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

Summary

EudraCT number	2007-003704-35
Trial protocol	GB BE FR ES BG DE GR Outside EU/EEA
Global end of trial date	02 December 2015

Results information

Result version number	v1 (current)
This version publication date	17 June 2016
First version publication date	17 June 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-174-0115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00734162
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	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@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	Final
Date of interim/final analysis	02 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

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	03 December 2008
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	Poland: 74
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Turkey: 2
Worldwide total number of subjects	106
EEA total number of subjects	99

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	106
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 3 sites in the United States, 8 sites in Poland, 3 sites in Romania, 2 sites in Bulgaria, 2 sites in France, 2 sites in Spain, and 1 site in Turkey. The first participant was screened on 03 December 2008. The last study visit occurred on 02 December 2015.

Pre-assignment

Screening details:

149 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF 12-14 years

Arm description:

TDF in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

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

Dosage and administration details:

Tenofovir disoproxil fumarate (TDF) 300 mg once daily

Arm title	Placebo 12-14 years

Arm description:

TDF placebo in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TDF placebo once daily

Arm title	Placebo 15-17 years

Arm description:

TDF placebo in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

Arm type	Placebo

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

Dosage and administration details:

TDF placebo once daily

Arm title	TDF 15-17 years

Arm description:

TDF in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

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

Dosage and administration details:

TDF 300 mg once daily

Number of subjects in period 1	TDF 12-14 years	Placebo 12-14 years	Placebo 15-17 years
Started	10	13	41
Completed	10	13	37
Not completed	0	0	4
Per protocol ALT elevation	-	-	2
Investigator's Discretion	-	-	2

Number of subjects in period 1	TDF 15-17 years
Started	42
Completed	41
Not completed	1
Per protocol ALT elevation	-
Investigator's Discretion	1

Period 2

Period 2 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	TDF 12-14 years

Arm description:

TDF in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

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

Dosage and administration details:

TDF 300 mg once daily

Arm title	TDF 15-17 years

Arm description:

TDF in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

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

Dosage and administration details:

TDF 300 mg once daily

Arm title	Placebo 12-14 years

Arm description:

TDF placebo in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

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

Dosage and administration details:

TDF 300 mg once daily

Arm title	Placebo 15-17 years

Arm description:

TDF placebo in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase

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

Dosage and administration details:

TDF 300 mg once daily

Number of subjects in period 2	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years
Started	10	41	13
Completed	7	39	12
Not completed	3	2	1
Withdrew Consent	1	-	1
Did Not Meet Entrance Criteria	-	-	-
Safety, Tolerability or Efficacy Reasons	1	-	-
Lost to follow-up	1	2	-
Joined	0	0	0
Switched prior to completing double-blind period	-	-	-

Number of subjects in period 2	Placebo 15-17 years
Started	37
Completed	36
Not completed	3
Withdrew Consent	1
Did Not Meet Entrance Criteria	1
Safety, Tolerability or Efficacy Reasons	-
Lost to follow-up	1
Joined	2
Switched prior to completing double-blind period	2

Baseline characteristics

Reporting groups	
Reporting group title	TDF 12-14 years
Reporting group description:	
TDF in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	TDF 15-17 years
Reporting group description:	
TDF in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	Placebo 12-14 years
Reporting group description:	
TDF placebo in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	Placebo 15-17 years
Reporting group description:	
TDF placebo in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	

Reporting group values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years
Number of subjects	10	42	13
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	13.3	16.1	13.2
standard deviation	± 0.82	± 0.75	± 0.69
Gender, Male/Female Units: participants			
Female	3	11	4
Male	7	31	9
Race Units: Subjects			
Asian	0	1	1
Black	0	1	0
White	10	39	12
Other	0	1	0
Alanine aminotransferase (ALT) normal at baseline			
The upper limit of normal (ULN) was 43 U/L for males and 34 U/L for females.			
Units: Subjects			
Normal	3	14	4
Abnormal	7	28	9
HBV Genotype Units: Subjects			
Genotype A	5	30	5
Genotype B	0	1	1
Genotype C	0	1	0

Genotype D	5	10	7
Hepatitis B e Antigen (HBeAg) status at baseline Units: Subjects			
Negative	1	3	0
Positive	9	39	13
ALT level at baseline Units: U/L			
arithmetic mean	77	106	101
standard deviation	± 54.8	± 116.4	± 95.4
HBV DNA level at baseline Units: Log_10 copies/mL			
arithmetic mean	8.26	7.95	8.61
standard deviation	± 1.455	± 1.421	± 1.166

