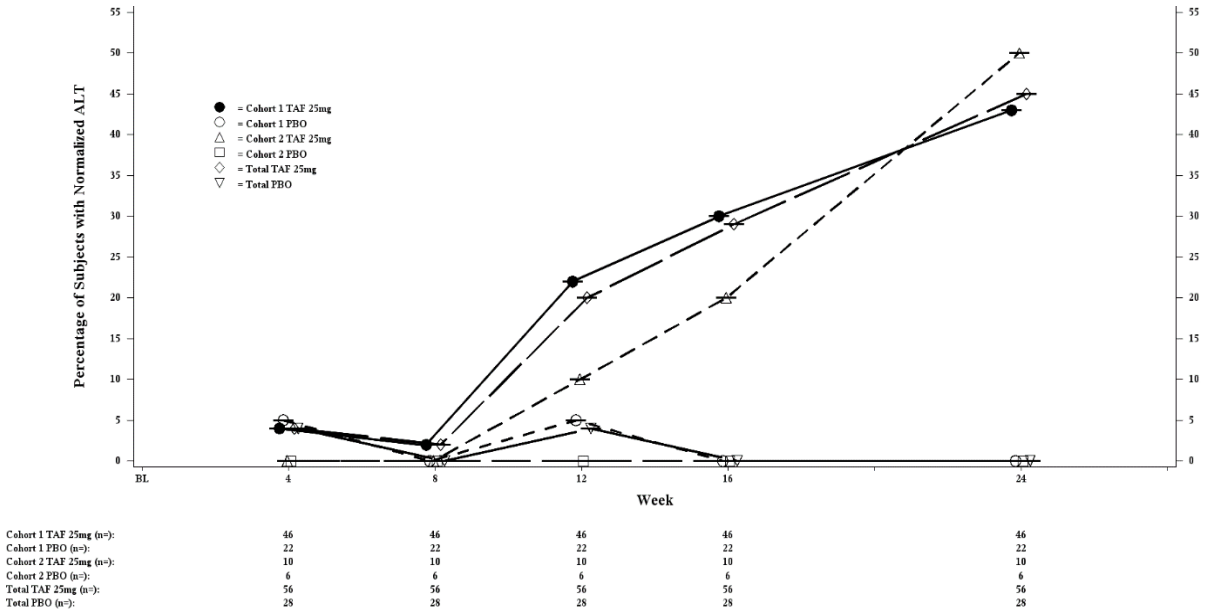
This was observed across Cohort 1 and Cohort 2 Group 1 and therefore consistently demonstrates efficacy that is clinically important across the study population.



ALT = alanine aminotransferase; BL = baseline; PBO = placebo; TAF = tenofovir alafenamide; ULN = upper limit of normal
ULN for central lab was defined as 34 U/L for females aged 2 or older or males aged 1 to 9 years old and 43 U/L for males aged older than 9 years.
Source: GS-US-320-1092 Week 24 Interim CSR, Figure 15.11.8

Figure 14: Proportion of participants with normalised ALT based on Central Lab normal range by visit

(Missing = Failure) (Full Analysis Set With Baseline Abnormal ALT)



AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; BL = baseline; PBO = placebo; TAF = tenofovir alafenamide
Upper limit of normal for ALT was equal to 30 U/L based on the AASLD normal range for paediatric participants.
Source: GS-US-320-1092 Week 24 Interim CSR, Figure 15.11.7

Figure 15: Proportion of participants with normalised ALT based on AASLD normal range by visit (Missing = Failure) (Full Analysis Set With Baseline Abnormal ALT)

Change from baseline in ALT

For the TAF groups, ALT decreased from baseline during 24 weeks of double-blind treatment. The decreases from baseline in ALT were significantly greater for the TAF group compared with the placebo group from Week 4 to Week 24. At Week 24, overall results (Cohort 1 and Cohort 2 Group 1) for the median (Q1, Q3) change from baseline in ALT for each treatment group were:

- TAF: −32.0 U/L (−65.0, −7.0 U/L), placebo: −2.5 U/L (−15.0, 22.0 U/mL); *P* = 0.0002

Serological Analysis

HBeAg loss and seroconversion

Overall, at Week 24, 4 of 58 participants (6.9%) in the TAF group and 1 of 29 participants (3.4%) in the placebo group had experienced HBeAg loss/seroconversion; the between-group difference was not statistically significant (P = 0.5242).

In 3 of the 4 participants in the TAF group who had HBeAg loss, the loss occurred early (i.e., at Week 12) and was maintained through Week 24, and all 4 of these participants had confirmed HBeAg seroconversion at Week 24. The one participant in the placebo group who had HBeAg loss by Week 24 also achieved seroconversion at this same time point.

The proportions of participants with HBeAg loss and seroconversion were also analysed by visit using the M = E method; results using the M = E method were generally similar to those using the M = F method.

HBsAg loss and seroconversion

No participant in the TAF and placebo groups had HBsAg loss or seroconversion by Week 24 using both the M = F or M = E approaches.

Change from baseline in serum HBsAg levels

Overall, at baseline, the mean (SD) HBsAg level was 4.43 (0.576) log10 IU/mL in the TAF group and 4.58 (0.545) log10 IU/mL in the placebo group. Mean decreases from baseline in serum HBsAg levels were observed in both the TAF and placebo groups over 24 weeks. Overall, the median (Q1, Q3) change from baseline in serum HBsAg levels was small but significantly higher in the TAF group compared to placebo at Week 24, with a −0.18 (−0.36, −0.02) decrease in the TAF group compared to 0 (−0.20, 0.02) in the placebo group (P = 0.0309).

Fibrosis Analysis

At Week 24, the mean (SD) change in FibroTest scores from the baseline value was very small in each group, with a −0.01 (0.09) decrease in the TAF group and +0.03 (0.111) increase in the placebo group (P = 0.1257). As the anti-fibrosis response with oral antiviral therapy typically takes longer to develop than a reduction in necroinflammation, which appears early in treatment (as reflected in ALT normalization results), the minimal fibrosis response with TAF treatment at Week 24 was not unexpected.

Analysis of Palatability and Acceptability

The majority of participants in the study had a neutral or positive acceptability response at baseline up to Week 24 in the palatability and acceptability assessment. Overall, 46% of participants reported being able to taste the drug, while 50% reported not being able to taste the drug at Week 24. Of those who responded as being able to taste the drug, 33.0% responded "Neither dislike or like", 1.1% responded "Dislike moderately" and 3.4% responded "Dislike very much", with the remainder having a more positive opinion of drug taste.

Clinical virology

Clinical virology analyses were performed for paediatric participants with CHB 6 to < 18 years old, weighing ≥ 25 kg who received TAF in Study GS-US-320-1092. Resistance analyses were performed on populations with HBV isolated from serum for all participants who met pre-specified criteria. Resistance surveillance was conducted in participants receiving TAF only, as those randomised to placebo did not receive active antiviral therapy.

Resistance analysis was evaluated at Week 24 using the HBV DNA quantification assay cutoff of 20 IU/mL and the HBV sequencing assay cutoff of 69 IU/mL.

Sequence analysis was conducted on Week 24 samples for TAF on-treatment participants with HBV DNA ≥ 69 IU/mL at Week 24, including participants with virologic breakthrough, virologic blip, and viremia, and their corresponding baseline samples.

Virologic breakthrough was defined as ≥ 1 $\log_{10}$ IU/mL increase from nadir in HBV DNA or, confirmed HBV DNA ≥ 69 IU/mL if HBV DNA was previously < 69 IU/mL for 2 consecutive visits. If a participant met one of these criteria at only 1 visit, the participant was classified as having a virologic blip. Viremia was defined as having persistent HBV DNA levels above 20 IU/mL over the course of treatment.

Phenotypic analysis was conducted for participants who developed an emerging amino acid substitution at a conserved site (versus a polymorphic site) of the HBV polymerase/reverse transcriptase (pol/RT), regardless of whether the participant experienced virologic breakthrough and for participants who developed changes at polymorphic residues in the HBV pol/RT if the changes were observed in more than one participant.

The results of the baseline genotypic analyses are summarized in the table below. Of the HBV genotypes, genotype D (40.9%) was the most commonly observed followed by genotype C (22.7%), then genotype B (21.6%). Notably, participants in Cohort 2 Group 1 included a numerically higher proportion with genotype D compared to participants in Cohort 1: Cohort 1 (TAF 36.2%, placebo 34.8%), Cohort 2 Group 1 (TAF 58.3%, placebo 66.7%). Additionally, 6 participants were identified with genotype A virus (6.8%), 1 participant was mixed genotype (1.1%), and 6 participants were not able to be genotyped (6.8%).

Table 16: Summary of Baseline Genotypic Analyses

HBV Genotype	Cohort 1, Placebo (n = 23)	Cohort 1, TAF (n = 47)	Cohort 2 Group 1, Placebo, (n = 6)	Cohort 2 Group 1, TAF (n = 12)	Total (n = 88)
HBV Genotype A	1 (4.3%)	4 (8.5%)	0	1 (8.3%)	6 (6.8%)
HBV Genotype B	5 (21.7%)	10 (21.3%)	1 (16.7%)	3 (25.0%)	19 (21.6%)
HBV Genotype C	7 (30.4%)	11 (23.4%)	1 (16.6%)	1 (8.3%)	20 (22.7%)
HBV Genotype D	8 (34.8%)	17 (36.2%)	4 (66.7%)	7 (58.3%)	36 (40.9%)
Mixed Genotype	0	1 (2.1%)	0	0	1 (1.1%)
Genotype undetermined	2 (8.7%)	4 (8.5%)	0	0	6 (6.8%)

HBV = hepatitis B virus; TAF = tenofovir alafenamide
Subjects with genotype undetermined were included in the analysis.
Source: Study PC-320-2021, Section 3.2, Table 2

In this resistance surveillance analysis from Study GS-US-320-1092, out of a total of 88 paediatric participants with CHB who were randomised and treated with TAF 25 mg once daily in Cohort 1 (n = 47; placebo, n = 23) and Cohort 2 Group 1 (n = 12; placebo, n = 6) for 24 weeks, 39 (44%) TAF-treated participants qualified for viral sequence analysis. Out of these, 2 patients qualified for phenotypic evaluation. Results of phenotypic evaluation are summarised in the table below. Samples with a fold-change in the EC50 greater than 2-fold indicate reduced susceptibility to TAF.

In **Cohort 1** TAF group, 30 participants qualified for sequence analysis with majority of participants (27 of 30, 90%) being viraemic with HBV DNA ≥ 69 IU/mL at Week 24. One participant in Cohort 1 qualified for phenotypic analysis due to a unique conserved site change. No HBV pol/RT amino acid substitutions associated with resistance to TAF were detected through 24 weeks of treatment.

In **Cohort 2 Group 1** TAF group, 9 participants qualified for sequence analysis with majority of participants (8 of 9, 88.9%) being viraemic with HBV DNA ≥ 69 IU/mL at Week 24. One participant qualified for phenotypic analysis due to a unique conserved site change. No HBV pol/RT amino acid substitutions associated with resistance to TAF were detected through 24 weeks of treatment.

Table 17: Phenotypic Evaluation of 2 Qualified Participants in the TAF Group

Isolate	Cohort	Baseline and Changes From Baseline in HBV pol/RT[a]	TAF EC_{50} (nM)[b]	TAF Fold Change[c]
54506-baseline	1	Wild-type	74.73	NA
54506-Week 24	1	**rtV112V/I**	72.03	0.98
54506-Week 24-Clone 5	1	**rtV112I**	AF	NA[d]
54579-baseline	2	Wild-type	43.85	NA
54579-Week 24	2	**R167R/G**	53.19	1.23
Controls				
pHY92[e]		Wild-type	38.64	NA
ADV-R[f]		rtA181V+rtN236T	150.45	3.98

AF = assay failure, EC_{50} = half-maximal effective concentration; HBV = hepatitis B virus; NA = not applicable; TAF = tenofovir alafenamide; qPCR = quantitative polymerase chain reaction
a Conserved site changes are noted in bold.
b EC_{50} value was generated by analyses of intracellular HBV DNA levels by qPCR.
c Define as EC_{50} of Week 24 sample/EC_{50} of corresponding baseline sample. A value 2-fold or less is within assay variability.
d Not available due to low replication capacity.
e pHY92 is a genotype A lab strain reference control.
f ADV-R (rtA181V+rtN236T) is generated based on pHY92 backbone and confers slightly reduced susceptibility to TAF.
Source: Study PC-320-2021, Section 3.5, Table 7

Overall, the relatively high proportions of participants in this study who qualified for sequence analysis was not unexpected due to the short (24 week) treatment duration, high baseline viral loads, and the high proportion of subjects with genotype D chronic HBV in the study population.

The majority of participants (n = 35) that qualified for sequence analysis were persistently viraemic in the absence of virologic breakthrough.

Virologic breakthrough was infrequent (n = 2) and was not associated with sequence changes in pol/RT.

Sequence analysis showed that the majority of participants had no sequence change from baseline.

No HBV amino acid substitutions associated with resistance to TAF were detected through 24 weeks of double-blind treatment.

