Clinical trial results:
A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients With Chronic Hepatitis B Infection

Summary

EudraCT number	2012-000586-20
Trial protocol	PL BG Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	28 July 2021
First version publication date	28 July 2021

Trial information

Trial identification

Sponsor protocol code	GS-US-174-0144

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01651403
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000533-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	02 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the antiviral efficacy of tenofovir disoproxil fumarate (tenofovir DF; TDF) versus placebo in pediatric population (aged 2 to < 12 years at the time of enrollment) with chronic hepatitis B (CHB) infection.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Romania: 23
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Bulgaria: 1
Worldwide total number of subjects	90
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	88
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Asia, and Europe.The first participant was screened on 06 December 2012. The last Week 192 study visit occurred on 02 June 2020.

Pre-assignment

Screening details:

176 participants were screened.

Period 1

Period 1 title	Double-Blind Period (Through Week 48/72)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Tenofovir Disoproxil Fumarate

Arm description:

Blinded Randomized Phase: Tenofovir disoproxil fumarate (TDF) tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Arm type	Experimental
Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Tablet, Oral powder
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Arm title	Placebo

Arm description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Arm type	Placebo

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Oral powder, Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder, Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Number of subjects in period 1[1]	Tenofovir Disoproxil Fumarate	Placebo
Started	60	29
Completed	56	25
Not completed	4	4
Withdrew Consent/Assent	3	3
Participant Noncompliance	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant who was randomized but not treated was not included in the Safety Analysis Set for Period table 1 reported above.

Period 2

Period 2 title	Open-Label Phase (Weeks 49/73-192)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tenofovir Disoproxil Fumarate

Arm description:

Blinded Randomized Phase: Tenofovir disoproxil fumarate (TDF) tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Arm type	Experimental

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Oral powder, Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Arm title	Placebo

Arm description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Arm type	Placebo
Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Viread®
Pharmaceutical forms	Tablet, Oral powder
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder, Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Number of subjects in period 2	Tenofovir Disoproxil Fumarate	Placebo
Started	56	25
Completed	35	11
Not completed	21	14
Withdrew Consent/Assent	6	4
Investigator decision	2	1
Continuing Study	13	9

Baseline characteristics

Reporting groups

Reporting group title	Tenofovir Disoproxil Fumarate

Reporting group description:

Blinded Randomized Phase: Tenofovir disoproxil fumarate (TDF) tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Reporting group title	Placebo

Reporting group description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Reporting group values	Tenofovir Disoproxil Fumarate	Placebo	Total
Number of subjects	60	29	89
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	6	7	
standard deviation	± 2.5	± 3.2	-
Gender categorical Units: Subjects			
Female	27	12	39
Male	33	17	50
Ethnicity Units: Subjects			
Not Hispanic or Latino	60	29	89
Race Units: Subjects			
Asian	41	17	58
Black or African American	4	1	5
White	15	11	26
Hepatitis B Virus Surface Antigen (HBsAg) Units: Subjects			
Positive	60	29	89

Negative	0	0	0
Hepatitis B e antigen (HBeAg) Units: Subjects			
Positive	56	29	85
Negative	4	0	4
HBeAb Units: Subjects			
Positive	4	0	4
Negative or Missing	56	29	85
HBV DNA Units: log10 IU/mL			
arithmetic mean	8.089	8.133	
standard deviation	± 0.7208	± 1.2538	-
Spine Bone Mineral Density Units: g/cm^2			
arithmetic mean	0.586	0.626	
standard deviation	± 0.1196	± 0.1567	-

End points

End points reporting groups

Reporting group title	Tenofovir Disoproxil Fumarate

Reporting group description:

Blinded Randomized Phase: Tenofovir disoproxil fumarate (TDF) tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Reporting group title	Placebo

Reporting group description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Reporting group title	Tenofovir Disoproxil Fumarate

Reporting group description:

Blinded Randomized Phase: Tenofovir disoproxil fumarate (TDF) tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Reporting group title	Placebo

Reporting group description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Subject analysis set title	TDF (Blinded Randomized Phase)
Subject analysis set type	Full analysis

Subject analysis set description:

Blinded Randomized Phase: TDF tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Subject analysis set title	Placebo (Blinded Randomized Phase)
Subject analysis set type	Full analysis

Subject analysis set description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Subject analysis set title	TDF to TDF
Subject analysis set type	Full analysis

Subject analysis set description:

Blinded Randomized Phase: TDF tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Subject analysis set title	Placebo to TDF
Subject analysis set type	Full analysis

Subject analysis set description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3).