Reporting group values	Placebo 15-17 years	Total	
Number of subjects	41	106	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	15.9		
standard deviation	± 0.82	-	
Gender, Male/Female Units: participants			
Female	15	33	
Male	26	73	
Race Units: Subjects			
Asian	0	2	
Black	0	1	
White	37	98	
Other	4	5	
Alanine aminotransferase (ALT) normal at baseline			
The upper limit of normal (ULN) was 43 U/L for males and 34 U/L for females.			
Units: Subjects			
Normal	8	29	
Abnormal	33	77	
HBV Genotype Units: Subjects			
Genotype A	29	69	
Genotype B	1	3	
Genotype C	0	1	
Genotype D	11	33	
Hepatitis B e Antigen (HBeAg) status at baseline Units: Subjects			
Negative	6	10	
Positive	35	96	

ALT level at baseline Units: U/L arithmetic mean standard deviation	 101 ± 89.5	 -	
HBV DNA level at baseline Units: Log_10 copies/mL arithmetic mean standard deviation	 8.12 ± 1.451	 -	

End points

End points reporting groups

Reporting group title	TDF 12-14 years
Reporting group description:	
TDF in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	Placebo 12-14 years
Reporting group description:	
TDF placebo in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	Placebo 15-17 years
Reporting group description:	
TDF placebo in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	TDF 15-17 years
Reporting group description:	
TDF in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	TDF 12-14 years
Reporting group description:	
TDF in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	TDF 15-17 years
Reporting group description:	
TDF in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	Placebo 12-14 years
Reporting group description:	
TDF placebo in participants 12-14 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Reporting group title	Placebo 15-17 years
Reporting group description:	
TDF placebo in participants 15-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Subject analysis set title	Total TDF 12-17 Years
Subject analysis set type	Full analysis
Subject analysis set description:	
TDF in participants 12-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	
Subject analysis set title	Total Placebo 12-17 Years
Subject analysis set type	Full analysis
Subject analysis set description:	
TDF in participants 12-17 years of age in the Randomized Phase, followed by TDF in the Open-Label Phase	

Primary: Percentage of Participants With HBV DNA < 400 Copies/mL at Week 72

End point title	Percentage of Participants With HBV DNA < 400 Copies/mL at Week 72

End point description:

The percentage of participants with HBV DNA < 400 copies/mL at Week 72 was summarized by treatment and age group (grouped by baseline age for analysis), using the missing = failure (M = F) analysis with the double-blind efficacy evaluation (DBEE) algorithm.

In the M = F analysis method, all missing data were considered as failure to meet the outcome measure

threshold. This method was combined with the DBEE algorithm, which included all available data for the double-blind period, and any data for the open-label period were not included; data generated during treatment-free follow-up from subjects who achieved HBsAg loss and entered treatment-free follow-up during double-blind treatment period were included.

Full Analysis Set: participants who were randomized and received at least one dose of study drug.

End point type	Primary

End point timeframe:

Week 72

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)	90	88.1	0	0

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)	88.5	0		

Statistical analyses

Statistical analysis title	Difference between treatment arms

Statistical analysis description:

Analysis is the difference between treatment groups in the proportion of participants who met the outcome measure criterion, controlling for randomization age group.

Comparison groups	TDF 12-14 years v TDF 15-17 years v Placebo 12-14 years v Placebo 15-17 years
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - A p-value of < 0.05 was considered statistically significant.

Primary: Percentage of Participants With at Least a 6% Decrease From Baseline in Bone Mineral Density (BMD) of the Spine at Week 72

End point title	Percentage of Participants With at Least a 6% Decrease From Baseline in Bone Mineral Density (BMD) of the Spine at Week 72[2]

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

In contrast with what was previously reported in the interim Week 72 CSR, 1 participant met the primary safety endpoint of at least a 6% decrease from baseline in spine BMD at Week 72, based on the final BMD data analysis. The apparent discrepancy was due to the correction factor applied to the subject-specific BMD calculations performed at the time of the Interim Week 72 clinical study report that could not take into account the actual Week 72 phantom data (ie, calibration test used in longitudinal clinical trials to monitor and adjust for shifts in the DXA scanner calibration over time), which were not provided by the site at that time. The correction factor applied to the final analysis has been properly based on all phantom data through the end of Week 72, as well as through the end of Week 192.