Ancillary analyses

N/A

Summary of main study

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

Table 18: Summary of Efficacy for trial GS-US-320-1092

Title: A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection			
Study identifier	GS-US-320-1092		
Design	This is an ongoing, randomized (2:1), double-blind, placebo-controlled, multicenter study of the safety, tolerability, PK, and antiviral activity of TAF administered once daily in treatment-naive and treatment-experienced adolescents and children with CHB. This study included an interim analysis for adolescent participants aged 12 to < 18 years weighing ≥ 35 kg (Cohort 1), and children aged 6 to < 12 years weighing ≥ 25 kg (Cohort 2 Group 1), who are receiving the adult dose of TAF 25 mg once daily. <u>Cohort 1:</u> At least 69 male and female adolescent participants (12 to < 18 years of age) were planned to be enrolled and randomized to receive either the blinded TAF 25 mg tablet or placebo-to-match (PTM) tablet once daily through Week 24. Randomization was stratified by age (12 to < 15 and 15 to < 18 years of age). <u>Cohort 2:</u> At least 75 children were planned to be enrolled in Cohort 2 of the study. Cohort 2 is divided into 3 dose groups (Groups 1, 2, and 3) by age and weight, with enrolment into each dose group divided into 2 parts: Part A (mandatory intensive PK to confirm the dose) and Part B. The interim analysis was performed when all participants in Cohort 1 and Cohort 2 Group 1 had completed their Week 24 visit or prematurely discontinued from the study.		
	Duration:		The duration of double-blind treatment was 24 weeks. After completing the double-blind phase, all Cohort 1 and Cohort 2 Group 1 participants were eligible to roll over to receive open label TAF 25 mg once daily for up to an additional 216 weeks (total planned duration of study treatment was 240 weeks).
Hypothesis	Superiority over placebo		
Treatments groups	Cohort 1 (12 to < 18 years of age weighing ≥ 35 kg), TAF group		TAF 25 mg once daily, 47 patients randomised, treated and completed
	Cohort 1 (12 to < 18 years of age weighing ≥ 35 kg), placebo group		Placebo-to-match, 23 patients randomised, treated and completed
	Cohort 2 (6 to < 12 years of age weighing ≥ 25 kg), TAF group		TAF 25 mg once daily, 12 patients randomised, treated and completed
	Cohort 2 (6 to < 12 years of age weighing ≥ 25 kg), placebo group		Placebo-to-match, 6 patients randomised, treated and completed
Endpoints and definitions	Primary endpoints	Efficacy	percentage of participants with plasma HBV DNA < 20 IU/mL at Week 24
		Pharmacokinetics	AUC_{tau} for TAF at steady-state in Cohort 2 Group 1
		Safety	Incidence of treatment-emergent serious adverse events (SAEs) and all treatment-emergent adverse events (AEs) in participants treated with TAF or placebo at Week 24

	Secondary endpoints	Efficacy	• The percentage of participants with plasma HBV DNA < 20 IU/mL at Weeks 48, 96, and 240 • The proportion of participants with plasma HBV DNA < 20 IU/mL (target not detected) at Weeks 24, 48, 96, and 240 • The percentage of participants with ALT normalization at Weeks 24, 48, 96, and 240 • The percentage of participants achieving the composite end point of both ALT normalization and HBV DNA < 20 IU/mL at Weeks 24, 48, 96, and 240 • The change from baseline in fibrosis as assessed by FibroTest at Weeks 24, 48, 96, and 240 • The percentage of participants with HBeAg loss and seroconversion to anti-HBe at Weeks 24, 48, 96, and 240 (HBeAg positive participants only) • The percentage of participants achieving the composite end point of both HBeAg seroconversion and HBV DNA < 20 IU/mL at Weeks 24, 48, 96, and 240 (HBeAg positive participants only) • The percentage of participants achieving the composite end points of ALT normalization, HBeAg seroconversion, and HBV DNA < 20 IU/mL at Weeks 24, 48, 96, and 240 (HBeAg positive participants only) • The percentage of participants with HBsAg loss and seroconversion to anti-HBs at Weeks 24, 48, 96, and 240 • The change from baseline in HBsAg log10 IU/mL at Weeks 24, 48, 96, and 240 • Incidence of resistance mutations at Weeks 24, 48, 96, and 240 • Assessment of acceptability/palatability of study drug at baseline and Weeks 4, 24, and 36
		Pharmacokinetics	• AUC_{last}, C_{max}, C_{last}, T_{max}, T_{last}, λ_z, CL/F, V_z/F and $t_{1/2}$ for TAF and AUC_{tau} and C_{tau} for TFV

		Safety	• Graded laboratory abnormalities, Tanner Stage assessments, selected bone and renal safety parameters, including percentage change from baseline in BMD of whole body (minus head) and lumbar spine performed by dual-energy x-ray absorptiometry (DXA) scan, and change in sCR, and eGFR by the Schwartz formula to evaluate the safety and tolerability of the treatment regimen at Weeks 24, 48, 96, and 240 • Incidence of treatment-emergent SAEs and all treatment-emergent AEs in participants treated with TAF or placebo for 24 weeks followed by open-label TAF at Weeks 48, 96, and 240 • Evaluation of sCR, glucose, phosphate, urine retinol-binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio at Weeks 4, 8, 12, 24, and 48
Database lock	16 August 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (all randomised participants who received at least 1 dose of study drug) at Week 24		
Descriptive statistics and estimate variability	Treatment group	TAF	Placebo
	Number of subjects	59	29
	HBV DNA < 20 IU/mL	11/59 (18.6%)	0/29(0%)
	95% CI	9.7% to 30.9%	0.0% to 11.9%
Effect estimate per comparison	Primary endpoint	Comparison groups	TAF vs. Placebo
		HBV DNA < 20 IU/mL	18.5%
		95% CI	5.4% to 31.6%
		P-value	0.0137
Notes	Of the 47 participants receiving TAF in Cohort 1, 10 participants (21.3%) reached the primary endpoint but only 1 participant (8.3%) of the 12 participants receiving TAF in Cohort 2 Group 1 reached the primary endpoint. Suppression rate at Week 24 in HBeAg-positive adults treated with TAF 25 mg once daily in the Phase 3 Study GS-US-320-0110 was 34.6% (201/581 participants had HBV DNA < 29 IU/mL).		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study GS-US-320-1092 is an ongoing double-blind, placebo-controlled, multicenter study of the safety, tolerability, PK, and antiviral activity of TAF administered once daily in treatment-naive and treatment-experienced adolescents and children with CHB. The primary efficacy endpoint for Study GS-US-320-1092 was the proportion of participants with plasma HBV DNA < 20 IU/mL at Week 24. The primary cut-off of HBV DNA was < 20 IU/mL to reflect the current HBV DNA assay LLOQ. Secondary efficacy endpoints included additional analysis of HBV DNA and analyses of ALT, noninvasive changes in liver

fibrosis (i.e., serum FibroTest), HBeAg and HBsAg serology, virological resistance, and acceptability/palatability analysis. A total of 161 participants were screened and a total of 88 eligible participants were randomised (47 Cohort 1 TAF participants, 23 placebo participants; 12 Cohort 2 Group 1 TAF participants, 6 placebo participants). The data presented are from the interim, primary endpoint analysis for safety, efficacy, and PK, which was conducted when all participants in Cohort 1 (adolescents 12 to less than 18 years of age and weighing at least 35 kg) and Cohort 2 Group 1 (paediatric participants 6 to < 12 years of age and weighing at least 25 kg) had completed their Week 24 (i.e., primary endpoint) visit or prematurely discontinued from the study.

TAF is currently approved for use in adult and adolescent patients with CHB weighing at least 35 kg in the EU and other regions. Therefore, in particular the data from Cohort 2 Group 1 are relevant for this application to extend the indication to CHB-infected children from 6 years and older and weighing at least 25 kg.

The study population and inclusion/exclusion criteria are acceptable to the CHMP. Only paediatric patients with CLcr ≥ 80 mL/min/1.73m2 using the Schwartz formula were eligible for the study (TAF is renally excreted). In consequence, there is no information on efficacy of TAF in paediatric patients with impaired renal function. The MAH therefore proposed to include the sentence "*No data are available to make dose recommendations in children aged less than 12 years with renal impairment*" in section 4.2 of the SmPC. This is considered acceptable.

The justification of the dose and duration of treatment used for Study GS-US-320-1092 is in principle agreed. For further discussion of the adequacy of the TAF dosage of 25 mg for use in CHB patients 6 to < 12 years weighing ≥ 25 kg, please see sections PK and popPK.

The duration of double-blind treatment for both cohorts was 24 weeks. After completing the double-blind phase, all participants were eligible to roll over to receive open label TAF 25 mg once daily for up to an additional 216 weeks, which is agreed.

The primary endpoint of this study is the proportion of participants with plasma HBV DNA < 20 IU/mL (the current limit of detection) at Week 24. Primary analysis was originally planned to be at Week 48. However, amendment 1 of the study protocol included a change to Week 24. This was accepted by the PDCO after consultation with the IDWP. The IDWP considered that 24 weeks for the double-blind, placebo-controlled phase is acceptable, but that 48-week data are necessary for the benefit/risk evaluation, particularly for the assessment of efficacy and resistance data. This interim analysis only contained data covering 24 weeks of treatment, which was considered to be insufficient to conclude on comparable efficacy of TAF treatment in CHB-infected children aged 6 to 12 years and weighing ≥ 25 kg and adults. Given that the last subject finished the double-blind phase on 12 August 2021, data covering 48 weeks of treatment was available for the participants who received TAF in the double-blind phase. To enable adequate assessment of efficacy, the applicant provided 48-week data for the primary and secondary efficacy endpoints delineating the respective overall efficacy as well as efficacy in the individual cohorts. Corresponding data from studies in CHB-infected adults were also provided for comparison.

Although more participants from Cohort 2 Group 1 reached the primary endpoint of HBV DNA < 20 IU/mL at Week 48 (3/12 (25%)) than at Week 24, the proportion was still lower than in Cohort 1 (19/47 (40.4%)). Furthermore, a lower proportion of participants from Cohort 1 (44.7%) and Cohort 2 Group 1 (41.7%) than adult participants (63.9%) reached the endpoint of HBV DNA ≤ 29 IU/ml. Importantly, however, mean declines in HBV DNA from baseline were similar also at Week 48 for all cohorts, with mean (SD) log10 IU/mL of -5.65 (1.78) for Cohort 1, -5.88 (0.86) for Cohort 2 Group 1 and -5.75 (1.31) for adults. Thus, although there were considerable differences in the proportions of participants reaching HBV DNA ≤ 20 IU/mL (or 29 IU/mL), mean declines in HBV DNA from baseline

were similar. The CHMP is of the opinion that this indicates similar efficacy of TAF treatment in this respect.

2.4.4. Conclusions on the clinical efficacy

Overall, the CHMP is of the view that viral suppression, ALT normalisation and change from baseline as well as HBeAg loss and seroconversion (further) improved from Week 24 to Week 48 and to a largely similar degree in Cohort 1 and Cohort 2 Group 1 and as compared to adult participants. Also, considering that the additional data provided for the PopPK model indicate comparable exposure of TFV (AUC_{tau}/C_{max}) between CHB-infected adults and children aged 6-12 years and weighing ≥ 25 kg and that, hence, an extrapolation of the adult CHB efficacy data to the paediatric patients aged 6 to <12 years is possible, it is overall concluded by the Committee that the efficacy data from study GS-US-320-1092 are regarded as sufficient to support this extension of indication.

Section 4.1 of the SmPC was amended accordingly:

Vemlidy is indicated for the treatment of chronic hepatitis B (CHB) in adults and paediatric patients 6 years of age and older weighing at least 25 kg (see section 5.1).

2.5. Clinical safety

In support of this application for extension of indications, the MAH presented safety data from the following clinical study:

Table 19: Overview Study GS-US-320-1092

Study	Study Design	Double-blind Treatment Regimen	No. of Randomized Participants[a]	Participant Population	Location
Study GS-US-320-1092	Phase 2, randomized, double-blind study	TAF group: TAF 25 mg tablet once daily Placebo Group: placebo-to-match TAF 25 mg tablet once daily 24 weeks of double-blind treatment[b]	Cohort 1: TAF: N = 47 Placebo: 23 Cohort 2 Group 1: TAF: N = 12 Placebo: N = 6	Cohort 1: 12 to < 18 years old weighing ≥35 kg Cohort 2 Group 1: 6 to < 12-year-old weighing ≥ 25 kg	**CSR:** GS-US-320-1092 Week 24 Interim CSR

CHB = chronic hepatitis B virus; CSR = clinical study report; No. = number; TAF = tenofovir alafenamide

a Participants in Cohort 1 were stratified based on age (12 to < 15 years and 15 to < 18 years).

b The double-blind period will be followed by the open-label extension period for up to an additional 216 weeks (through Week 240) where all participants will receive TAF 25 mg daily.

Patient exposure

All randomized participants received at least 1 dose of study drug and were included in the Safety Analysis Set. All 88 participants who were randomized completed the double-blind study drug. No participants discontinued study drug or the study during the double-blind phase.

Overall, the majority of participants in each treatment group (TAF and placebo) had received blinded study drug at the time of the Week 24 data cutoff (TAF 98.3%, 58 of 59 participants; placebo 96.6%, 28 of 29 participants). Overall exposure was similar between the 2 treatment groups, with a median (Q1, Q3) exposure of 24.1 (24.0, 24.4) weeks for participants who received TAF and 24.1 (24.0, 24.6) weeks for participants who received placebo.

Adverse events

Summary of Adverse Events

An overall summary of AEs by treatment group during the double-blind phase of Study GS-US-320-1092 are presented in the table below. Overall, the incidence of AEs was similar between TAF and placebo treatment groups. In total, 59.3% (35 participants) in the TAF group and 55.2% (16 participants) in the placebo group experienced at least 1 AE during double-blind treatment.

The majority of the AEs in both TAF and placebo groups were Grade 1 (mild) in severity and were considered unrelated to study drug by the investigator. More participants in the TAF group (16.9%, 10 participants) compared with the placebo group (10.3%, 3 participants) experienced an AE considered by the investigator to be related to study drug. Two participants in the placebo group experienced a Grade 3 (severe) AE. No Grade 3 AEs occurred in the TAF group, and no participant in either treatment group experienced a Grade 4 (life threatening) AE. The incidence of serious adverse events (SAEs) was higher in the placebo group compared to the TAF group. None of the SAEs were considered to be related to TAF.

No deaths occurred during the double-blind phase of the study, and no participant experienced an AE that led to premature study drug discontinuation.