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Subject analysis set title	TDF to TDF (Open-Label Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Subject analysis set title	Placebo to TDF (Open-Label Phase)
Subject analysis set type	Safety analysis

Subject analysis set description:

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).

Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Primary: Percentage of Participants With Serum HBV DNA < 400 Copies/mL (69 IU/mL) at Week 48 (Missing = Failure Approach)

End point title	Percentage of Participants With Serum HBV DNA < 400 Copies/mL (69 IU/mL) at Week 48 (Missing = Failure Approach)

End point description:

The Full Analysis Set (FAS) included randomized participants who have received at least 1 dose of study drug. Participants will be analyzed according to the treatment to which they were randomized. The missing equals failure approach was used where all participants with missing data were considered to have failed to achieve the endpoint.

End point type	Primary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (confidence interval 95%)	76.7 (64.0 to 86.6)	6.9 (0.8 to 22.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline and region strata

Statistical analysis title	Statistical Analysis 2 - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Fisher exact

Notes:

[2] - Fisher's exact test without adjusting for strata at baseline

Primary: Percentage of Participants With Serum HBV DNA < 400 Copies/mL (69 IU/mL) at Week 48 (Missing = Excluded Approach)

End point title	Percentage of Participants With Serum HBV DNA < 400 Copies/mL (69 IU/mL) at Week 48 (Missing = Excluded Approach)

End point description:

Participants in the Full Analysis Set with available data were analyzed. The missing equals failure approach was used where all participants with missing data were excluded.

End point type	Primary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	26		
Units: percentage of participants				
number (confidence interval 95%)	83.6 (71.2 to 92.2)	7.7 (0.9 to 25.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline and region strata

Secondary: Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion at Week 48

End point title	Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion at Week 48

End point description:

HBeAg seroconversion was defined as HBeAg loss and a change from HBeAb negative or missing at baseline to HBeAb positive. Serologically Evaluable FAS For HBeAg loss/seroconversion: participants who were randomized and had received at least 1 dose of study drug, and with HBeAg positive and HBeAb negative or missing at baseline. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	29		
Units: percentage of participants				
number (not applicable)	25.0	24.1		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.935 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - 2-sided Cochran-Mantel-Haenszel test adjusted for age at baseline and region strata

Secondary: Percentage of Participants With Normal Alanine Aminotransferase (ALT) at Week 48, Based on the American Association for the Study of Liver Diseases (AASLD) Normal Range

End point title	Percentage of Participants With Normal Alanine Aminotransferase (ALT) at Week 48, Based on the American Association for the Study of Liver Diseases (AASLD) Normal Range

End point description:

Normal ALT was defined as ≤ 30 U/L for males and females 0−12 years based on the AASLD pediatric normal range. Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	51.7	17.2		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Percentage of Participants With Normal ALT at Week 192, Based on the AASLD Normal Range

End point title	Percentage of Participants With Normal ALT at Week 192, Based on the AASLD Normal Range

End point description:

Normal ALT was defined as ≤ 30 U/L for males and females 0-12 years based on the AASLD pediatric normal range. Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	71.7	51.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normal ALT at Week 48, Based on the Central Lab Normal Range

End point title	Percentage of Participants With Normal ALT at Week 48, Based on the Central Lab Normal Range

End point description:

Normal ALT was defined as ≤ 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old based on the central lab normal range. Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	65.0	17.2		

Statistical analyses

Statistical analysis title	Statistical Analysis: TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Percentage of Participants With Normal ALT at Week 192, Based on the Central Lab Normal Range

End point title	Percentage of Participants With Normal ALT at Week 192, Based on the Central Lab Normal Range

End point description:

Normal ALT was defined as ≤ 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old based on the central lab normal range. Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	80.0	62.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normalized ALT at Week 48, Based on the AASLD Normal Range

End point title	Percentage of Participants With Normalized ALT at Week 48, Based on the AASLD Normal Range

End point description:

Normal ALT was defined as ≤ 30 U/L for males and females 0-12 years based on the AASLD pediatric normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	28		
Units: percentage of participants				
number (not applicable)	51.7	17.9		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [7]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Percentage of Participants With Normalized ALT at Week 192, Based on the AASLD Normal Range

End point title	Percentage of Participants With Normalized ALT at Week 192, Based on the AASLD Normal Range

End point description:

Normal ALT was defined as ≤ 30 U/L for males and females 0-12 years based on the AASLD pediatric normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	28		
Units: percentage of participants				
number (not applicable)	71.7	50.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normalized ALT at Week 48, Based on the Central Lab Normal Range