Safety Analysis Set: participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline to Week 72

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)	0	2.4	0	0

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)	1.9	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 48, 96, 144, and 192

End point title	Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 48, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Full Analysis Set

End point type	Secondary

End point timeframe:

Weeks 48, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	90	85.7	0	0
Week 96	90	88.1	53.8	68.3
Week 144	100	90.5	69.2	85.4
Week 192	90	85.7	76.9	73.2

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	86.5	0		
Week 96	88.5	64.8		
Week 144	92.3	81.5		
Week 192	86.5	74.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normal Alanine Aminotransferase (ALT) at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With Normal Alanine Aminotransferase (ALT) at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Full Analysis Set

End point type	Secondary

End point timeframe:

Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	70	76.2	30.8	26.8
Week 72	80	76.2	30.8	41.5
Week 96	80	76.2	69.2	65.9
Week 144	60	71.4	69.2	75.6
Week 192	80	71.4	84.6	75.6

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	75	27.8		
Week 72	76.9	38.9		
Week 96	76.9	66.7		
Week 144	69.2	74.1		
Week 192	73.1	77.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL and Normal ALT at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With HBV DNA < 400 Copies/mL and Normal ALT at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Full Analysis Set

End point type	Secondary

End point timeframe:

Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	70	69	0	0
Week 72	80	69	0	0
Week 96	80	73.8	46.2	51.2
Week 144	60	69	53.8	68.3
Week 192	80	64.3	69.2	63.4

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	69.2	0		
Week 72	71.2	0		
Week 96	75	50		
Week 144	67.3	64.8		
Week 192	67.3	64.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < 169 Copies/mL at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With HBV DNA < 169 Copies/mL at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Full Analysis Set

End point type	Secondary

End point timeframe:

Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	80	81	0	0
Week 72	90	83.3	0	0
Week 96	90	88.1	53.8	63.4
Week 144	90	88.1	69.2	82.9
Week 192	90	83.3	76.9	73.2

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	80.8	0		
Week 72	84.6	0		
Week 96	88.5	61.1		
Week 144	88.5	79.6		
Week 192	84.6	74.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hepatitis B Surface Antigen (HBsAg) Loss at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With Hepatitis B Surface Antigen (HBsAg) Loss at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis), using the M = F.

Full Analysis Set

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	0	0	0	0
Week 72	0	2.4	0	0
Week 96	0	2.4	0	0
Week 144	0	2.4	0	0
Week 192	0	2.4	0	0

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	0	0		
Week 72	1.9	0		
Week 96	1.9	0		
Week 144	1.9	0		
Week 192	1.9	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Seroconversion at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With HBsAg Seroconversion at Weeks 48, 72, 96, 144, and 192

End point description:

HBsAg seroconversion was defined as change of detectable antibody to HBsAg from negative to positive. Data were summarized by treatment and age group (grouped by baseline age for analysis), using the M = F.

Full Analysis Set

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	0	0	0	0
Week 72	0	2.4	0	0
Week 96	0	2.4	0	0
Week 144	0	2.4	0	0
Week 192	0	0	0	0

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	0	0		
Week 72	1.9	0		
Week 96	1.9	0		
Week 144	1.9	0		
Week 192	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least a 6% Decrease From Baseline in Spine BMD at Weeks 48, 96, 144, and 192

End point title	Percentage of Participants With at Least a 6% Decrease From Baseline in Spine BMD at Weeks 48, 96, 144, and 192

End point description:

The percentage of participants reported is the cumulative incidence from baseline to the respective time point. Data were summarized by treatment and age group (grouped by baseline age for analysis).

Safety Analysis Set

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	0	0	0	0
Week 96	0	2.4	0	0
Week 144	0	2.4	0	0
Week 192	0	4.8	0	4.9

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	0	0		
Week 96	1.9	0		
Week 144	1.9	0		
Week 192	3.8	3.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least a 6% Decrease From Baseline in Whole Body BMD at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With at Least a 6% Decrease From Baseline in Whole Body BMD at Weeks 48, 72, 96, 144, and 192

End point description:

The percentage of participants reported is the cumulative incidence from baseline to the respective time point. Data were summarized by treatment and age group (grouped by baseline age for analysis).

Safety Analysis Set

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	42	13	41
Units: percentage of participants				
number (not applicable)				
Week 48	0	0	0	0
Week 72	0	0	0	0
Week 96	0	0	0	0
Week 144	0	0	0	2.4
Week 192	0	0	0	2.4

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: percentage of participants				
number (not applicable)				
Week 48	0	0		
Week 72	0	0		
Week 96	0	0		
Week 144	0	1.9		
Week 192	0	1.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spine Bone Mineral Density (BMD) at Week 48

End point title	Percent Change From Baseline in Spine Bone Mineral Density (BMD) at Week 48

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	39	10	38
Units: percentage change				
arithmetic mean (standard deviation)	9.234 (± 3.4782)	2.114 (± 3.6023)	9.038 (± 6.6575)	4.435 (± 4.9091)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: percentage change				
arithmetic mean (standard deviation)	3.51 (± 4.5507)	5.562 (± 5.6772)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spine BMD at Week 72

End point title	Percent Change From Baseline in Spine BMD at Week 72

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 72

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	41	12	37
Units: percentage change				
arithmetic mean (standard deviation)	11.516 (± 3.8818)	3.589 (± 4.5633)	14.131 (± 9.9563)	6.117 (± 6.0624)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: percentage change				
arithmetic mean (standard deviation)	5.144 (±	8.08 (±		