Table 20: Study GS US 320 1092: Overall Summary of Treatment Emergent Adverse Events (Safety Analysis Set)

	Total		
Participants Experiencing, n (%)	**TAF 25 mg (N = 59)**	**Placebo (N = 29)**	**Overall (N = 88)**
Any AE	35 (59.3%)	16 (55.2%)	51 (58.0%)
Any Grade 3 or 4 AE	0	2 (6.9%)	2 (2.3%)
Any Grade 2, 3, or 4 AE	8 (13.6%)	5 (17.2%)	13 (14.8%)
Any study drug-related AE	10 (16.9%)	3 (10.3%)	13 (14.8%)
Any Grade 3 or 4 study drug-related AE	0	1 (3.4%)	1 (1.1%)
Any Grade 2, 3, or 4 study drug-related AE	1 (1.7%)	1 (3.4%)	2 (2.3%)
Any SAE	1 (1.7%)	2 (6.9%)	3 (3.4%)
Any study drug-related SAE	0	1 (3.4%)	1 (1.1%)
Any AE leading to premature study drug discontinuation	0	0	0
Any AE leading to dose modification or study drug interruption	1 (1.7%)	1 (3.4%)	2 (2.3%)
Death	0	0	0

AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA, Version 24.0.
Severity grades were defined by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1 (01 April 2015).
Death included any death that occurred during the study.
Treatment-emergent events during the double-blind phase began on or after the blinded study drug first dose date up to 3 days after permanent discontinuation of the blinded study drug or up to the first dose date of open-label study drug, depending on which was earlier, or led to blinded study drug discontinuation.
Source: GS-US-320-1092 Week 24 Interim CSR Table 15.11.2.1.1

Table 21: Study GS US 320 1092: Treatment-Emergent Adverse Events - Safety Analysis Set Double-Blind Phase

	Cohort 1		Cohort 2 Group 1		Total		
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)	Overall (N=88)
Subjects Experiencing Any Treatment-Emergent Adverse Event	29 (61.7%)	12 (52.2%)	6 (50.0%)	4 (66.7%)	35 (59.3%)	16 (55.2%)	51 (58.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	0	2 (8.7%)	0	0	0	2 (6.9%)	2 (2.3%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	7 (14.9%)	3 (13.0%)	1 (8.3%)	2 (33.3%)	8 (13.6%)	5 (17.2%)	13 (14.8%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	8 (17.0%)	3 (13.0%)	2 (16.7%)	0	10 (16.9%)	3 (10.3%)	13 (14.8%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	0	1 (4.3%)	0	0	0	1 (3.4%)	1 (1.1%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)	2 (2.3%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	1 (2.1%)	2 (8.7%)	0	0	1 (1.7%)	2 (6.9%)	3 (3.4%)

Common Adverse Events

The summary of AEs reported in ≥ 5% participants in either treatment group, in descending overall incidence is presented in the table below.

The AE with the highest incidence in both treatment groups was headache (10.2% of participants in the TAF group and 13.8% of participants in the placebo group). Other AEs reported in ≥ 5% of participants in the TAF group were abdominal pain upper, vitamin D decreased, and upper respiratory tract infection (8.5% each), nasopharyngitis and nausea (6.8% each), and cough, rhinitis allergic, and vitamin D deficiency (5.1% each).

Other AEs reported in ≥ 5% of participants in the placebo group were abdominal pain upper, vitamin D decreased, nasopharyngitis, ALT increased, ankle fracture, aspartate aminotransferase (AST) increased, and rhinitis (6.9% each).

Table 22: GS-US-320-1092: Adverse Events Reported in ≥ 5% Participants in Either Treatment Group (Safety Analysis Set, Double-blind Phase)

Preferred Term	Total		
	TAF 25 mg (N = 59)	Placebo (N = 29)	Overall (N = 88)
Headache	6 (10.2%)	4 (13.8%)	10 (11.4%)
Abdominal pain upper	5 (8.5%)	2 (6.9%)	7 (8.0%)
Vitamin D decreased	5 (8.5%)	2 (6.9%)	7 (8.0%)
Nasopharyngitis	4 (6.8%)	2 (6.9%)	6 (6.8%)
Upper respiratory tract infection	5 (8.5%)	1 (3.4%)	6 (6.8%)
Nausea	4 (6.8%)	1 (3.4%)	5 (5.7%)
Cough	3 (5.1%)	0	3 (3.4%)
Rhinitis allergic	3 (5.1%)	0	3 (3.4%)
Vitamin D deficiency	3 (5.1%)	0	3 (3.4%)
Rhinitis	0	2 (6.9%)	2 (2.3%)
Ankle fracture	0	2 (6.9%)	2 (2.3%)
Aspartate aminotransferase increased	0	2 (6.9%)	2 (2.3%)
Alanine aminotransferase increased	0	2 (6.9%)	2 (2.3%)

AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA, Version 24.0.
Multiple AEs were counted only once per participant for each system organ class, high-level term, and preferred term.
Treatment-emergent AEs during the double-blind phase began on or after the blinded study drug first dose date up to 3 days after permanent discontinuation of the blinded study drug.
Source: GS-US-320-1092 Week 24 Interim CSR Table 15.11.2.1.2

Related Adverse Events

Overall, 10 participants (16.9%) in the TAF group and 3 participants (10.3%) in the placebo group had AEs that were assessed by the investigator as related to study drug. Overall, headache was the most commonly reported study drug-related AE in participants who received TAF, reported in 8.5% (5 participants). Other study drug-related AEs that occurred in > 1 participant who received TAF were nausea (5.1%, 3 participants), abdominal pain upper (3.4%, 2 participants), and fatigue (3.4%, 2 participants).

Serious adverse event/deaths/other significant events

Serious Adverse Events

Overall, 3 participants, all in Cohort 1, experienced an SAE during the double-blind phase, 1 participant in the TAF group and 2 participants in the placebo group.

- One participant (TAF) experienced an SAE of Grade 2 scarlet fever from Day 106 to Day 110; considered not related to the study drug; no action was taken with study drug as a result of the SAE.
- Two participants (placebo) experienced an SAE: Grade 3 ankle fracture (Day 7, trauma related); and Grade 3 ALT increased (Day 27, considered related to study drug).

Deaths

No deaths occurred during the double-blind phase of Study GS-US-320-1092.

Analysis of Adverse Events of special interest

Bone Safety

Bone Mineral Density

The table below presents the mean and median percentage change from baseline in spine and whole body BMD at Week 24. At baseline, overall mean spine BMD values were similar for the TAF and placebo groups. At Week 24 of double-blind treatment, overall mean spine BMD had increased in both the TAF and placebo groups; no statistically significant differences were noted between treatment groups. The mean (SD) percent increase from baseline in spine BMD at Week 24 was +1.6% (5.13%) for the TAF group and +1.9% (2.80%) for the placebo group (P = 0.7672). Median spine BMD values for both treatment groups in Cohort 2 Group 1 were similar, indicating the negative mean value of 1.2% (TAF) was driven by an outlier in this small sample size of 11 participants.

At baseline, overall mean whole body BMD values were similar for the TAF and placebo groups. At Week 24 of double-blind treatment, mean whole body BMD had increased in both the TAF and placebo groups; no statistically significant differences were noted between treatment groups. The mean (SD) percent increase from baseline in whole body BMD at Week 24 was +1.9% (2.64%) for the TAF group and +2.0% (2.55%) for the placebo group (P = 0.8274; table below).

Table 23: GS-US-320-1092: Percentage Change From Baseline in Spine and Whole Body BMD at Week 24 (Observed Data) (Spine and Whole Body DXA Analysis Sets, Double-blind Phase)

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25 mg	Placebo	TAF 25 mg	Placebo	TAF 25 mg	Placebo	*P* Value
Spine BMD							
Baseline (g/cm^2)							
N	42	21	12	6	54	27	
Mean (SD)	0.979 (0.1789)	0.979 (0.1727)	0.732 (0.1268)	0.713 (0.1041)	0.924 (0.1970)	0.920 (0.1941)	0.9363
Median (Q1, Q3)	0.995 (0.830, 1.120)	0.960 (0.920, 1.030)	0.730 (0.685, 0.780)	0.695 (0.670, 0.770)	0.930 (0.760, 1.060)	0.940 (0.770, 1.000)	
% change at Week 24							
N	37	18	11	5	48	23	
Mean (SD)	2.409 (3.3099)	1.925 (3.0776)	−1.216 (8.5533)	1.896 (1.6566)	1.578 (5.1310)	1.919 (2.7960)	0.7672
Median (Q1, Q3)	1.408 (0.000, 3.750)	1.574 (0.000, 3.529)	1.449 (−5.556, 5.634)	1.429 (1.299, 2.273)	1.429 (0.000, 4.326)	1.429 (0.000, 3.529)	
Whole Body BMD							
Baseline (g/cm^2)							
N	44	21	12	6	56	27	
Mean (SD)	0.910 (0.1002)	0.933 (0.1208)	0.723 (0.0661)	0.680 (0.0690)	0.870 (0.1215)	0.877 (0.1536)	0.8307
Median (Q1, Q3)	0.935 (0.825, 0.980)	0.920 (0.870, 0.980)	0.720 (0.695, 0.745)	0.655 (0.640, 0.720)	0.865 (0.770, 0.970)	0.880 (0.800, 0.970)	
% change at Week 24							
N	39	18	11	5	50	23	
Mean (SD)	1.517 (2.2603)	1.855 (2.5644)	3.207 (3.4900)	2.670 (2.6816)	1.888 (2.6360)	2.032 (2.5509)	0.8274
Median (Q1, Q3)	1.124 (0.000, 2.778)	1.968 (0.000, 4.082)	3.750 (1.538, 5.714)	3.030 (0.000, 4.167)	1.473 (0.000, 3.529)	2.151 (0.000, 4.124)	

ANOVA = analysis of variance; BMD = bone mineral density; CSR = clinical study report; DXA = dual-energy x-ray absorptiometry; SD = standard deviation; Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; vs = versus
Spine BMD was calculated using the 'SpineTotalAdequate' region.
Whole body BMD was calculated using the 'BodyTotalNoHead' region.
Percent Change = change from baseline at a postbaseline visit divided by the baseline value * 100.
Only participants with nonmissing spine BMD at baseline were included in the Spine/Whole Body DXA Analysis Set.
P value was based on an ANOVA model including treatment as a fixed effect.
Source: GS-US-320-1092 Week 24 Interim CSR Tables 15.11.10.2 and 15.11.10.4

Categorical Distribution of Percentage Change From Baseline in Bone Mineral Density

Overall, differences between TAF and placebo in the categorical percent change from baseline were not statistically significant at Week 24 for either spine BMD (P = 0.8885) or whole body BMD (P = 0.6864).

The cumulative incidence of ≥ 4% decrease from baseline in spine and whole body BMD at Week 24 was assessed. In total, 4 participants (all in the TAF group, Cohort 2 Group 1) had a ≥ 4% decrease in spine BMD (3 participants) or whole body BMD (1 participant). No participant experienced both ≥ 4% decrease from baseline in spine and whole body BMD at Week 24. By BMD Z-scores, a clinically relevant marker, all 4 participants remained within normal range for their age and gender.

Spine and Whole Body Bone Mineral Density Z-Scores

Spine and whole body BMD was also assessed using available BMD Z-scores. The Z-score for any BMD value is the number of standard deviations it lies below or above the mean BMD of an age, sex, and race matched control group, and is dependent upon the DXA machine used (ie, Hologic or Lunar). A Z-

score ≤ −2.0 is below the expected range for age and is considered to reflect a clinically relevant degree of low body mass or BMD, while a Z score > −2.0 is within the expected range for age. Overall, there was no statistically significant difference between treatment groups in shifts from baseline in spine or whole body BMD Z scores at Week 24 (P = 0.5105 and P = 0.1137, respectively).

Spine and whole body BMD Z-scores were similar for the TAF and placebo groups at baseline. For both treatment groups, observed mean spine and whole body BMD Z score values were within the normal range for the participant population from baseline through 24 weeks of double blind treatment.

Most participants in both treatment groups had spine and whole body BMD Z-scores > −1 at baseline and at Week 24.

Overall, 3 participants (2 participants in Cohort 1 and 1 participant in Cohort 2 Group 1) who received TAF had a spine or whole body BMD Z-score ≤ −2 at Week 24 that also had a BMD Z score ≤ −2 at baseline.

Fracture Events

Fracture events during the double-blind phase of the study occurred in 3 participants, all within the placebo group. All fracture events were trauma-related, considered by the investigator to be unrelated to study drug, and did not result in study drug discontinuation.

Fracture events included Grade 1 hand fracture, Grade 1 ankle fracture, and Grade 3 fibula fracture and ankle fracture. No action was taken with study drug for any of these trauma-related fracture events. All 3 of these participants had spine and whole body BMD Z-scores within the expected age range.

Bone Events

No participant had a bone event other than fractures described above, and no participant had an AE of BMD decrease during double-blind treatment.

Bone Biochemical Markers

The table below presents median percentage change from baseline in serum markers of bone turnover, including serum markers of bone formation (osteocalcin, procollagen type 1 N-terminal propeptide [P1NP]) and bone resorption (C-telopeptide) at Week 24. At baseline, overall median levels of biomarkers were similar between TAF and placebo groups and there were no statistically significant differences between groups in median changes of bone biomarkers (including serum parathyroid hormone and 25-hydroxyvitamin D) from baseline at Week 24.

Descriptive statistics and by-participant listings for all biochemical bone markers are provided in GS-US-320-1092 Week 24 Interim CSR Tables 15.11.11.1 through 15.11.11.14 and Listings 16.2.8.1.14.1, 16.2.8.1.14.2, and 16.2.8.1.14.3.