End point title	Percentage of Participants With Normalized ALT at Week 48, Based on the Central Lab Normal Range

End point description:

Normal ALT was defined as ≤ 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old based on the central lab normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	27		
Units: percentage of participants				
number (not applicable)	65.5	14.8		

Statistical analyses

Statistical analysis title	Statistical Analysis- TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Percentage of Participants With Normalized ALT at Week 192, Based on the Central Lab Normal Range

End point title	Percentage of Participants With Normalized ALT at Week 192, Based on the Central Lab Normal Range

End point description:

Normal ALT was defined as ≤ 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old based on the central lab normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all

participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	27		
Units: percentage of participants				
number (not applicable)	79.3	59.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on AASLD Normal Range) at Week 48

End point title	Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on AASLD Normal Range) at Week 48

End point description:

Normal ALT was defined as ≤ 30 U/L for males and females 0−12 years based on the AASLD pediatric normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	28		
Units: percentage of participants				
number (not applicable)	46.7	7.1		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on AASLD Normal Range) at Week 192

End point title	Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on AASLD Normal Range) at Week 192

End point description:

Normal ALT was defined as ≤ 30 U/L for males and females 0-12 years based on the AASLD pediatric normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	28		
Units: percentage of participants				
number (not applicable)	70.0	42.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on Central Lab Normal Range) at Week 48

End point title	Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on Central Lab Normal Range) at Week 48

End point description:

Normal ALT was defined as ≤ 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old based on the central lab normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary
End point timeframe:	
Week 48	

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	27		
Units: percentage of participants				
number (not applicable)	53.4	7.4		

Statistical analyses

Statistical analysis title	Statistical Analysis- TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on Central Lab Normal Range) at Week 192

End point title	Composite Endpoint of Percentage of Participants With HBV DNA < 400 Copies/mL (69 IU/mL) and Normalized ALT (Based on Central Lab Normal Range) at Week 192

End point description:

Normal ALT was defined as ≤ 34 U/L for females aged 2-15 years old or males aged 1-9 years old, and ≤ 43 U/L for males aged 10-15 years old based on the central lab normal range. ALT normalization was defined as an ALT value that changed from above the normal range at baseline to within the normal range at the given postbaseline visit. Participants in the Full Analysis Set with abnormal ALT values at baseline were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary
End point timeframe:	
Week 192	

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	27		
Units: percentage of participants				
number (not applicable)	75.9	55.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < 169 Copies/mL (29 IU/mL) at Week 48

End point title	Percentage of Participants With HBV DNA < 169 Copies/mL (29 IU/mL) at Week 48

End point description:

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	71.7	6.9		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[11] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Percentage of Participants With HBV DNA < 169 Copies/mL (29 IU/mL) at Week 192

End point title	Percentage of Participants With HBV DNA < 169 Copies/mL (29 IU/mL) at Week 192

End point description:

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	81.7	62.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Loss at Week 48

End point title	Percentage of Participants With HBsAg Loss at Week 48

End point description:

HBsAg Loss was defined as a change from HBsAg positive or missing at baseline to HBsAg negative. Serologically Evaluable Full Analysis Set For HBsAg Loss/Seroconversion; The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	3.3	3.4		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded

	Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999 [12]
Method	Cochran-Mantel-Haenszel

Notes:

[12] - 2-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline and region strata

Secondary: Percentage of Participants With HBsAg Loss at Week 192

End point title	Percentage of Participants With HBsAg Loss at Week 192

End point description:

HBsAg Loss was defined as a change from HBsAg positive or missing at baseline to HBsAg negative. Serologically Evaluable Full Analysis Set For HBsAg Loss/Seroconversion; The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	10.0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Seroconversion at Week 48

End point title	Percentage of Participants With HBsAg Seroconversion at Week 48

End point description:

HBsAg seroconversion was defined as HBsAg loss and a change from HBsAb negative or missing at baseline to HBsAb positive. Serologically Evaluable Full Analysis Set For HBsAg Loss/Seroconversion; The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Seroconversion at Week 192

End point title	Percentage of Participants With HBsAg Seroconversion at Week 192

End point description:

HBsAg seroconversion was defined as HBsAg loss and a change from HBsAb negative or missing at baseline to HBsAb positive. Serologically Evaluable Full Analysis Set For HBsAg Loss/Seroconversion; The missing equals failure approach was used where all participants with missing data were considered to have failed to reach the endpoint.

End point type	Secondary

End point timeframe:

Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 48

End point title	Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 48

End point description:

Participants in the Full Analysis Set with serum samples available at baseline and with HBV DNA ≥ 69 IU/mL at Week 48 were analyzed.