5.4291)	7.8996)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spine BMD at Week 96

End point title	Percent Change From Baseline in Spine BMD at Week 96

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 96

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	40	11	39
Units: percentage change				
arithmetic mean (standard deviation)	13.811 (± 4.6712)	4.196 (± 4.8021)	16.687 (± 10.4359)	4.272 (± 7.0463)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: percentage change				
arithmetic mean (standard deviation)	6.119 (± 6.12)	7.003 (± 9.3658)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spine BMD at Week 144

End point title	Percent Change From Baseline in Spine BMD at Week 144

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary
End point timeframe: Baseline; Week 144	

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	39	10	38
Units: percentage change				
arithmetic mean (standard deviation)	19.224 (± 8.7594)	5.289 (± 5.8084)	21.346 (± 13.4709)	6.144 (± 8.3286)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	48		
Units: percentage change				
arithmetic mean (standard deviation)	8.133 (± 8.5611)	9.311 (± 11.3262)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Spine BMD at Week 192
End point description: Data were summarized by treatment and age group (grouped by baseline age for analysis). Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 192	

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	37	11	35
Units: percentage change				
arithmetic mean (standard deviation)	23.933 (± 8.5166)	6.673 (± 7.287)	25.036 (± 14.2346)	6.867 (± 9.3736)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage change				
arithmetic mean (standard deviation)	10.05 (± 10.1637)	11.212 (± 13.1459)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Whole Body BMD at Week 48

End point title	Percent Change From Baseline in Whole Body BMD at Week 48

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	39	13	37
Units: percentage change				
arithmetic mean (standard deviation)	5.123 (± 3.8309)	1.339 (± 1.9324)	5.47 (± 3.4958)	3.236 (± 2.8573)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	50		
Units: percentage change				
arithmetic mean (standard deviation)	2.048 (± 2.783)	3.817 (± 3.1576)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Whole Body BMD at Week 72

End point title	Percent Change From Baseline in Whole Body BMD at Week 72

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 72

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	41	13	38
Units: percentage change				
arithmetic mean (standard deviation)	7.282 (± 3.9156)	2.141 (± 2.6284)	8.48 (± 4.477)	4.335 (± 3.4073)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	51		
Units: percentage change				
arithmetic mean (standard deviation)	3.067 (± 3.4819)	5.391 (± 4.0902)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Whole Body BMD at Week 96

End point title	Percent Change From Baseline in Whole Body BMD at Week 96

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 96

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	40	12	38
Units: percentage change				
arithmetic mean (standard deviation)	8.034 (± 3.4973)	3.023 (± 3.2063)	10.056 (± 5.4296)	4.291 (± 4.3195)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	50		
Units: percentage change				
arithmetic mean (standard deviation)	3.943 (± 3.773)	5.675 (± 5.1858)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Whole Body BMD at Week 144

End point title	Percent Change From Baseline in Whole Body BMD at Week 144

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 144

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	11	38
Units: percentage change				
arithmetic mean (standard deviation)	10.94 (± 4.8819)	3.529 (± 3.1734)	12.638 (± 5.9973)	4.73 (± 5.2213)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	49		

Units: percentage change				
arithmetic mean (standard deviation)	4.949 (± 4.5753)	6.505 (± 6.2944)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Whole Body BMD at Week 192

End point title	Percent Change From Baseline in Whole Body BMD at Week 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	35	12	34
Units: percentage change				
arithmetic mean (standard deviation)	13.923 (± 4.6139)	4.295 (± 3.7318)	14.797 (± 6.4993)	4.549 (± 5.4494)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	46		
Units: percentage change				
arithmetic mean (standard deviation)	6.086 (± 5.4029)	7.223 (± 7.2666)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Spine BMD at Week 48

End point title	Change From Baseline in Z-score for Spine BMD at Week 48

End point description:

To assess any effect of treatment on growth, Z-scores were used to express the deviation from a reference population for lumbar spine BMD. A Z-score of 0 indicated that a subject was typical of the

population for their age, ethnicity, and gender. A negative Z-score indicated that the subject's recorded value was lower than typical for their age, ethnicity, and gender. A positive Z-score indicates that the subject's recorded value was higher than typical for their age, ethnicity, and gender. Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	41	12	37
Units: z-score				
arithmetic mean (standard deviation)	0.02 (± 0.247)	-0.1 (± 0.255)	0.04 (± 0.393)	0.05 (± 0.322)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: z-score				
arithmetic mean (standard deviation)	-0.08 (± 0.256)	0.05 (± 0.337)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Spine BMD at Week 72