Table 24: GS-US-320-1092: Percentage Changes From Baseline in Bone Laboratory Parameters at Week 24 (Safety Analysis Set)

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo (*P* Value)
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	
Serum C-Telopeptides (ng/mL)							
Baseline							
N	47	22	12	6	59	28	0.5457
Median (Q1, Q3)	1.2 (0.8, 1.8)	1.1 (0.7, 1.6)	2.1 (1.6, 2.7)	1.9 (1.4, 2.3)	1.4 (0.9, 2.0)	1.3 (0.8, 1.8)	
% change at Week 24							
N	47	22	12	6	59	28	0.8916
Median (Q1, Q3)	0.0 (−13.3, 7.4)	−8.4 (−14.2, 14.3)	1.9 (−17.7, 26.3)	24.8 (18.4, 33.0)	0.0 (−15.6, 13.7)	−4.1 (−14.0, 24.8)	
Serum Osteocalcin (ng/mL)							
Baseline							
N	46	22	12	6	58	28	0.6750
Median (Q1, Q3)	59.75 (37.67, 94.23)	63.37 (38.76, 97.89)	97.64 (84.74, 134.90)	116.05 (98.76, 123.60)	73.50 (42.09, 98.32)	76.18 (39.53, 111.95)	
% change at Week 24							
N	46	22	12	6	58	28	0.8719
Median (Q1, Q3)	−10.46 (−22.73, 11.60)	−15.79 (−28.00, 7.66)	3.69 (−8.39, 23.13)	20.78 (−1.21, 25.36)	−8.66 (−17.91, 15.95)	−5.00 (−22.66, 16.67)	
Serum Parathyroid hormone (pg/mL)							
Baseline							
N	47	22	12	6	59	28	0.5159
Median (Q1, Q3)	31.6 (22.1, 50.4)	40.2 (26.8, 51.2)	42.3 (33.0, 45.9)	36.8 (34.1, 38.1)	37.6 (24.2, 47.7)	37.7 (27.9, 50.5)	
% change at Week 24							
N	47	22	12	6	59	28	0.8168
Median (Q1, Q3)	1.7 (−19.5, 61.7)	8.4 (−36.5, 66.4)	−4.0 (−26.8, 40.6)	22.5 (6.5, 60.4)	1.7 (−19.5, 59.4)	17.6 (−28.3, 63.4)	

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo (*P* Value)
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	
25-hydroxyvitamin D (ng/mL)							
Baseline							
N	47	22	12	6	59	28	0.6077
Median (Q1, Q3)	20.8 (15.6, 26.0)	19.2 (16.1, 24.9)	19.6 (17.2, 24.0)	20.2 (7.6, 35.5)	20.8 (16.8, 25.9)	19.4 (15.5, 25.1)	
% change at Week 24							
N	47	22	12	6	59	28	0.1511
Median (Q1, Q3)	8.2 (−11.8, 45.1)	−0.3 (−31.7, 15.9)	1.5 (−21.7, 39.0)	−18.3 (−36.7, 19.7)	8.2 (−11.9, 45.1)	−1.5 (−36.1, 15.9)	
Serum Bone Procollagen Type 1 N-terminal Propeptide							
Baseline							
N	47	22	12	6	59	28	0.9168
Median (Q1, Q3)	322.80 (146.20, 587.10)	336.55 (146.50, 626.90)	796.60 (588.50, 1241.00)	842.60 (626.60, 878.20)	420.50 (166.00, 656.20)	480.30 (194.40, 802.05)	
% change at Week 24							
N	47	22	12	6	59	28	0.1659
Median (Q1, Q3)	−22.50 (−33.67, −9.16)	−22.37 (−32.81, −0.16)	−7.18 (−30.87, 9.76)	23.67 (9.16, 31.42)	−21.10 (−33.67, −5.95)	−3.31 (−31.53, 15.96)	

CSR = clinical study report; Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; vs = versus
Baseline value was the last available value collected on or prior to first dose of study drug. Change = Change from baseline; % Change = Change from baseline at a postbaseline visit/baseline * 100%.
P values were based on a 2-sided Wilcoxon rank sum test.
Source: GS-US-320-1092 Week 24 Interim CSR Tables 15.11.11.3, 15.11.11.4, 15.11.11.6, 15.11.11.7, and 15.11.11.14.

Renal Safety

Renal Adverse Events

One participant in TAF Cohort 2 Group 1 experienced non-serious, Grade 1 proteinuria on Day 2 of double-blind treatment. The AE was considered not related to study drug and no action was taken in response to the event. The AE resolved on Day 203.

Renal Laboratory Parameters

At baseline, median (Q1, Q3) estimated glomerular filtration rate (eGFR) was not significantly different for the TAF and placebo groups (TAF 154 [137, 169] mL/min, placebo 149 [143, 180] mL/min). Slight fluctuations in median eGFR were noted for both treatment groups over time. At Week 24, a greater decrease in median eGFR was noted in the TAF group compared with placebo (TAF −9 (−19, 2) mL/min; placebo −1 (−7, 7) mL/min; P = 0.0303; table below), while median eGFR remained within normal range at Week 24 in both groups and at no time point during double-blind treatment did any participant in either treatment group have an eGFR value that dropped below the normal range cutoff of 90 mL/min/1.73m^2.

Table 25: GS-US-320-1092: Median (Q1, Q3) Change From Baseline in eGFRSchwartz (mL/min) at Week 24 (Safety Analysis Set, Double-blind Phase)

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25 mg (N = 47)	Placebo (N = 23)	TAF 25 mg (N = 12)	Placebo (N = 6)	TAF 25 mg (N = 59)	Placebo (N = 29)	*P* Value
Baseline							
N	47	23	12	6	59	29	0.8071
Median	154	145	154	173	154	149	
Q1, Q3	137, 169	142, 175	142, 169	152, 189	137, 169	143, 180	
At Week 24							
N	45	21	12	5	57	26	0.1516
Median	140	148	148	179	142	151	
Q1, Q3	127, 165	134, 155	128, 168	150, 184	128, 166	138, 162	
Change at Week 24							
N	45	21	12	5	57	26	0.0303
Median	−6	0	−14	−1	−9	−1	
Q1, Q3	−19, 2	−7, 6	−21, 4	−5, 24	−19, 2	−7, 7	

CSR = clinical study report; eGFR = estimated glomerular filtration rate; Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; vs = versus
Change = Change from baseline. Baseline value was the last available value collected on or prior to first dose of blinded treatment.
P values were based on a 2-sided Wilcoxon rank sum test.
Source: GS-US-320-1092 Week 24 Interim CSR Table 15.11.6.2.14

At baseline, mean serum creatinine levels were similar for participants in the TAF (0.65 mg/dL) and placebo groups (0.65 mg/dL) overall. Serum creatinine remained similar to baseline during the double-blind phase for both the TAF and placebo groups, with mean increases from baseline of +0.05 mg/dL and +0.01 mg/dL, respectively, at Week 24. When evaluated by treatment cohort, at Week 24, a greater increase in mean serum creatinine was noted in the TAF groups compared with placebo (Cohort 1 mean increase from baseline of 0.04 mg/dL and 0.02 mg/dL for TAF and placebo, respectively; Cohort 2 Group 1 mean increase from baseline of 0.05 mg/dL and a mean decrease 0.01 mg/dL for TAF and placebo, respectively.

No graded creatinine abnormalities were noted during the double-blind phase.

Confirmed renal abnormalities were defined as an increase from baseline in creatinine ≥ 0.3 mg/dL, an increase from baseline in creatinine ≥ 0.5 mg/dL, occurrence of serum phosphorous below 2.0 mg/dL, eGFRSchwartz < 50 mL/min, or eGFRSchwartz < 70 mL/min at 2 consecutive postbaseline visits. No participant had a confirmed renal abnormality through Week 24, after receiving double blind treatment.

All 88 participants had at least 1 postbaseline urine protein value. Of these, the majority of participants in each treatment group did not have any treatment-emergent proteinuria, as assessed by dipstick analysis. Most of the occurrences of proteinuria by dipstick were Grade 1 (TAF 22.2%, 13 of 59 participants; placebo 10.3%, 3 of 29 participants); no participant in either treatment group had Grade 3 proteinuria by dipstick. When evaluated by treatment cohort, a similar proportion of participants had Grade 1 proteinuria in Cohort 1 and Cohort 2 Group 1.

At Week 24, median (Q1, Q3) percentage decreases from baseline occurred in both the TAF and placebo groups for the renal biomarkers of urine retinol-binding protein to creatinine ratio and urine beta 2 microglobulin to creatinine ratio; these between-group differences were not statistically significant (P = 0.5681 and P = 0.6300, respectively). Similar results were seen when evaluated by study cohort.

Laboratory findings

The majority of participants had a postbaseline graded laboratory abnormality during the double blind phase, with a higher proportion occurring in the placebo group (74.6% of participants who received TAF and 96.6% of participants who received placebo). The graded abnormalities in both treatment groups were mainly Grade 1 or 2. A similar percentage of participants in each group had Grade 3 or 4 laboratory abnormalities (TAF 11.9%, 7 participants total; placebo 13.8%, 4 participants).

A Grade 3 hematology abnormality of decreased platelets was noted in 1 participant (TAF, Cohort 1) at Week 12 (49 ×103/uL) (normal range 140-400 × 103/uL). This participant had a low platelet level at baseline (51 ×103/uL) and platelet levels fluctuated at Grade 1 and Grade 2 toxicity through double-blind treatment.

Grade 3 or 4 chemistry abnormalities included increased ALT (TAF 6.8%, 4 participants; placebo 6.9%, 2 participants) and increased AST (placebo 6.9%, 2 participants). Urinalysis Grade 3 or 4 abnormalities included occult blood (1 participant in each group, Cohort 1), and hematuria (TAF 9.1%, 3 participants, placebo 6.3%, 1 participant).

Alanine aminotransferase elevation and ALT flare were evaluated during the double-blind phase as follows:

Elevation of ALT was defined as serum ALT > 2 × baseline value and > 10 × upper limit of normal, with or without associated symptoms. All treatment emergent ALT elevations, including confirmed ALT elevations (referred to as an ALT flare, which was defined as elevated ALT at two consecutive postbaseline visits) were summarized for the double-blind phase.

During double-blind treatment, 1 participant (1.7%) in the TAF group and 2 participants (6.9%) in the placebo group met criteria for ALT elevation. Two participants (both in the placebo group) experienced an ALT flare, one of which was reported as an SAE. Both of the participants with ALT flare had graded elevations in ALT at baseline, total bilirubin values remained normal, neither had an increase in HBV DNA; and both remained HBsAg positive. Both of the participants were also HBeAg positive at the time of ALT flare and one of the two participants experienced HBeAg loss at Week 24.

Overall, fasting lipid parameters remained stable during double-blind treatment, with no major between-group differences at Week 24. Median (Q1, Q3) changes from baseline at Week 24 for fasting lipid parameters in each treatment group were as follows:

- Total cholesterol: TAF −3 (−9, 11) mg/dL; placebo −2 (−9, 13) mg/dL
- Low-density lipoprotein (LDL) cholesterol: TAF 1 (−8, 10) mg/dL; placebo 0 (−9, 16) mg/dL

- High-density lipoprotein (HDL) cholesterol: TAF 0 (−6, 3) mg/dL; placebo 0 (−6, 7) mg/dL
- Total cholesterol to HDL ratio: TAF 0.0 (−0.2, 0.3) mg/dL; placebo 0.0 (−0.1, 0.3) mg/dL
- Triglycerides: TAF −1 (−16, 17) mg/dL; placebo −5 (−26, 9) mg/dL

Median (Q1, Q3) changes from baseline at Week 24 for fasting glucose were:

- TAF 1 (−3, 4) mg/dL; placebo 1 (−2, 3) mg/dL

No participant in either treatment group had a Grade 3 or 4 abnormality in any fasting metabolic parameters.

Tanner Staging

As expected for the study population of Cohort 1 (adolescent participants aged 12 to < 18 years), the majority of males and females were categorized at Tanner Stage 3 through 5 through Week 24 and for the study population of Cohort 2 Group 1 (children aged 6 to < 12 years weighing ≥ 25 kg), the majority of males and females were categorized at Tanner Stage 1 to 2 (prepubertal) through Week 24.

Body Weight, Height, and Body Mass Index

Body weight, height, and BMI at baseline were similar between the treatment groups. Median (Q1, Q3) changes in body weight, height, and BMI from baseline at Week 24 were similar for TAF and placebo.

During double-blind treatment, the median change from baseline in Z scores for body weight, height, and BMI at Week 24 was not statistically different between TAF and placebo.

Safety in special populations

No additional safety analyses for intrinsic or extrinsic factors were performed in Study GS-US-320-1092. Therefore, no new findings relevant to intrinsic and extrinsic factors are submitted with this update to the initial application.

Safety related to drug-drug interactions and other interactions

No drug interaction studies with TAF have been conducted in paediatric participants with CHB 6 to <18 years old. No new findings relevant to the co-administration of TAF with other drugs are submitted with this update to the marketing application.

Discontinuation due to adverse events

No participant prematurely discontinued the double-blind phase of the study due to an AE.

Post marketing experience

No post marketing safety data were submitted.

2.5.1. Discussion on clinical safety

The MAH submitted safety data from Study GS-US-320-1092 in support of this application of extension of indication. Vemlidy is already approved in adolescents aged 12 years and older with body weight at least 35kg, which corresponds to Cohort 1 of Study GS-US-320-1092. For the population applied for in this extension of indication application (paediatric patients between 6 and 12 years of age and weighing at least 25 kg), safety data were limited to 12 patients who received TAF during Study GS-US-320-1092 (Cohort 2 Group 1). This was considered acceptable by the CHMP since the popPK modelling indicates that exposure (AUC_{tau} and C_{max}) is comparable between paediatric patients aged 6 to 12 years and weighing ≥ 25 kg and adults with CHB infection.