End point type	Secondary

End point timeframe: Baseline; Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	26		
Units: participants	5	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 96

End point title	Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 96
End point description: Participants in the Full Analysis Set with serum samples available at baseline and with HBV DNA ≥ 69 IU/mL at Week 96 were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 96	

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	12		
Units: participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 144

End point title	Number of Participants With Sequence Changes From Baseline

	Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 144

End point description:

Participants in the Full Analysis Set with serum samples available at baseline and with HBV DNA ≥ 69 IU/mL at Week 144 were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 144

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	1		
Units: participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 192

End point title	Number of Participants With Sequence Changes From Baseline Within the HBV Polymerase for Participants Who Were Viremic (HBV DNA ≥ 400 Copies/mL [69 IU/mL]) Including Participants With Confirmed Virologic Breakthrough at Week 192

End point description:

Participants in the Full Analysis Set with serum samples available at baseline and with HBV DNA ≥ 69 IU/mL at Week 192 were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥ 4% Decrease From Baseline in Spine Bone Mineral Density (BMD) at Week 48

End point title	Percentage of Participants With ≥ 4% Decrease From Baseline in Spine Bone Mineral Density (BMD) at Week 48

End point description:

Spine Dual X-Ray Absorptiometry (DXA) Analysis Set: all randomized participants who received at least 1 dose of study drug and had nonmissing baseline
spine bone mineral density values.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	18.3	6.9		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF (Blinded Randomized Phase) v Placebo (Blinded Randomized Phase)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Exact Chan-Zhang method
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	25.1

Notes:

[13] - Comparison of the difference in percentages

Secondary: Percentage of Participants With ≥ 4% Decrease From Baseline in Spine BMD at Week 192

End point title	Percentage of Participants With ≥ 4% Decrease From Baseline in Spine BMD at Week 192

End point description:

Participants in the Spine DXA Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	29		
Units: percentage of participants				
number (not applicable)	18.3	6.9		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	TDF to TDF v Placebo to TDF
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Exact Chan-Zhang method
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	25.1

Notes:

[14] - Comparison of the difference in percentages

Secondary: Percent Change From Baseline in BMD of Spine at Week 48

End point title	Percent Change From Baseline in BMD of Spine at Week 48
End point description:	
Participants in the Spine DXA Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline; Week 48	

End point values	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	25		
Units: Percent change in spine BMD				
arithmetic mean (standard deviation)	3.798 (± 5.9118)	7.557 (± 4.9790)		

Statistical analyses

Statistical analysis title	Statistical Analysis - TDF vs Placebo
Comparison groups	Placebo (Blinded Randomized Phase) v TDF (Blinded Randomized Phase)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [15]
Method	ANOVA

Notes:

[15] - two-sided superiority test

Secondary: Percent Change From Baseline in BMD of Spine at Week 192

End point title	Percent Change From Baseline in BMD of Spine at Week 192

End point description:

Participants in the Spine DXA Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 192

End point values	TDF to TDF	Placebo to TDF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	18		
Units: Percent change in spine BMD				
arithmetic mean (standard deviation)	19.168 (± 12.2805)	26.085 (± 14.2586)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose date up to the Week 192 Data Cut for Open-Label Phase;
Additional adverse event data will be reported after study is completed and final analysis is done.

Adverse event reporting additional description:

Safety Analysis all randomized participants who have received at least 1 dose of study drug. Participants were analyzed according to the treatment to which they received during the blinded phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	TDF (Blinded Randomized Phase)

Reporting group description:

Blinded Randomized Phase: TDF tablet or oral powder once daily (up to 300 mg depending on weight) for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Reporting group title	Placebo (Blinded Randomized Phase)

Reporting group description:

Blinded Randomized Phase: Placebo tablet or oral powder once daily for 72 weeks (protocol amendment 2) or 48 weeks (protocol amendment 3)

Reporting group title	TDF to TDF (Open-Label Phase)

Reporting group description:

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).
Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Reporting group title	Placebo to TDF (Open-Label Phase)

Reporting group description:

Open-Label Treatment Phase: After Week 72 (protocol amendment 2) or Week 48 (protocol amendment 3), participants switched to open-label TDF treatment for an additional 120 weeks (protocol amendment 2) or 144 weeks (protocol amendment 3).
Open-Label Extension Phase: After Week 192, participants are offered open-label TDF treatment until it was commercially available in that country for treatment of chronic HBV in individuals of their age and weight.