End point title	Change From Baseline in Z-score for Spine BMD at Week 72

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 72

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	41	12	37
Units: z-scores				
arithmetic mean (standard deviation)	-0.1 (± 0.312)	-0.05 (± 0.325)	0.09 (± 0.498)	0.1 (± 0.339)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: z-scores				
arithmetic mean (standard deviation)	-0.06 (± 0.32)	0.1 (± 0.378)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Spine BMD at Week 96

End point title	Change From Baseline in Z-score for Spine BMD at Week 96

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 96

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	40	11	39
Units: z-score				
arithmetic mean (standard deviation)	-0.19 (± 0.365)	-0.07 (± 0.356)	-0.02 (± 0.498)	-0.13 (± 0.414)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	50		
Units: z-score				
arithmetic mean (standard deviation)	-0.1 (± 0.357)	-0.11 (± 0.431)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Spine BMD at Week 144

End point title	Change From Baseline in Z-score for Spine BMD at Week 144

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 144

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	39	10	38
Units: z-score				
arithmetic mean (standard deviation)	-0.2 (± 0.56)	-0.05 (± 0.417)	-0.16 (± 0.625)	-0.04 (± 0.405)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	48		
Units: z-score				
arithmetic mean (standard deviation)	-0.08 (± 0.447)	-0.06 (± 0.455)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Spine BMD at Week 192

End point title	Change From Baseline in Z-score for Spine BMD at Week 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary
End point timeframe: Baseline; Week 192	

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	37	11	35
Units: z-score				
arithmetic mean (standard deviation)	-0.24 (± 0.518)	0.08 (± 0.544)	-0.26 (± 0.654)	-0.05 (± 0.504)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: z-score				
arithmetic mean (standard deviation)	0.02 (± 0.548)	-0.1 (± 0.543)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Whole Body BMD at Week 48

End point title	Change From Baseline in Z-score for Whole Body BMD at Week 48

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary
End point timeframe: Baseline; Week 48	

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	39	13	37
Units: z-score				
arithmetic mean (standard deviation)	0.02 (± 0.426)	-0.15 (± 0.257)	0.1 (± 0.37)	0.04 (± 0.308)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	50		
Units: z-score				
arithmetic mean (standard deviation)	-0.12 (± 0.298)	0.05 (± 0.322)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Whole Body BMD at Week 72

End point title	Change From Baseline in Z-score for Whole Body BMD at Week 72

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 72

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	41	13	38
Units: z-score				
arithmetic mean (standard deviation)	0.02 (± 0.398)	-0.19 (± 0.338)	0.2 (± 0.45)	0.06 (± 0.306)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	51		
Units: z-score				
arithmetic mean (standard deviation)	-0.16 (± 0.355)	0.09 (± 0.349)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Whole Body BMD at Week 96

End point title	Change From Baseline in Z-score for Whole Body BMD at Week 96

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 96

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	40	12	38
Units: z-score				
arithmetic mean (standard deviation)	-0.12 (± 0.294)	-0.19 (± 0.451)	0.09 (± 0.528)	-0.06 (± 0.432)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	50		
Units: z-score				
arithmetic mean (standard deviation)	-0.18 (± 0.424)	-0.03 (± 0.456)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Whole Body BMD at Week 144

End point title	Change From Baseline in Z-score for Whole Body BMD at Week 144

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 144

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	38	11	38
Units: z-score				
arithmetic mean (standard deviation)	-0.27 (± 0.431)	-0.21 (± 0.473)	-0.06 (± 0.554)	-0.16 (± 0.468)

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	49		
Units: z-score				
arithmetic mean (standard deviation)	-0.22 (± 0.462)	-0.14 (± 0.484)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Z-score for Whole Body BMD at Week 192

End point title	Change From Baseline in Z-score for Whole Body BMD at Week 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis).

Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	35	12	34
Units: z-score				
arithmetic mean (standard deviation)	-0.34 (± 0.499)	-0.11 (± 0.524)	-0.21 (± 0.486)	-0.19 (± 0.517)

End point values	Total TDF 12-	Total Placebo		

	17 Years	12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	46		
Units: z-score				
arithmetic mean (standard deviation)	-0.16 (± 0.521)	-0.19 (± 0.504)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Changes in Drug-Resistant Mutations During the Study

End point title	Number of Participants With Changes in Drug-Resistant Mutations During the Study

End point description:

The number of participants with changes in drug-resistant mutations during the study was summarized.

End point type	Secondary

End point timeframe:

Baseline through Week 192

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	54		
Units: participants				
New TDF Drug-Resistant Mutations	0	0		
Enrichment of TDF Drug-Resistant Mutations	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were HBeAg-Positive at Baseline and Who Had HBeAg Loss at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants Who Were HBeAg-Positive at Baseline and Who Had HBeAg Loss at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Participants in the Full Analysis Set who were HBeAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	39	13	35
Units: percentage of participants				
number (not applicable)				
Week 48	11.1	17.9	7.7	8.6
Week 72	11.1	23.1	23.1	11.4
Week 96	44.4	30.8	38.5	28.6
Week 144	44.4	38.5	53.8	34.3
Week 192	33.3	43.6	53.8	37.1

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: percentage of participants				
number (not applicable)				
Week 48	16.7	8.3		
Week 72	20.8	14.6		
Week 96	33.3	31.3		
Week 144	39.6	39.6		
Week 192	41.7	41.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were HBeAg-Positive at Baseline and Who Had HBeAg Seroconversion at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants Who Were HBeAg-Positive at Baseline and Who Had HBeAg Seroconversion at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Participants in the Full Analysis Set who were HBeAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	39	13	35
Units: percentage of participants				
number (not applicable)				
Week 48	11.1	15.4	7.7	8.6
Week 72	11.1	23.1	23.1	11.4
Week 96	44.4	30.8	38.5	25.7
Week 144	33.3	38.5	53.8	34.3
Week 192	33.3	38.5	53.8	37.1

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: percentage of participants				
number (not applicable)				
Week 48	14.6	8.3		
Week 72	20.8	14.6		
Week 96	33.3	29.2		
Week 144	37.5	39.6		
Week 192	37.5	41.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were HBeAg-Positive at Baseline Who Had HBV DNA < 400 Copies/mL, Normal ALT, and HBeAg Loss/Seroconversion at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants Who Were HBeAg-Positive at Baseline Who Had HBV DNA < 400 Copies/mL, Normal ALT, and HBeAg Loss/Seroconversion at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Participants in the Full Analysis Set who were HBeAg-positive at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	39	13	35
Units: percentage of participants				
number (not applicable)				
Week 48	11.1	12.8	0	0
Week 72	11.1	15.4	0	0
Week 96	44.4	28.2	30.8	22.9
Week 144	22.2	30.8	46.2	25.7
Week 192	33.3	28.2	46.2	25.7

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	48		
Units: percentage of participants				
number (not applicable)				
Week 48	12.5	0		
Week 72	14.6	0		
Week 96	31.3	25		
Week 144	29.2	31.3		
Week 192	29.2	31.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Abnormal ALT at Baseline Who Had Normalized ALT at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With Abnormal ALT at Baseline Who Had Normalized ALT at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Participants in the Full Analysis Set with abnormal ALT at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	28	9	33
Units: percentage of participants				
number (not applicable)				
Week 48	85.7	71.4	11.1	21.2
Week 72	85.7	71.4	22.2	33.3
Week 96	85.7	78.6	66.7	63.6
Week 144	57.1	71.4	66.7	72.7
Week 192	85.7	75	77.8	69.7

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	42		
Units: percentage of participants				
number (not applicable)				
Week 48	74.3	19		
Week 72	74.3	31		
Week 96	80	64.3		
Week 144	68.6	71.4		
Week 192	77.1	71.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Abnormal ALT at Baseline Who Had HBV DNA < 400 Copies/mL and Normalized ALT at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants With Abnormal ALT at Baseline Who Had HBV DNA < 400 Copies/mL and Normalized ALT at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Participants in the Full Analysis Set with abnormal ALT at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	28	9	33
Units: percentage of participants				
number (not applicable)				
Week 48	85.7	71.4	0	0
Week 72	85.7	71.4	0	0
Week 96	85.7	78.6	55.6	54.5
Week 144	57.1	71.4	66.7	69.7
Week 192	85.7	67.9	77.8	57.6

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	42		
Units: percentage of participants				
number (not applicable)				
Week 48	74.3	0		
Week 72	74.3	0		
Week 96	80	54.8		
Week 144	68.6	69		
Week 192	71.4	61.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were HBeAg-Positive With Abnormal ALT at Baseline Who Had HBV DNA < 400 Copies/mL, Normalized ALT, and HBeAg Loss/Seroconversion at Weeks 48, 72, 96, 144, and 192

End point title	Percentage of Participants Who Were HBeAg-Positive With Abnormal ALT at Baseline Who Had HBV DNA < 400 Copies/mL, Normalized ALT, and HBeAg Loss/Seroconversion at Weeks 48, 72, 96, 144, and 192

End point description:

Data were summarized by treatment and age group (grouped by baseline age for analysis) using the missing = failure method.

Participants in the Full Analysis Set who were HBeAg-Positive with abnormal ALT at baseline were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 72, 96, 144, and 192

End point values	TDF 12-14 years	TDF 15-17 years	Placebo 12-14 years	Placebo 15-17 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	27	9	33
Units: percentage of participants				
number (not applicable)				
Week 48	16.7	18.5	0	0
Week 72	16.7	22.2	0	0
Week 96	50	33.3	33.3	24.2
Week 144	33.3	29.6	55.6	27.3
Week 192	50	29.6	55.6	27.3

End point values	Total TDF 12-17 Years	Total Placebo 12-17 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	42		
Units: percentage of participants				
number (not applicable)				
Week 48	18.2	0		
Week 72	21.2	0		
Week 96	36.4	26.2		
Week 144	30.3	33.3		
Week 192	33.3	33.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline through end of the Open-Label Phase (up to 4 years)	
Adverse event reporting additional description:	
Safety Analysis Set	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Double-Blind TDF
Reporting group description:	
Adverse events reported in this group occurred during the Randomized Phase (+7 days for participants who did not continue to the Open-Label Phase) and includes all participants who received double-blind TDF during the Randomized Phase of the study.	
Reporting group title	Double-Blind Placebo
Reporting group description:	
Adverse events reported in this group occurred during the Randomized Phase (+7 days for participants who did not continue to the Open-Label Phase) and includes all participants who received placebo during the Randomized Phase of the study.	
Reporting group title	Open-Label TDF-TDF
Reporting group description:	
Adverse events reported in this group occurred during the Open-Label Phase and includes all participants who received double-blind TDF during the Randomized Phase of the study and continued to the Open-Label Phase.	
Reporting group title	Open-Label Placebo-TDF
Reporting group description:	
Adverse events reported in this group occurred during the Open-Label Phase and includes all participants who received placebo during the Randomized Phase of the study and continued to the Open-Label Phase.	

Serious adverse events	Double-Blind TDF	Double-Blind Placebo	Open-Label TDF-TDF
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 52 (9.62%)	11 / 54 (20.37%)	8 / 51 (15.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menstrual disorder			

subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 51 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Blood creatinine increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucose urine present			

subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Protein urine present			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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 fracture			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 51 (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
Jaw fracture			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Ligament sprain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Multiple injuries			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Patella fracture			

subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 51 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 51 (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
Gastroduodenitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 51 (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
Peptic ulcer perforation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 52 (1.92%)	7 / 54 (12.96%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 54 (1.85%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 54 (0.00%)	0 / 51 (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

Serious adverse events	Open-Label Placebo-TDF		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 52 (19.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug dependence			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			

subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Glucose urine present				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Protein urine present				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase abnormal				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaw fracture				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroduodenitis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peptic ulcer perforation			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 52 (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	Double-Blind TDF	Double-Blind Placebo	Open-Label TDF-TDF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 52 (65.38%)	40 / 54 (74.07%)	30 / 51 (58.82%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 52 (3.85%)	5 / 54 (9.26%)	0 / 51 (0.00%)
occurrences (all)	2	5	0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	2 / 51 (3.92%)
occurrences (all)	3	0	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	0 / 51 (0.00%)
occurrences (all)	1	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 52 (3.85%)	9 / 54 (16.67%)	1 / 51 (1.96%)
occurrences (all)	2	18	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 52 (0.00%)	5 / 54 (9.26%)	1 / 51 (1.96%)
occurrences (all)	0	5	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	1 / 51 (1.96%)
occurrences (all)	6	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 52 (5.77%)	7 / 54 (12.96%)	1 / 51 (1.96%)
occurrences (all)	3	12	2
Diarrhoea			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	3 / 51 (5.88%)
occurrences (all)	4	1	4
Nausea			
subjects affected / exposed	2 / 52 (3.85%)	3 / 54 (5.56%)	0 / 51 (0.00%)
occurrences (all)	2	4	0
Toothache			

subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	1 / 51 (1.96%)
occurrences (all)	1	5	3
Constipation			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	0 / 51 (0.00%)
occurrences (all)	1	4	0
Vomiting			
subjects affected / exposed	0 / 52 (0.00%)	3 / 54 (5.56%)	0 / 51 (0.00%)
occurrences (all)	0	7	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 52 (0.00%)	4 / 54 (7.41%)	0 / 51 (0.00%)
occurrences (all)	0	15	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	0 / 51 (0.00%)
occurrences (all)	3	3	0
Epistaxis			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	0 / 51 (0.00%)
occurrences (all)	3	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 52 (0.00%)	5 / 54 (9.26%)	0 / 51 (0.00%)
occurrences (all)	0	5	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 52 (3.85%)	10 / 54 (18.52%)	2 / 51 (3.92%)
occurrences (all)	2	10	2
Nail disorder			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Pharyngitis			
subjects affected / exposed	15 / 52 (28.85%)	11 / 54 (20.37%)	9 / 51 (17.65%)
occurrences (all)	16	17	12
Nasopharyngitis			
subjects affected / exposed	5 / 52 (9.62%)	12 / 54 (22.22%)	6 / 51 (11.76%)
occurrences (all)	8	21	11

Upper respiratory tract infection			
subjects affected / exposed	5 / 52 (9.62%)	7 / 54 (12.96%)	3 / 51 (5.88%)
occurrences (all)	6	9	3
Bronchitis			
subjects affected / exposed	2 / 52 (3.85%)	1 / 54 (1.85%)	6 / 51 (11.76%)
occurrences (all)	2	1	7
Rhinitis			
subjects affected / exposed	5 / 52 (9.62%)	3 / 54 (5.56%)	3 / 51 (5.88%)
occurrences (all)	5	3	4
Tonsillitis			
subjects affected / exposed	2 / 52 (3.85%)	4 / 54 (7.41%)	2 / 51 (3.92%)
occurrences (all)	3	4	2
Gastroenteritis			
subjects affected / exposed	2 / 52 (3.85%)	2 / 54 (3.70%)	0 / 51 (0.00%)
occurrences (all)	2	2	0
Respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)	2 / 54 (3.70%)	1 / 51 (1.96%)
occurrences (all)	1	2	1
Viral infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	5
Herpes zoster			
subjects affected / exposed	0 / 52 (0.00%)	3 / 54 (5.56%)	0 / 51 (0.00%)
occurrences (all)	0	3	0

Non-serious adverse events	Open-Label Placebo-TDF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 52 (59.62%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 13 2 / 52 (3.85%) 3 2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 0 / 52 (0.00%) 0 0 / 52 (0.00%) 0		
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 12		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1 0 / 52 (0.00%) 0 1 / 52 (1.92%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Nail disorder subjects affected / exposed occurrences (all)	 6 / 52 (11.54%) 6 0 / 52 (0.00%) 0		
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all)	 13 / 52 (25.00%) 14 12 / 52 (23.08%) 20 7 / 52 (13.46%) 9 4 / 52 (7.69%) 7 1 / 52 (1.92%) 2		

Tonsillitis			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Respiratory tract infection			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2008	• The requirement for daily multivitamin to contain 100% of RDA for vitamin D was changed to require 100% of country-specific RDA for vitamin D. • The study phase (Phase 3) was added to the protocol. • Given the pediatric age range of study participants, the absolute requirement for contraception was changed to apply to sexually-active males and females of reproductive potential. • The drug dispensing schedule was corrected to reflect that subjects were provided with sufficient supplies for 4 to 8 weeks of dosing during Weeks 1 to 96. Thereafter, subjects were provided with sufficient supplies for 12 weeks of dosing. • The definition of overdose was corrected to match the text for definition of overdose in the existing approved Gilead Drug Safety and Public Health Standard Operating Procedure (SOP), effective date 07 January 2008.
17 February 2009	• The primary endpoint was changed from a composite of HBV DNA < 400 copies/mL and ALT normal at Week 72 to the single endpoint of HBV DNA < 400 copies/mL. This was done because the protocol permitted entry based upon historical ALT in the event that ALT was not > 2 x the upper limit of normal at screening. Thus, some subjects may have been enrolled who had intermittent ALT elevations but a normal ALT at the time of baseline such that the composite endpoint would not be fully evaluable. • The requirement for protocol-specified unblinding of treatment assignment in relation to persistent Grade 4 ALT was removed. Additionally, in the event where Grade 4 ALT was maintained for 16 weeks and in the case of ALT flare, both considered situations of medical need, serial HBV DNA values from Screen through time of event were made available to the investigator. This protected the blind of the study but permitted the investigator to use HBV DNA to make a medical management decision regarding the subjects with Grade 4 ALT. • The inclusion criteria were modified to permit up to 50% of subjects enrolled to be HBeAg-negative. It was originally felt there would be a paucity of such subjects due to the natural course of chronic HBV infection in children and adolescents (ie, most in the "immune tolerant" phase). However, initial screening indicated that approximately 50% of potential subjects have HBeAg-negative disease.
01 June 2012	• Analysis of the primary endpoint was planned to occur at Week 72. Additional efficacy and safety analyses to be conducted after Week 72 were considered secondary. • A Treatment Extension period was added instead of a separate rollover study. Subjects who were 17 years of age or younger at the last visit (Week 192) were offered the opportunity to continue in an extension of the study, where they would receive open-label TDF 300 mg until they reached 18 years of age or until standard of care therapy was initiated. • Safety contact information was updated and reporting procedures were updated to include the process for special situations. • The DXA window was increased to ± 15 days for visits occurring after Week 72. Visit window through Week 72 remained unchanged at ± 1 week (7 days).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22544804