The safety data of Cohort 2 Group 1 are in principle comparable to safety data from Cohort 1 (adolescents) and adults. For a more profound comparison, the MAH provided week 48 interim safety data from Study GS-US-320-1092, which included data from patients who received TAF over 48 weeks in the double-blind (DB) and OL phases for participants in Cohort 1 and Cohort 2 Group 1, and patients in the PBO group who crossed-over to TAF (PBO-TAF) at Week 24 and entered the OL phase. Furthermore, a comparison of these data to week 48 data from adult studies (GS-US-320-0108 and GS-US-320-0110) was presented. Overall, it was concluded by the Committee that Vemlidy was well tolerated during paediatric Study GS-US-320-1092 until week 48 and no new safety signal was identified.

The MAH further committed that long-term data from open-label phase will be provided as soon as possible.

Serious adverse event and deaths

Serious Adverse Events

During double-blind phase of Study GS-US-320-1092, SAEs were reported in three patients. One patient in the TAF group (Cohort 1) experienced an SAE of Grade 2 scarlet fever considered not related to study drug. The other two SAEs were observed in the placebo group (ankle fracture, Grade 3 ALT increased). No SAEs were observed in the target paediatric population (paediatric patients between 6 and 12 years of age and weighing at least 25 kg). Overall, no safety signal could be identified.

Deaths

No deaths occurred during the double-blind phase of Study GS-US-320-1092.

Analysis of Adverse Events of special interest

Bone Safety

Regarding the provided information from Study GS-US-320-1092 week 48 data about bone safety, overall, 3 patients in the TAF group (1 in Cohort 1 and 2 in Cohort 2 Group 1) and 2 patients in the PBO-TAF group (Cohort 1 and Cohort 2 Group 1, one each) had ≥ 4% BMD decreases from baseline in spine and whole body BMD at Week 48 and 3 additional patients (1 from Cohort 1 and 2 from Cohort 2 Group 1) had a ≥ 4% decrease in BMD at spine or whole body after Week 48, while a ≥ 4% decrease was transient for 3 out of these 8 patients and all 8 patients had normal Z-scores for their age at Week 48 and subsequently recorded study visits. For both treatment groups, observed mean spine and whole body BMD Z-score values were within the normal range from baseline through Week 48.

Fracture events were reported in 2 patients during the OL phase (patella fracture [Cohort 1 TAF group] and tibia fracture [Cohort 2 Group 1 PBO-TAF group]). Both fracture events were trauma-related, considered by the investigator to be unrelated to study drug.

Overall, the MAH included specific information about changes in bone mineral density in Study GS-US-320-1092 into Section 5.1 of the SmPC. Specifically, a table was included with information about bone mineral density decreases of 4% or greater for paediatric patients at weeks 24 and 48, which is agreed by the CHMP. Furthermore, the MAH adapted the warning on BMD in section 4.4 and the information in section 4.8 of the SmPC in this regard, as follows:

Section 4.4

Paediatric population

Reductions in BMD (≥4%) of the spine and of total body-less-head (TBLH) have been reported in some paediatric patients aged between 6 and <12 years who received Vemlidy. There are uncertainties associated with the long-term effects of bone and renal toxicity on the growing bone, including the risk of fracture. Therefore, a multidisciplinary approach is recommended to decide the appropriate monitoring during treatment.

Furthermore, the following paragraph in Section 4.8 of the SmPC was amended as follows:

Section 4.8

Paediatric population

The safety of Vemlidy was evaluated in 88 HBV infected treatment-naïve and treatment-experienced paediatric patients aged 12 to < 18 years weighing ≥ 35 kg (TAF group N=47, placebo group N=23) and 6 to < 12 years weighing ≥ 25 kg (TAF group N=12, placebo group N=6) through Week 24 in a randomized, double-blind, placebo-controlled clinical study GS-US-320-1092. In this study no new adverse reactions have been described in paediatric patients aged 6 years and older living with CHB as compared to adult subjects. After 24 weeks of treatment with Vemlidy, reductions in BMD of the spine and of whole body BMD ≥ 4% have been reported in 33.3% (4/12) and 8.3% (1/12) of children aged 6 to < 12 years weighing at least 25 kg (see section 4.4).

The warning on BMD in section 4.4 of the SmPC was also implemented in section 2 of the PL as follows (marked in **bold**):

2. What you need to know before you take Vemlidy

…

Warnings and precautions

…

Children and adolescents

Do not give this medicine to children who are under 6 years old, or weighing less than 25 kg. It has not been tested in children aged less than 6 years old, and or weighing less than 25 kg.

Bone problems. Reductions in bone density have been reported in some paediatric patients who received Vemlidy and long-term effects on growing bone, including the risk of fractures, are uncertain. Your doctor will carefully decide how to monitor this possible risk. Tell your doctor if any bone pain or fractures occur.

In addition to the precautionary statement concerning the bone safety in children 6 to < 12 years weighing ≥ 25 kg, the CHMP is of the view that these events in children and adolescents should be monitored in upcoming PSURs. Furthermore, it shall be noted that the SmPC of Vemlidy (and of the other medicinal products containing TAF) will be subject to further revisions/amendments when more data becomes available.

Renal Safety

Overall, one renal Adverse Event was reported in one patient in the TAF group from Cohort 2 Group 1 (non-serious, grade 1 proteinuria, considered not related to study drug).

The median change from baseline in $eGFR_{Schwartz}$ (mL/min) at Week 24 was more pronounced in TAF treated patients in Cohort 2 Group 1 (-14) compared to adolescents in Cohort 1 (-6) and higher as in the placebo group (-1). At Week 24, a greater increase in mean serum creatinine was noted in the TAF groups compared with placebo (Cohort 1 mean increase from baseline of 0.04 mg/dL and 0.02 mg/dL for TAF and placebo, respectively; Cohort 2 Group 1 mean increase from baseline of 0.05 mg/dL and a mean decrease 0.01 mg/dL for TAF and placebo, respectively). No graded creatinine abnormalities were noted during the double-blind phase. No patient had a confirmed renal abnormality through Week 24, after receiving double blind treatment. Most of the occurrences of proteinuria by dipstick were Grade 1 (TAF 22.2%, 13 of 59 participants; placebo 10.3%, 3 of 29 participants); no participant in either treatment group had Grade 3 proteinuria by dipstick. When evaluated by treatment cohort, a similar proportion of participants had Grade 1 proteinuria in Cohort 1 and Cohort 2 Group 1. No significant differences in week 24 median percentage decreases from baseline for the renal biomarkers of urine retinol-binding protein to creatinine ratio and urine beta 2 microglobulin to creatinine ratio was observed between TAF groups and placebo groups and between cohorts.

As outlined in the SmPC of Vemlidy (section 4.4), a potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded. It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with this treatment and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of this medicinal product should be considered. In addition, the paragraph "*Paediatric population*", as requested above, should be added to address the uncertainties on the impact of long-term exposure of TAF in children on the growing bone in terms of fracture risk associated with renal toxicity. Furthermore, the SmPC of Vemlidy (and of the other medicinal products containing tenofovir alafenamide) could be subject to further revisions/amendments when more data becomes available.

In addition, the MAH should continue to monitor renal safety with Vemlidy in paediatric patients and adolescents via routine Pharmacovigilance.

Laboratory findings

Overall, no differences in laboratory findings could be identified between TAF group and placebo group and between Cohort 1 and Cohort 2 Group 1. No safety signal could be identified.

Discontinuation due to adverse events

No participant prematurely discontinued the double-blind phase of the study due to an AE.

2.5.2. Conclusions on clinical safety

Overall, Vemlidy was well tolerated during paediatric Study GS-US-320-1092. Specific information about changes in bone mineral density were introduced into sections 4.4, 4.8 and 5.1 of the SmPC.

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.

2.5.3. Direct Healthcare Professional Communication

N/A

2.6. Risk management plan

The MAH submitted an updated RMP version 9.1 in the framework of a variation procedure to extend the indication to include treatment of chronic hepatitis B-infected children from 6 years and older and weighing at least 25 kilograms for Vemlidy, based on the interim results from Week 24 clinical study report (CSR) for Cohort 1 and Cohort 2 Group 1 and supporting modular summaries for the category 3 study GS-US-320-1092, 'A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection'.

The MAH submitted safety data from Study GS-US-320-1092 in support of this application of extension of indication. Vemlidy is already approved in adolescents aged 12 years and older with body weight at least 35kg, which corresponds to Cohort 1 of Study GS-US-320-1092. Safety data for this extension of indication application (paediatric patients between 6 and 12 years of age and weighing at least 25 kg) are limited to 12 patients who received TAF during Study GS-US-320-1092 (Cohort 2 Group 1) for 24 weeks.

However, considering that the last subject finished the double-blind phase of Study GS-US-320-1092 in August 2021, the CHMP requested the MAH to provide 48 week safety data for the patients who received TAF in the double-blind phase. These safety data, together with longer-term data from open-label phase are necessary to allow for a more in-depth safety assessment and comparison with available data for adults. Therefore, a further interim submission of Week 96 safety data for study GS-US-320-1092 was considered appropriate. Of note, a 96w cut off analysis to evaluate the open-label safety of TAF given once daily in adolescents and children with CHB is already planned according to Study 1092 Protocol.

As requested by CHMP and PRAC the Applicant planned to submit the long-term (Week 96) safety data (Cohort 1 and Cohort 2 Group 1) from Study GS-US-320-1092 in Q3 2023 as outlined in the updated EU RMP v 9.1.

The revised RMP v 9.1 has been integrated with the outcome of the approved EMEA/H/C/004169/II/0038 procedure.

As also recommended by CHMP, the MAH should present, in upcoming PSURs, bone related events in children and adolescents.

2.7. CHMP conclusion on Safety Specification and Safety Concerns

The MAH submitted a Risk Management Plan updated to version 8.2, dated 17 May 2022.

The MAH was requested to provide an integrated updated RMP version; version 9.1 was provided accordingly (i.e. version containing the approved outcome of EMEA/H/C/004169/II/0038 procedure

and the ongoing EMEA/H/C/004169/II/0040 procedure).

Table SVIII.1: Summary of safety concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety information in adults and children 6 years of age and older weighing at least 25 kg
	Development of resistance in long-term use
	Safety in pregnancy and lactation
	Safety in HBV infected patients with renal impairment (CrCl < 50 mL/min)

2.8. Pharmacovigilance plan

2.8.1. Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
GS-US-320-0108 Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF versus TDF in HBeAg-negative participants with CHB	*Safety concern(s) addressed:* Missing information: Long-term safety information in adults; Development of drug resistance in long-term use *Objectives:* To evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative adult participants with CHB	*Study design:* Randomized, double-blind clinical study with an open label extension phase with TAF *Study population:* Participants who are 18 years of age and older, with HBeAg-negative, CHB	Submission of Week 384 final report	Q2 2023
GS-US-320-0110 Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF versus TDF in HBeAg-positive participants with CHB	*Safety concern(s) addressed:* Missing information: Long-term safety information in adults; Development of drug resistance in long-term use *Objectives:* To evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive adult participants with CHB	*Study design:* Randomized, double-blind clinical study with an open label extension phase with TAF *Study population:* Participants who are at least 18 years of age and older, with HBeAg-positive, CHB	Submission of Week 384 final report	Q2 2023

Study title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due dates
GS-US-320-1092 A randomized, double-blind evaluation of the pharmacokinetics, safety, and antiviral efficacy of TAF in children and adolescent participants with CHB virus infection	*Safety concern(s) addressed:* Missing information: Long-term safety information in adolescents *Objectives:* To evaluate the safety and efficacy of TAF in adolescents with CHB and to evaluate the PK, safety and efficacy of TAF in children with CHB	*Study design:* Randomized, double-blind, placebo-controlled clinical study with an open-label extension phase with TAF *Study population:* Treatment-naïve and treatment-experienced, adolescents and children, males and females, with CHB who are HBeAg--positive or HBeAg-negative	Submission of Week 96 safety update (Cohort 1, and Cohort 2 Group 1)	Q3 2023
			Submission of final report	Q3 2025
Antiretroviral Pregnancy Registry	*Safety concern(s) addressed:* Missing information: Safety in pregnancy and lactation *Objectives:* To collect information on the risk of birth defects in patients exposed to TAF during pregnancy	*Study design:* Prospective, observational, exposure-registration, and follow-up study *Study population:* Pregnant patients exposed to antiretroviral drugs	Submission of interim reports	In the Vemlidy PSUR (data lock point [DLP] and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

2.8.2. Overall conclusions on the PhV Plan

The Committee, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Submission of long-term (Week 96) safety data (Cohort 1, and Cohort 2 Group 1) from Study GS-US-320-1092 in Q3 2023 has been outlined in the updated EU RMP v9.1. RMP Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities has been updated accordingly.

2.9. Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorization efficacy studies.

2.10. Risk minimisation measures

2.10.1. Routine Risk Minimisation Measures

Only routine risk minimization measures are in place for Vemlidy.

Vemlidy is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of chronic hepatitis B

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimization activities
Missing Information	
Long-term safety information in adults and ~~adolescents~~ children 6 years of age and older weighing at least 25 kg	No routine risk minimization measures are considered necessary.
Development of resistance in long-term use	No routine risk minimization measures are considered necessary.
Safety in pregnancy and lactation	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2
Safety in HBV infected patients with renal impairment (CrCl < 50 mL/min)	Routine risk communication: SmPC sections 4.2, 4.4 and 5.2 PL section 2

With this submission, no changes to the RMMs are proposed. Missing information "Long-term safety information in adults and adolescents" has been reformulated in "Long-term safety information in adults and children 6 years of age and older weighing at least 25 kg" according to proposed amendments in RMP Part II. This is endorsed by the Committee.

2.10.2. Additional risk minimisation measures

Routine risk minimization activities as described in Part V Section V.1 are considered sufficient to manage the safety concerns of the medicinal product.

2.10.3. Overall conclusions on risk minimisation measures

The Committee, having considered the updated data submitted, is of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indications.

2.11. Part VI Summary of the risk management plan

Proposed amendments to the RMP have appropriately been reflected in the Summary of the risk management plan.

2.12. Overall conclusion on the RMP

The changes to the RMP are considered acceptable to the Committee.

2.13. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to extend the indication to include treatment of chronic hepatitis B-infected children from 6 years and older and weighing at least 25 kilograms. In addition, the MAH took the opportunity to update the wording in section 4.6 of the SmPC related to breastfeeding and pregnancies. The Package Leaflet (PL) is updated accordingly.

Changes are also made to the PI to bring it in line with the current QRD template version.

In addition, the list of local representatives in Romania in the PL is being revised.

2.13.1. 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:

Paediatric patients aged 6 years and older and weighing at least 25 kilograms will receive the currently approved strength and pharmaceutical form for Vemlidy (i.e. 25 mg tablets) and no significant changes have been made to the package leaflet of the authorised strength of Vemlidy with the addition of the new indication. Paragraphs concerning the paediatric population are added. Design, layout, and format are continued. Key messages concerning safe use are not affected. Therefore, the Consultation with Target Patient Groups (eCTD 0002) that was provided within the initial marketing authorisation application can be used to demonstrate that the leaflet meets the requirements of article 59(3) of Council Directive 2001/83/EC.

2.13.2. Additional monitoring

N/A

2.13.3. Quick Response (QR) code

N/A

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic hepatitis B (CHB) is a major public health care issue worldwide and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure. Following acute HBV infection, 5% to 10% of adults and up to 90% of children fail to produce an immune response adequate to clear the infection; these individuals become chronic carriers of the virus. Individuals who develop CHB are at substantial risk of cirrhosis, hepatic decompensation, and HCC, which will afflict 15% to 40% of patients with CHB in the absence of effective treatment. The World Health Organization (WHO) estimates that 296 million people were living with CHB infection in 2019, with 1.5 million new infections each year. In 2013, an estimated 686,000 deaths were due to HBV infection, placing it among the top 20 causes of mortality worldwide.

3.1.2. Available therapies and unmet medical need

The goal of anti-HBV therapy in children, as in adults, is to improve long-term survival and quality of life by reducing disease progression to cirrhosis, decompensated liver disease, and HCC. The aim of oral antiviral treatment for CHB infection is to achieve and maintain suppression of viral replication to prevent or reduce the development of these complications.

The majority of children aged 2 to < 18 years have persistently normal alanine aminotransferase (ALT) values and high levels of HBV DNA, consistent with the immune-tolerant phase. However, immune activation does occur in a minority of children in whom antiviral therapy can provide benefits with regard to halting disease progression and its complications later in childhood or during young adulthood. All current guidelines suggest that antiviral therapy be considered in HBeAg positive children who have both elevated ALT and HBV DNA levels with the goal of achieving and maintaining viral suppression and producing sustained HBeAg seroconversion. Although HBeAg negative CHB is less commonly seen in children, it is generally accepted that long-term treatment is required in the absence of confirmed HBsAg seroconversion in HBeAg negative children with elevated ALT and HBV DNA levels.

Treatment options for children are similar to those for adults. Tenofovir disoproxil fumarate (TDF), a nucleotide analogue reverse transcriptase inhibitor with antiviral activity against both HBV and HIV, and entecavir (ETV), a nucleoside analogue reverse transcriptase inhibitor, are both recommended as first line treatment in all major guidelines for adults with CHB. Similarly, all major guidelines updated since approval of tenofovir alafenamide (TAF) in 2016 also list this agent as a first-line treatment in adults. Although TDF is approved for use in children and adolescent patients aged 2 to < 18 years with chronic HBV, bone and renal toxicities, including proximal tubulopathy and Fanconi syndrome, have been reported with TDF. The negative effects of TDF on bone metabolism, especially in adolescents and children who have not attained peak bone mass, are clinically concerning. Tenofovir alafenamide currently is only indicated for adults and adolescents (aged 12 years and older with body weight at least 35 kg).

3.1.3. Main clinical studies

Study GS-US-320-1092 is an ongoing double-blind, placebo-controlled, multicenter study of the safety, tolerability, PK, and antiviral activity of TAF administered once daily in treatment-naive and treatment-experienced adolescents and children with CHB. Participants were randomised to receive either blinded TAF 25 mg tablets or placebo tablets once daily through Week 24, and the primary efficacy endpoint was the percentage of participants who achieved HBV DNA < 20 IU/mL at Week 24. Following double blind treatment for 24 weeks, all participants were eligible to roll over to receive open label TAF for up to an additional 216 weeks (through Week 240).

The data presented are from the interim, primary endpoint analysis for safety, efficacy, and PK, which was conducted when all participants in Cohort 1 (adolescents 12 to less than 18 years of age and weighing at least 35 kg) and Cohort 2 Group 1 (paediatric participants 6 to < 12 years of age and weighing at least 25 kg) had completed their Week 24 (i.e., primary endpoint) visit or prematurely discontinued from the study. In response to the RSI, the MAH also provided 48-week efficacy and safety data for the participants from the TAF groups who received TAF for an additional 24 weeks during the open label phase and a comparison with data of HBeAg-positive adults treated with TAF 25 mg once daily in the Phase 3 Study GS-US-320-0110.

TAF is currently approved for use in adult and adolescent patients with CHB weighing at least 35 kg in the EU and other regions. Therefore, in particular the data from Cohort 2 Group 1 are relevant for this application to extend the indication to CHB-infected children from 6 years and older and weighing at least 25 kg.

3.2. Favourable effects

The provided data indicate that the popPK model reasonably well captured the observed TFV concentrations in paediatric HBV patients. The boxplots comparing exposure metrics (AUC, C_{max} and C_{tau}) of younger patients to the 90% prediction interval of adult exposure showed that median AUC of the younger patients was below the median of adult values but the 25% to 75% interval was still comprised in the adult 90% prediction interval. Therefore, AUC values can be considered comparable between adults and younger patients with HBV. C_{max} values in younger patients were also similar to adult C_{max}. Hence, extrapolation of efficacy and safety data from adults to children 6 to < 12 years of age and weighing at least 25 kg is generally considered acceptable.

The percentage of participants with plasma HBV DNA < 20 IU/mL at Week 24 was significantly higher in the TAF group (18.6% [11/59 participants]; 95% CI: 9.7% to 30.9%) than in the placebo group (0% [0/29 participants]; 95% CI: 0.0% to 11.9%) (P = 0.0137). Thus, the primary efficacy endpoint was met.

Furthermore, treatment with TAF resulted in rapid, progressive and substantial mean declines in HBV DNA levels over time. A similar mean decrease in HBV DNA levels was observed for participants in Cohort 1 and Cohort 2 Group 1 and adult participants from study GS-US-320-0110. Thus, while achievement of virologic suppression below HBV DNA < 20 IU/mL was more common in Cohort 1 than in Cohort 2 Group 1 (21.3% for Cohort 1 and 8.3% for Cohort 2 Group 1 at Week 24 and 40.4% for Cohort 1 and 25% for Cohort 2 Group 1 at Week 48), virologic suppression with respect to reduction in HBV DNA levels over time was similar. Moreover, a similar rate of ALT normalisation over time was observed for participants in Cohort 1 and Cohort 2 Group 1 (for both Central Lab and AASLD criteria; although ALT normalisation following AASLD criteria was lower in Cohort 2 Group 1 than in Cohort 1 at early time points, it was similar at Week 24 and Week 48) and adult participants from study GS-US-320-0110. These supportive data suggest largely similar efficacy of TAF treatment in paediatric

participants 6 to < 12 years of age weighing at least 25 kg, adolescents 12 to < 18 years of age weighing at least 35 kg and adults.

No HBV amino acid substitutions associated with resistance to TAF were detected in clinical isolates from paediatric patients. As part of the response to the RSI, the MAH submitted the Week 48 Virology Study Report for Study GS-US-320-1092 (Report No. PC-320-2022). One participant qualified for phenotypic analysis due to a conserved site change (V112V/I). This is the same subject who had a conserved site change (V112V/I) at week 24. Phenotypic analysis showed that there was no change in sensitivity to TAF compared to the baseline isolate at week 24 and week 48. Analyses regarding polymorphic site change N118N/T indicated that there is no association with reduced susceptibility or resistance to TAF. Overall, the clinical virology data of study GS-US-320-1092 do not indicate a higher risk for the development of resistance in paediatric subjects from 6 to < 18 years of age receiving TAF 25 mg once daily after 48 weeks of treatment.

3.3. Uncertainties and limitations about favourable effects

C_{tau} was clearly lower in younger HBV patients compared to adults with HBV, even the upper whisker boundary was below the 5th percentile of the adult 90% prediction interval. Since the applied dose for HBV patients aged 6 to 12 years is the same as for adults, a higher TAF dose for treatment of younger patients was considered questionable for safety reasons. The MAH submitted an updated analysis of the exposure in paediatric patients compared to adults. Particularly for C_{tau}, a considerable proportion of paediatric patients had lower exposures as compared to adults. The underlying reason of this finding remains unclear, in particular as flat dosing of 25 mg QD was used for paediatric and adult participants, which raises the question if the presented data on TAF and TFV exposure in paediatric CHB patients are correct. Thus, the safety concerns regarding the question where the remaining drug might be distributed and how it is metabolised were not fully addressed. However, the MAH argued that the efficacy response rate was not dependent upon the C_{tau} concentration, which is agreed.

In the population PK model used for evaluation of the PK in the paediatric population of Biktarvy and Vemlidy, no impact of indication (HIV versus HBV) on clearance in the paediatric population was found. This is seen to be in contradiction to the observed exposures differing between the two indications (lower exposure in paediatric HBV patients as compared to paediatric HIV patients), which indicates potential differences in clearance, as also mentioned by the MAH. This limits the credibility of the model. The MAH provided additional VPCs and exposure boxplots and argued that differences between CHB and HIV patients in the former results may have occurred due to the limitations of a non-compartmental PK analysis. No VPC stratified by weight was submitted (all weights ≥ 25 kg bodyweight were presented in one summarised plot).

In Study GS-US-320-1092, suppression rates at Week 24 (18.6% for all participants, 21.3% for Cohort 1 and 8.3% for Cohort 2 Group 1) were generally lower than those observed at Week 24 in HBeAg-positive adults treated with TAF 25 mg once daily in the Phase 3 Study GS-US-320-0110 (34.6% [201/581] participants had HBV DNA < 29 IU/mL). In particular, of the 12 participants receiving TAF in Cohort 2 Group 1, only 1 participant (8.3%) reached the primary endpoint. Thus, the 24-week data are not sufficient to conclude on efficacy of TAF treatment in this population. Of note, primary analysis was originally planned to be at Week 48. However, amendment 1 of the study protocol included a change to Week 24, which was accepted by the PDCO after consultation with the IDWP. The IDWP considered that 24 weeks for the double-blind, placebo-controlled phase is acceptable, but that 48-week data are necessary for the benefit/risk evaluation, particularly for the assessment of efficacy and resistance data. In response to the RSI, the MAH provided the requested 48-week efficacy data and a comparison with adult data:

The primary endpoint of HBV DNA < 20 IU/mL was reached by 10/47 (21.3%) participants from Cohort 1 at Week 24 and 19/47 (40.4%) at Week 48. Of the participants from Cohort 2 Group 1, 1/12 (8.3%) had reached the primary endpoint at Week 24 whereas 3/12 (25%) did so at Week 48. Thus, although more participants from Cohort 2 Group 1 reached the primary endpoint at Week 48 than at Week 24, the proportion was still lower than in Cohort 1. As mentioned before, possible explanations for this are the higher proportion of participants with high baseline viral load (75% versus 64% with baseline HBV DNA level ≥8.0 log10 IU/mL) and a higher proportion of the participants with HBV genotype D (58.3% versus 39.5%) – both factors that have been associated with a slower rate of viral suppression. Furthermore, it needs to be considered that only 12 patients were investigated in Cohort 2 Group 1 of study GS-US-320-1092. Therefore, the significance of the efficacy data from Cohort 2 Group 1 is too limited to draw any firm conclusion.

For comparison with adult data from study GS-US-320-0110, the threshold for HBV DNA had to be adjusted to the LLOQ at that time of ≤ 29 IU/ml. Under these conditions, 21/47 (44.7%) participants from Cohort 1, 5/12 (41.7%) participants from Cohort 2 Group 1 and 371/581 (63.9%) adult participants reached the endpoint. Thus, a lower proportion of participants from Cohort 1 and Cohort 2 Group 1 than adult participants reached this endpoint. Possible explanations, also in this case, are the higher proportion of paediatric participants with high baseline viral load (66% vs 47% with baseline HBV DNA level ≥8.0 log10 IU/mL) and a higher proportion of the participants with HBV genotype D (44% versus 23%).

Importantly, mean declines in HBV DNA from baseline were similar at Week 48 for all cohorts with mean (SD) log10 IU/mL of -5.65 (1.78) for Cohort 1, -5.88 (0.86) for Cohort 2 Group 1 and -5.75 (1.31) for adults. Thus, although there were considerable differences in the proportions of participants reaching HBV DNA ≤ 20 IU/mL (or 29 IU/mL), mean declines in HBV DNA from baseline were similar. This indicates comparable efficacy of TAF treatment in this respect.

Subgroup analysis confirmed that the subgroup with high viral load (≥8.0 log10 IU/mL) at baseline, representing the majority of the paediatric participants (66.1%), still showed a less robust treatment response at Week 48. However, there was notable improvement in HBV DNA levels as compared to Week 24. Moreover, the proportion with HBV DNA ≤ 20 IU/mL increased from 6.7% at Week 24 to 26.7% at Week 48 for Cohort 1 and from 0.0% to 22.2% for Cohort 2 Group 1. Thus, also in the subgroups with higher viral load, viral suppression improved over time and to a similar degree.

Of the participants in the respective TAF groups, 39.5% from Cohort 1 and 58.3% from Cohort 2 Group 1 had HBV genotype D at baseline. No participant with genotype D had achieved plasma HBV DNA ≤ 20 IU/mL at Week 24. At Week 48, 3/17 (17.6%) participants from Cohort 1 and 1/7 (14.3%) participants from Cohort 2 Group 1 with genotype D had achieved HBV DNA ≤ 20 IU/mL. An additional 2/17 (11.8%) participants and 2/7 (28.6%) participants achieved HBV DNA between 20 and 69 IU/mL, respectively. Thus, also in the subgroup of participants with HBV genotype D, viral suppression improved over time and to a similar degree.

Of note, the progressive increase in ALT normalisation over the 48-week treatment period suggests that the proportion of participants with normalised ALT may even further increase over time with long-term treatment. The persistence of ALT normalization on long-term treatment trends will be monitored through Week 240 in the open-label extension phase of the study.

The proportion of participants with abnormal ALT at baseline that had achieved normalised ALT was similar or larger for participants of Cohort 1 and Cohorts 2 Group 1 than for adult participants at both Week 24 and Week 48 and for both Central Lab criteria and AASLD criteria.

Median (Q1, Q3) change from baseline in ALT at Week 48 was similar for participants in Cohort 1 and Cohort 2 Group 1 with -38.0 U/L (-70.0, -12.0) and -30.0 U/L (-82.0, -2.5), respectively. In adult

participants, ALT decrease was larger with -55.0 U/L (-106.0, -25.0). However, as mentioned above, median (Q1, Q3) ALT at baseline also was higher for adult participants (85 U/L (61, 139)) than for paediatric participants (65 U/L (50, 109)), which relativises this difference.

Consistent with early serological outcomes in paediatric studies with TDF (GS-US-174-0144 and GS-US-174-0115), the impact of TAF treatment on serological endpoints (HBeAg loss/seroconversion and HBsAg loss/seroconversion) was not different to placebo at Week 24. At Week 48, similar proportions of participants from Cohort 1 (7/46 (15.2%)) and Cohort 2 Group 1 (3/12 (25.0%)) and adult participants (13.8%) showed HBeAg loss. Furthermore, similar proportions of participants from Cohort 1 (6/46 participants (13.0%), Cohort 2 Group 1 (2/12 participants (16.7%)) and adult participants (10.3%) achieved HBeAg seroconversion. HBsAg loss and seroconversion were achieved by no paediatric participants and only very few adult participants (4 participants (0.7%) and 3 participants, respectively) until Week 48. Longer term treatment is needed to more fully assess the impact of TAF on serological outcomes. There was only minimal fibrosis response after 48 weeks of treatment. Longer term treatment is needed to more fully assess the impact of TAF on fibrosis response in this population. The MAH committed to provide long-term data from the open label phase as soon as possible.

Overall, viral suppression, ALT normalisation and change from baseline as well as HBeAg loss and seroconversion (further) improved from Week 24 to Week 48 and to a largely similar degree in Cohort 1 and Cohort 2 Group 1 and as compared to adult participants. The differences in the proportions of participants achieving HBV DNA ≤ 20 IU/mL (or 29 IU/mL) between Cohort 2 Group 1 and Cohort 1 as well as compared to adult participants can largely be attributed to baseline characteristics (relatively higher proportion of participants with high baseline viral load and higher prevalence of HBV genotype D). The differences in absolute changes in ALT levels between paediatric and adult participants can similarly be attributed to the higher baseline ALT levels in adults. Also, considering that the additional data provided for the PopPK model indicate comparable exposure of TFV (AUC_{tau}/C_{tau}) between CHB-infected adults and children aged 6-12 years and weighing ≥ 25 kg (see Q1 above) and that, hence, an extrapolation of the adult CHB efficacy data to the paediatric patients aged 6 to <12 years is possible, it is overall concluded that the efficacy data from study GS-US-320-1092 are regarded as sufficient to support this extension of indication.

3.4. Unfavourable effects

The MAH submitted week 24 safety data from Study GS-US-320-1092 in support of this application of extension of indication which included data from Cohort 1 (adolescents aged 12 years and older with body weight at least 35kg, already approved) and Cohort 2 Group 1 (paediatric patients between 6 and 12 years of age and weighing at least 25 kg, applied for in this application of extension of indication). Safety data from the target population is limited to 12 patients who received TAF during Study GS-US-320-1092.

Overall, the rate of AEs in Study GS-US-320-1092 was slightly higher in the TAF group (59.3%) compared to the placebo group (55.2%). The rate of AEs was slightly lower in the target population Cohort 2 Group 1 (50%) compared to Cohort 1 (61.7%). Furthermore, the rate of patients experiencing grade 2, 3 or 4 AEs was higher in Cohort 1 (14.9% vs. 8.3%).

When comparing frequently reported AEs in Cohort 1 and Cohort 2 Group 1 (reported in more than one patient), abdominal pain (Cohort 1: 8.5% [n=4] vs. Cohort 2 Group 1: 25% [n=3]) and nausea (Cohort 1: 4.3% [n=2] vs. Cohort 2 Group 1: 16.7% [n=2]) were more frequently registered in the target group of Cohort 2 which are already labelled adverse reactions. In general, the reported AEs in

the TAF groups are in line with the AEs reported during the adults Studies GS-US-320-0108 and GS-US-320-0110 (week 48 and data beyond).

Overall, for more patients in the TAF group (16.9%, n=10) AEs were considered as related to study drug compared to the placebo group (10.3%, n=3). No differences in reporting of related AEs was observed between Cohort 1 and Cohort 2 Group 1.

SAEs were reported in three patients. One patient in the TAF group (Cohort 1) experienced an SAE of Grade 2 scarlet fever considered not related to study drug. The other two SAEs were observed in the placebo group (ankle fracture, Grade 3 ALT increased). No SAEs were observed in the target paediatric population.

No deaths occurred during the double-blind phase of Study GS-US-320-1092.

No patient prematurely discontinued the double-blind phase of the study due to an AE.

As requested, the MAH provided week 48 interim safety data from Study GS-US-320-1092, which included data from patients who received TAF over 48 weeks in the double-blind (DB) and OL phases for participants in Cohort 1 and Cohort 2 Group 1, and patients in the PBO group who crossed-over to TAF (PBO-TAF) at Week 24 and entered the OL phase. Furthermore, a comparison of these data to week 48 data from adult studies (GS-US-320-0108 and GS-US-320-0110) was presented.

Overall, the rate of AEs in Cohort 2 Group 1 in Study GS-US-320-1092 until week 48 was slightly lower compared to the rate in Cohort 1 (66.7% [n=8] vs. 74.5% [n=47]). When comparing to adult week 48 data the rate of AEs was comparable (70.2%, n=608). A slightly higher rate of patients in Cohort 2 Group 1 developed grade 2, 3 or 4 AEs until week 48 compared to Cohort 1 of Study GS-US-320-1092 and adult data (33.3% [n=4] vs. 25.5% [n=12] vs. 25.5% [n=221]). However, due to the very limited number of patients in Cohort 2 Group 1 no conclusion can be drawn based on this minor difference.

The overall incidence of AEs at Week 48 for participants who switched from PBO to TAF at Week 24 (PBO-TAF) group was 55.2% (16/29 patients), which was the same as PBO participants at Week 24.

The most common AEs in the overall TAF group in Study GS-US-320-1092 at 48 weeks were headache (18.6% [11/59 patients]), nasopharyngitis (15.3% [9/59 patients]), upper respiratory tract infection, pyrexia, and abdominal pain upper (11.9% [7/59 patients]) each, and vitamin D decreased, cough, nausea, and diarrhoea (10.2% [6/59 patients]) each.

Similar AEs were reported most commonly in adults, however, in a lower rate compared to Study GS-US-320-1092: nasopharyngitis and upper respiratory tract infection (9.9% [86/866 patients]) each, headache (9.5% [82/866 patients]), cough (6.4% [55/866 patients]), and nausea (5% [43/866 patients]).

Nevertheless, the reported AEs between Cohort 1 and Cohort 2 Group 1 in Study GS-US-320-1092 were comparable and considering the limited number of paediatric patients treated, it can be concluded that these data are in general in accordance with the reported AEs in adults.

Most common AEs in paediatric patients treated with TAF for 24 weeks after 24 weeks on PBO were nasopharyngitis (13.8% [4/29 patients]), and vitamin D deficiency, osteoporosis and epistaxis (6.9% [2/29 patients]) each.

The rate of related AEs was higher in Study GS-US-320-1092 (Cohort 1: 31.9% [n=15], Cohort 2 Group 1: 25.0% [n=3]) than reported in adult studies (14.2% [n=123]). However, most commonly reported drug-related AEs in paediatric patients were known labelled ADRs for TAF (which may have led to the reporting as adverse reaction), such as headache (10.2% [6/59 patients]), nausea and abdominal pain upper (5.1% [3/59 patients] each), abdominal pain (3.4% [2/59 patients]) and fatigue

(3.4% [2/59 patients]). The incidence of drug-related AEs was slightly lower for the patients in Cohort 2 Group 1 (25.0% [3/12 patients]) versus Cohort 1 (31.9% [15/47 patients]) for which Vemlidy is already approved. Furthermore, in Cohort 2 Group 1 only single cases of related AEs were reported.

In the OL phase, 17.0% (15/88 patients) experienced drug-related AEs (18.6% [11/59 patients] in the TAF group and 13.8% [4/29 patients] in the PBO-TAF group). None of the drug-related AEs occurred in > 1 patient in the PBO-TAF group after switching from placebo to TAF.

No SAEs occurred in Cohort 2 Group 1 through Week 48 who received TAF. However, it should be considered that only 12 paediatric patients were investigated in Cohort 2 Group 1, which limits the significance of the safety data. Information about reductions in bone mineral density (BMD ≥ 4%) of the lumbar spine and of whole body have been included in sections 4.4, 4.8 and 5.1 of the SmPC which is agreed.

Overall, Vemlidy was well tolerated during paediatric Study GS-US-320-1092 until week 48 and no new safety signal was identified.

3.5. Uncertainties and limitations about unfavourable effects

Safety data of the target population (paediatric patients between 6 and 12 years of age and weighing at least 25 kg) are limited to 12 patients who received TAF over 24 weeks during Study GS-US-320-1092 (Cohort 2 Group 1). This is in general acceptable since the popPK modelling indicate that exposure (AUC_{tau} and C_{max}) is comparable between paediatric patients aged 6 to 12 years and weighing ≥ 25 kg and adults with CHB infection and an extrapolation of the adult safety data to the paediatric population is possible.

The MAH further committed that long-term data from open-label phase will be provided as soon as possible.

When comparing PK data in patients with CHB between adults, adolescents and the target population paediatric patients between 6 and 12 years of age and weighing at least 25 kg measured during Study GS-US-320-1092 (limited data), in children between 6-12 years, C_{max} and AUC_{tau} of TAF are significantly higher compared to adults, in case of TFV the exposure is lower in children while C_{max} is comparable with adult data (see section PK). Safety parameter C_{max} of TAF was twice as high in Cohort 2 Group 1 (387.7 ng/mL) compared to adolescents (187.8 ng/mL) and adults (177.6 ng/mL). However, TAF is metabolised rapidly ($t_{1/2}$ 0.5h) and metabolite TFV is considered as mainly responsible for efficacy and safety. C_{max} of TFV was comparable between patients of different ages (Cohort 1: 15.3 ng/mL, Cohort 2 Group 1: 17.4 ng/mL, adults: 17.2 ng/mL).

Bone Safety

To analyse the impact of TAF on bone mineralization in children and adolescents aged 6-<18 years old, the MAH provided information about bone mineral density, fracture events, bone events and bone biochemical markers evaluated during blinded 24 weeks treatment of TAF vs. placebo of Study GS-US-320-1092. Data from the target paediatric population (paediatric patients between 6 and 12 years of age and weighing at least 25 kg) is limited to 12 patients who received TAF in Cohort 2 Group 1.

Furthermore, the MAH provided information from Study GS-US-320-1092 week 48 data about bone mineral density, fracture events, bone events and bone biochemical markers.

Overall, 3 patients in the TAF group (1 in Cohort 1 and 2 in Cohort 2 Group 1) and 2 patients in the PBO-TAF (Cohort 1 and Cohort 2 Group 1, one each) group had ≥ 4% BMD decreases from baseline in spine and whole body BMD at Week 48 and 3 additional patients (1 from Cohort 1 and 2 from Cohort 2 Group 1) had a ≥ 4% decrease in BMD at spine or whole body after Week 48, while a ≥ 4% decrease

was transient for 3 out of these 8 patients and all 8 patients had normal Z-scores for their age at Week 48 and subsequently recorded study visits. For both treatment groups, observed mean spine and whole body BMD Z-score values were within the normal range from baseline through Week 48.

Fracture events were reported in 2 patients during the OL phase (patella fracture [Cohort 1 TAF group] and tibia fracture [Cohort 2 Group 1 PBO-TAF group]). Both fracture events were trauma-related, considered by the investigator to be unrelated to study drug.

Overall, the MAH included specific information about changes in bone mineral density in Study GS-US-320-1092 into Section 5.1 of the SmPC. Specifically, a table was included with information about bone mineral density decreases of 4% or greater for paediatric patients at weeks 24 and 48, which is agreed. Furthermore, the MAH adapted the warning on BMD in section 4.4 and the information in section 4.8 of the SmPC in this regard to the agreed wording in the EU SmPCs of Genvoya and Biktarvy. The warning on BMD in section 4.4 of the SmPC was also implemented accordingly, in section 2 of the PL.

Table 26: Effects Table for Vemlidy for the treatment of CHB in paediatric patients 6 years of age and older weighing at least 25 kg (Study GS-US-320-1092, data cut-off: 16 August 2021)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
efficacy	Primary endpoint: participants with plasma HBV DNA < 20 IU/mL at Week 24	%	18.6	0	Primary endpoint met for FAS but effect lower at both Week 24 and Week 48 for Cohort 2 Group 1 than for Cohort 1, and both lower than adults	(1)
efficacy	Secondary endpoint: change from baseline in HBV DNA levels at Week 24	log_{10} IU/mL	−4.98	−0.10	Similar HBV DNA declines in Cohort 1, Cohort 2 Group 1 and adults at Week 24 and Week 48	(1)
efficacy	Secondary endpoint: participants with normalised ALT at Week 24 (Central Lab criteria / AASLD criteria)	%	67.3 / 44.6	3.7 / 0	Similar ALT normalisation levels in Cohort 1, Cohort 2 Group 1 and adults at Week 24 and Week 48	(1)
Unfavourable Effects						
AEs	Reported rate Week 24	%	50.0 (Cohort 2 Group 1)	55.2 (Placebo group overall)	Week 48 safety data in accordance with adult data	(1)
ADRs	Reported rate Week 24	%	16.7% (Cohort 2 Group 1)	10.3% (Placebo group overall)	Week 48 data: Cohort 1: 31.9% [n=15], Cohort 2 Group 1: 25.0% [n=3]), adult studies: 14.2% [n=123] Most commonly reported drug-related AEs in paediatric patients were known labelled ADRs for TAF.	(1)
SAEs	Reported rate Week 24		0 (Cohort 2 Group 1)	6.9 (Placebo group overall)	Week 48 data: No SAEs reported in Cohort 2 Group 1	(1)

Notes: (1) CSR Study GS-US-320-1092

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The data from study GS-US-320-1092 presented here are from the interim, primary endpoint analysis for safety, efficacy, and PK at Week 24. Moreover, in response to the RSI, the MAH also provided 48-week efficacy data for the participants from the TAF groups who received TAF for an additional 24

weeks during the open label phase and a comparison with data of HBeAg-positive adults treated with TAF 25 mg once daily in the Phase 3 Study GS-US-320-0110.

The provided data indicate that the popPK model reasonably well captured the observed TFV concentrations in paediatric HBV patients. The boxplots comparing exposure metrics (AUC, C_{max} and C_{tau}) of younger patients to the 90% prediction interval of adult exposure showed that median AUC of the younger patients was below the median of adult values but the 25% to 75% interval was still comprised in the adult 90% prediction interval. Therefore, AUC values can be considered comparable between adults and younger patients with HBV. C_{max} values in younger patients were also similar to adult C_{max}. Hence, extrapolation of efficacy and safety data from adults to children 6 to < 12 years of age and weighing at least 25 kg is generally considered acceptable.

However, C_{tau} was clearly lower in younger HBV patients compared to adults with HBV, even the upper whisker boundary was below the 5th percentile of the adult 90% prediction interval. Since the applied dose for HBV patients aged 6 to 12 years is the same as for adults, a higher TAF dose for treatment of younger patients is not considered reasonable for safety reasons. The MAH submitted an updated analysis of the exposure in paediatric patients compared to adults. Particularly for C_{tau}, a considerable proportion of paediatric patients had lower exposures as compared to adults. The underlying reason of this finding remains unclear, in particular as flat dosing of 25 mg QD was used for paediatric and adult participants, which raises the question if the presented data on TAF and TFV exposure in paediatric CHB patients are correct. The MAH argued that the efficacy response rate was not dependent upon the C_{tau} concentration. However, safety concerns regarding the question where the remaining drug might be distributed and how it is metabolised were not addressed.

The primary efficacy endpoint of study GS-US-320-1092 was met (percentage of all 88 participants in the FAS with plasma HBV DNA < 20 IU/mL at Week 24 in TAF group vs. placebo group). However, the primary analysis population mainly consisted of adolescents aged 12 years and older with body weight at least 35 kg, for who Vemlidy is already approved, but only few children aged 6 to 12 years and weighing ≥ 25 kg were investigated, who are the population of interest for this application regarding extension of indication to paediatric patients 6 years of age and older weighing at least 25 kg.

Treatment with TAF resulted in rapid, progressive and substantial mean declines in HBV DNA levels over time. A similar mean decrease in HBV DNA levels was observed for participants in Cohort 1 and Cohort 2 Group 1 and adult participants from study GS-US-320-0110. Thus, while achievement of virologic suppression below HBV DNA < 20 IU/mL was more common in Cohort 1 than in Cohort 2 Group 1 (21.3% for Cohort 1 and 8.3% for Cohort 2 Group 1 at Week 24 and 40.4% for Cohort 1 and 25% for Cohort 2 Group 1 at Week 48), virologic suppression with respect to reduction in HBV DNA levels over time was similar. Moreover, a similar rate of ALT normalisation over time was observed for participants in Cohort 1 and Cohort 2 Group 1 (for both Central Lab and AASLD criteria; although ALT normalisation following AASLD criteria was lower in Cohort 2 Group 1 than in Cohort 1 at early time points, it was similar at Week 24 and Week 48) and adult participants from study GS-US-320-0110. These supportive data suggest largely comparable efficacy of TAF treatment in paediatric participants 6 to < 12 years of age weighing at least 25 kg, adolescents 12 to < 18 years of age weighing at least 35 kg and adults.

However, suppression rates at Week 24 in this study (18.6% for all participants, 21.3% for Cohort 1 and 8.3% for Cohort 2 Group 1) were generally lower than those observed at Week 24 in HBeAg-positive adults treated with TAF 25 mg once daily in the Phase 3 Study GS-US-320-0110 (34.6% [201/581] participants had HBV DNA < 29 IU/mL). Importantly, of the 12 children aged 6 to 12 years and weighing ≥ 25 kg receiving TAF, only 1 participant (8.3%) reached the primary endpoint. Thus, the 24-week data are not sufficient to conclude on efficacy of TAF treatment in this population. In

response to the RSI, the MAH provided the requested 48-week efficacy data and a comparison with adult data:

The primary endpoint of HBV DNA < 20 IU/mL was reached by 10/47 (21.3%) participants from Cohort 1 at Week 24 and 19/47 (40.4%) at Week 48. Of the participants from Cohort 2 Group 1, 1/12 (8.3%) had reached the primary endpoint at Week 24 whereas 3/12 (25%) did so at Week 48. Thus, although more participants from Cohort 2 Group 1 reached the primary endpoint at Week 48 than at Week 24, the proportion was still lower than in Cohort 1. Furthermore, a lower proportion of participants from Cohort 1 (44.7%) and Cohort 2 Group 1 (41.7%) than adult participants (63.9%) reached the endpoint of HBV DNA ≤ 29 IU/ml. Importantly, however, mean declines in HBV DNA from baseline were similar also at Week 48 for all cohorts with mean (SD) log10 IU/mL of -5.65 (1.78) for Cohort 1, -5.88 (0.86) for Cohort 2 Group 1 and -5.75 (1.31) for adults. Thus, although there were considerable differences in the proportions of participants reaching HBV DNA ≤ 20 IU/mL (or 29 IU/mL), mean declines in HBV DNA from baseline were similar. This indicates similar efficacy of TAF treatment in this respect.

The proportion of participants with abnormal ALT at baseline that had achieved normalised ALT was similar or larger for participants of Cohort 1 and Cohorts 2 Group 1 than for adult participants at both Week 24 and Week 48. Of note, the progressive increase in ALT normalisation over the 48-week treatment period suggests that the proportion of participants with normalised ALT may even further increase over time with long-term treatment. The impact of TAF treatment on serological endpoints (HBeAg loss/seroconversion and HBsAg loss/seroconversion) was not different to placebo at Week 24. At Week 48, similar proportions of participants from Cohort 1 (7/46 (15.2%)) and Cohort 2 Group 1 (3/12 (25.0%)) and adult participants (13.8%) showed HBeAg loss. Furthermore, similar proportions of participants from Cohort 1 (6/46 participants (13.0%), Cohort 2 Group 1 (2/12 participants (16.7%)) and adult participants (10.3%) achieved HBeAg seroconversion. There was only minimal fibrosis response after 48 weeks of treatment. Longer term treatment is needed to more fully assess the impact of TAF on these parameters. The MAH committed to provide long-term data from the open label phase as soon as possible.

Overall, viral suppression, ALT normalisation and change from baseline as well as HBeAg loss and seroconversion (further) improved from Week 24 to Week 48 and to a largely similar degree in Cohort 1 and Cohort 2 Group 1 and as compared to adult participants. Also, considering that the additional data provided for the PopPK model indicate comparable exposure of TFV (AUC_{tau}/C_{tau}) between CHB-infected adults and children aged 6-12 years and weighing ≥ 25 kg (see Q1 above) and that, hence, an extrapolation of the adult CHB efficacy data to the paediatric patients aged 6 to <12 years is possible, it is overall concluded that the efficacy data from study GS-US-320-1092 are regarded as sufficient to support this extension of indication.

3.6.2. Balance of benefits and risks

TAF is currently approved for use in adult and adolescent patients with CHB weighing at least 35 kg in the EU and other regions. Therefore, for this application to extend the indication to CHB-infected children from 6 years and older and weighing at least 25 kg, in particular the data from Cohort 2 Group 1 of study GS-US-320-1092 are relevant. The data presented here are from the interim, primary endpoint analysis for safety, efficacy, and PK at Week 24.

The provided data indicate that the popPK model reasonably well captured the observed TFV concentrations in paediatric HBV patients. AUC and C_{max} values in younger patients were comparable to those in adults. Hence, extrapolation of efficacy and safety data from adults to children 6 to < 12 years of age and weighing at least 25 kg is generally considered acceptable. However, C_{tau} was clearly

lower in younger HBV patients compared to adults with HBV. The underlying reason for this finding remains unclear, in particular as flat dosing of 25 mg QD was used for paediatric and adult participants. The MAH argued that the efficacy response rate was not dependent upon the C_{tau} concentration. However, safety concerns regarding the question where the remaining drug might be distributed and how it is metabolised were not addressed.

The primary efficacy endpoint of study GS-US-320-1092 was met (percentage of all 88 participants in the FAS with plasma HBV DNA < 20 IU/mL at Week 24 in TAF group vs. placebo group). However, the primary analysis population mainly consisted of adolescents aged 12 years and older with body weight at least 35 kg, for which Vemlidy is already approved, but only few children aged 6 to 12 years and weighing ≥ 25 kg, who are the population of interest for this application regarding extension of indication to paediatric patients 6 years of age and older weighing at least 25 kg.

A similar mean decrease in HBV DNA levels was observed for participants in Cohort 1 and Cohort 2 Group 1 and as compared to adult participants from study GS-US-320-0110. Moreover, a similar rate of ALT normalisation over time was observed for participants in Cohort 1 and Cohort 2 Group 1 and as compared to adult participants from study GS-US-320-0110. These supportive data suggest largely similar efficacy of TAF treatment in paediatric participants 6 to < 12 years of age weighing at least 25 kg, adolescents 12 to < 18 years of age weighing at least 35 kg and adults.

However, suppression rates at Week 24 in this study (18.6% for all participants, 21.3% for Cohort 1 and 8.3% for Cohort 2 Group 1) were generally lower than those observed at Week 24 in HBeAg-positive adults in the Phase 3 Study GS-US-320-0110 (34.6% [201/581] participants had HBV DNA < 29 IU/mL). Importantly, of the 12 children aged 6 to 12 years and weighing ≥ 25 kg receiving TAF, only 1 participant (8.3%) reached the primary endpoint. Thus, the 24-week data are not sufficient to conclude on efficacy of TAF treatment in this population. In response to the RSI, the MAH provided the requested 48-week efficacy data and a comparison with adult data:

Although more participants from Cohort 2 Group 1 reached the primary endpoint of HBV DNA < 20 IU/mL at Week 48 (3/12 (25%)) than at Week 24, the proportion was still lower than in Cohort 1 (19/47 (40.4%)). Furthermore, a lower proportion of participants from Cohort 1 (44.7%) and Cohort 2 Group 1 (41.7%) than adult participants (63.9%) reached the endpoint of HBV DNA ≤ 29 IU/ml. Importantly, however, mean declines in HBV DNA from baseline were similar also at Week 48 for all cohorts with mean (SD) log10 IU/mL of -5.65 (1.78) for Cohort 1, -5.88 (0.86) for Cohort 2 Group 1 and -5.75 (1.31) for adults. Thus, although there were considerable differences in the proportions of participants reaching HBV DNA ≤ 20 IU/mL (or 29 IU/mL), mean declines in HBV DNA from baseline were similar. This indicates similar efficacy of TAF treatment in this respect.

Overall, viral suppression, ALT normalisation and change from baseline as well as HBeAg loss and seroconversion (further) improved from Week 24 to Week 48 and to a largely similar degree in Cohort 1 and Cohort 2 Group 1 and as compared to adult participants. Also, considering that the additional data provided for the PopPK model indicate comparable exposure of TFV (AUC_{tau}/C_{tau}) between CHB-infected adults and children aged 6-12 years and weighing ≥ 25 kg (see Q1 above) and that, hence, an extrapolation of the adult CHB efficacy data to the paediatric patients aged 6 to <12 years is possible, it is overall concluded that the efficacy data from study GS-US-320-1092 are regarded as sufficient to support this extension of indication.

Hence, extension of indication from adult and adolescent patients with CHB weighing at least 35 kg to CHB-infected children from 6 years and older and weighing at least 25 kg is approved by the Committee.

3.6.3. Additional considerations on the benefit-risk balance

N/A

3.7. Conclusions

The overall benefit-risk balance of Vemlidy for the treatment of chronic hepatitis B in paediatric patients 6 to <12 years of age weighing at least 25 kg is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, 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 to include treatment of chronic hepatitis B-infected children from 6 years and older and weighing at least 25 kilograms for Vemlidy, based on the interim results from Week 24 clinical study report (CSR) for Cohort 1 and Cohort 2 Group 1 and supporting modular summaries for the category 3 study GS-US-320-1092, 'A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection'. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the MAH took the opportunity to update the wording in section 4.6 of the SmPC related to breastfeeding and pregnancies exposed to TAF, and to update the list of local representatives in the Package Leaflet.

An updated RMP version 9.1 has been provided.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.