Serious adverse events	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)	TDF to TDF (Open-Label Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 60 (16.67%)	2 / 29 (6.90%)	8 / 56 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	4 / 60 (6.67%)	1 / 29 (3.45%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	3 / 4	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pelvi-ureteric obstruction			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pharyngitis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatitis B			
subjects affected / exposed	1 / 60 (1.67%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			

subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 60 (0.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 29 (3.45%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo to TDF (Open-Label Phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			

subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pharyngitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute hepatitis B			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Adenovirus infection				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand-foot-and-mouth disease				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis viral				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TDF (Blinded Randomized Phase)	Placebo (Blinded Randomized Phase)	TDF to TDF (Open-Label Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 60 (63.33%)	16 / 29 (55.17%)	21 / 56 (37.50%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 60 (5.00%)	3 / 29 (10.34%)	0 / 56 (0.00%)
occurrences (all)	3	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 60 (3.33%)	2 / 29 (6.90%)	2 / 56 (3.57%)
occurrences (all)	2	2	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 60 (15.00%)	2 / 29 (6.90%)	4 / 56 (7.14%)
occurrences (all)	9	3	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 60 (5.00%)	1 / 29 (3.45%)	1 / 56 (1.79%)
occurrences (all)	3	1	1
Vomiting			
subjects affected / exposed	3 / 60 (5.00%)	1 / 29 (3.45%)	0 / 56 (0.00%)
occurrences (all)	5	1	0
Diarrhoea			
subjects affected / exposed	3 / 60 (5.00%)	1 / 29 (3.45%)	0 / 56 (0.00%)
occurrences (all)	3	1	0
Nausea			
subjects affected / exposed	3 / 60 (5.00%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	5 / 60 (8.33%)	1 / 29 (3.45%)	0 / 56 (0.00%)
occurrences (all)	6	1	0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 60 (0.00%)	2 / 29 (6.90%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 60 (15.00%)	2 / 29 (6.90%)	12 / 56 (21.43%)
occurrences (all)	29	12	51
Upper respiratory tract infection			
subjects affected / exposed	9 / 60 (15.00%)	5 / 29 (17.24%)	3 / 56 (5.36%)
occurrences (all)	9	6	5
Pharyngitis			
subjects affected / exposed	3 / 60 (5.00%)	3 / 29 (10.34%)	2 / 56 (3.57%)
occurrences (all)	4	4	2
Otitis media			
subjects affected / exposed	3 / 60 (5.00%)	1 / 29 (3.45%)	1 / 56 (1.79%)
occurrences (all)	3	1	1
Ear infection			
subjects affected / exposed	3 / 60 (5.00%)	0 / 29 (0.00%)	1 / 56 (1.79%)
occurrences (all)	3	0	1
Varicella			
subjects affected / exposed	3 / 60 (5.00%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences (all)	3	0	0
Tonsillitis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 29 (0.00%)	0 / 56 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Placebo to TDF (Open-Label Phase)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 0 / 25 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 0 / 25 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 2 / 25 (8.00%) 2 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	 0 / 25 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Pharyngitis	 1 / 25 (4.00%) 27 3 / 25 (12.00%) 3		

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2012	The changes were primarily updates to/clarification of study objectives, eligibility criteria, study procedures, and use of concomitant medications and oral contraception.
08 November 2012	- Updates to the design and conduct of the PK substudy in response to regulatory authority comments. - Participant dosing diaries, a section defining special situations and instructions for reporting special situations, and criterion and instructions for unblinding an investigator in the event of a medical emergency were also introduced. - Other changes included a change in medical monitor and clarification of study objectives, eligibility criteria, and procedures.
29 February 2016	Due to difficulty enrolling participants, to limit exposure of participants to Placebo-TDF, and upon agreement of the Food and Drug Administration (FDA) that approximately 90 participants would be sufficient to conduct the study, the primary efficacy endpoint was changed from Week 72 to Week 48. The amendment specified that upon completing 48 weeks of blinded treatment, all participants would switch to open-label TDF for the remainder of the study, and participants who were beyond Week 48 under the previous protocol would switch to open-label TDF at Week 72 (as originally planned). All participants would receive open-label TDF until Week 192 (end of study).
04 August 2016	- An extension treatment period was added, whereby all participants who completed the study were offered the opportunity to continue receiving open-label TDF until the time that TDF became commercially available for participants of their age and weight in the country of their enrollment. During the extension period, participants were to attend study visits every 12 weeks. Study procedures were updated accordingly. - Clarified the requirements for DXA scans and biochemical bone marker assessments performed at Week 192/end of study or premature discontinuation of study drug and updated the physical description of TDF 300 mg tablets.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported