Clinical trial results:
A Phase 3b, Randomized, Double-Blind, Double-Dummy Study Evaluating the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (DF) Monotherapy Versus Emtricitabine plus Tenofovir DF Fixed-Dose Combination Therapy in Subjects with Chronic Hepatitis B who are Resistant to Lamivudine

Summary

EudraCT number	2008-001464-36
Trial protocol	GB DE CZ HU ES AT GR BG
Global end of trial date	09 February 2015

Results information

Result version number	v1 (current)
This version publication date	25 February 2016
First version publication date	25 February 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-174-0121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00737568
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 Information Desk, Gilead Sciences International Ltd, +44 1223897 496, clinical.trials@gilead.com
Scientific contact	Clinical Trial Information Desk, Gilead Sciences International Ltd, +44 1223897 496, clinical.trials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the antiviral efficacy against hepatitis B virus (HBV) of once-daily tenofovir DF versus once-daily emtricitabine plus tenofovir DF combination treatment in subjects with lamivudine resistance

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	30 September 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: 32
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Turkey: 28
Country: Number of subjects enrolled	Canada: 90
Country: Number of subjects enrolled	Serbia: 36
Country: Number of subjects enrolled	New Zealand: 17
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	280
EEA total number of subjects	105

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)	0
Adults (18-64 years)	252
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and New Zealand. The first participant was screened on 30 September 2008. The last study visit occurred on 09 February 2015.

Pre-assignment

Screening details:

752 participants were screened. Randomization was stratified by hepatitis B e antigen (HBeAg) status (negative or positive) and alanine aminotransferase (ALT) level (≥ 2 × upper limit of normal [ULN] or < 2 × ULN) at screening.

Period 1

Period 1 title	Treatment Period Through Week 240
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	Tenofovir DF

Arm description:

Tenofovir DF once daily plus FTC/TDF placebo once daily

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

Dosage and administration details:

TDF 300 mg tablet once daily

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

Dosage and administration details:

FTC/TDF placebo once daily

Arm title	FTC/Tenofovir DF

Arm description:

FTC/TDF once daily plus TDF placebo once daily

Arm type	Experimental
Investigational medicinal product name	FTC/TDF
Investigational medicinal product code	
Other name	Emtricitabine/tenofovir DF, Truvada®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

FTC/TDF 200/300 mg tablet once daily

Investigational medicinal product name	Tenofovir DF placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TDF placebo once daily

Number of subjects in period 1	Tenofovir DF	FTC/Tenofovir DF
Started	141	139
Completed	121	118
Not completed	20	21
Investigator's discretion	6	5
Protocol violation	2	3
Safety, tolerability, or efficacy reason	3	4
Lost to follow-up	3	3
Withdrew consent	5	6
Study discontinued by sponsor	1	-

Period 2

Period 2 title	Treatment-Free Follow-up (TFFU) Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tenofovir DF

Arm description:

TDF once daily plus FTC/TDF placebo once daily. 1 participant not completing the 240 week treatment period enrolled in the TFFU period.

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

Dosage and administration details:

TDF 300 mg tablet once daily

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

Dosage and administration details:

FTC/TDF placebo once daily

Arm title	FTC/Tenofovir DF

Arm description:

FTC/TDF once daily plus TDF placebo once daily. 4 participants not completing the 240 week treatment period enrolled in the TFFU period.

Arm type	Experimental
Investigational medicinal product name	FTC/TDF
Investigational medicinal product code	
Other name	Emtricitabine/tenofovir DF, Truvada®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

FTC/TDF 200/300 mg tablet once daily

Investigational medicinal product name	Tenofovir DF placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TDF placebo once daily

Number of subjects in period 2[1]	Tenofovir DF	FTC/Tenofovir DF
Started	38	37
Completed	12	19
Not completed	26	18
Death	-	1
Withdrew consent	1	-
Started commercial therapy	25	17

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 103 participants in the Tenofovir DF group and 102 participants in the FTC/Tenofovir DF group did not enter the treatment-free follow-up (TFFU) period.

Baseline characteristics

Reporting groups	
Reporting group title	Tenofovir DF
Reporting group description:	
Tenofovir DF once daily plus FTC/TDF placebo once daily	
Reporting group title	FTC/Tenofovir DF
Reporting group description:	
FTC/TDF once daily plus TDF placebo once daily	

Reporting group values	Tenofovir DF	FTC/Tenofovir DF	Total
Number of subjects	141	139	280
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.1	46.3	
standard deviation	± 13.63	± 13.56	-
Gender categorical Units: Subjects			
Female	37	32	69
Male	104	107	211
Ethnicity Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	138	137	275
Unknown or not reported	1	1	2
Race Units: Subjects			
Asian	52	42	94
Black or African American	3	1	4
Native Hawaiian or other Pacific Islander	0	3	3
White	83	89	172
Other	3	4	7
ALT Normal at Baseline			
The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69, and 35 U/L for males and 32 U/L for females aged ≥ 69.			
Units: Subjects			
Abnormal	79	83	162
Normal	62	56	118
HBeAg Status at Baseline Units: Subjects			
Negative	76	71	147
Positive	65	68	133
Hepatitis B Virus (HBV) DNA Level at Baseline Units: log_10 copies/mL			

arithmetic mean	6.4	6.53	
standard deviation	± 1.826	± 1.968	-

End points

End points reporting groups

Reporting group title	Tenofovir DF
Reporting group description:	
Tenofovir DF once daily plus FTC/TDF placebo once daily	
Reporting group title	FTC/Tenofovir DF
Reporting group description:	
FTC/TDF once daily plus TDF placebo once daily	
Reporting group title	Tenofovir DF
Reporting group description:	
TDF once daily plus FTC/TDF placebo once daily. 1 participant not completing the 240 week treatment period enrolled in the TFFU period.	
Reporting group title	FTC/Tenofovir DF
Reporting group description:	
FTC/TDF once daily plus TDF placebo once daily. 4 participants not completing the 240 week treatment period enrolled in the TFFU period.	

Primary: Percentage of Participants With HBV DNA < 400 Copies/mL at Week 96

End point title	Percentage of Participants With HBV DNA < 400 Copies/mL at Week 96
End point description:	
Full Analysis Set: participants were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants with missing data were considered to have failed to achieve the endpoint.	
End point type	Primary
End point timeframe:	
Week 96	

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)	89.4	86.3		

Statistical analyses

Statistical analysis title	Difference in percentages
Statistical analysis description:	
The null hypothesis is that there is no difference between the FTC/TDF and TDF treatment groups. The alternative hypothesis is that there is a difference between the FTC/TDF and TDF treatment groups. These hypotheses were evaluated using a Cochran-Mantel-Haenszel (CMH) test, controlling for randomization strata, with the missing = failure method in which participants with missing data were considered to have failed to achieve the endpoint.	
Comparison groups	FTC/Tenofovir DF v Tenofovir DF

Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.43 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Comparative analysis

[2] - The p-value for the two-sided Cochran-Mantel-Haenszel test was controlled for strata (HBeAg status and ALT level).

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 48, 144, 192, and 240

End point title	Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 48, 144, 192, and 240

End point description:

Full Analysis Set, missing = failure method

End point type	Secondary

End point timeframe:

Weeks 48, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)				
Week 48	81.6	84.2		
Week 144	87.2	84.9		
Week 192	86.5	85.6		
Week 240	83	82.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < 169 Copies/mL at Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With HBV DNA < 169 Copies/mL at Weeks 48, 96, 144, 192, and 240

End point description:

Full Analysis Set, missing = failure method

End point type	Secondary

End point timeframe:

Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)				
Week 48	76.6	77.7		
Week 96	85.8	83.5		
Week 144	86.5	84.9		
Week 192	85.1	84.2		
Week 240	81.6	82		

Statistical analyses

No statistical analyses for this end point

Secondary: HBV DNA Level at Weeks 48, 96, 144, 192, and 240

End point title	HBV DNA Level at Weeks 48, 96, 144, 192, and 240

End point description:

Full analysis set; participants with HBV DNA measurements at the given time point were included in the analysis.

End point type	Secondary

End point timeframe:

Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: log10 copies/mL				
arithmetic mean (standard deviation)				
Week 48 (TDF: n=130; FTC/TDF: n=133)	2.42 (± 0.542)	2.48 (± 0.887)		
Week 96 (TDF: n=132; FTC/TDF: n=127)	2.29 (± 0.254)	2.28 (± 0.241)		
Week 144 (TDF: n=128; FTC/TDF: n=123)	2.26 (± 0.173)	2.29 (± 1.541)		
Week 192 (TDF: n=126; FTC/TDF: n=119)	2.25 (± 0.135)	2.23 (± 0.027)		
Week 240 (TDF: n=118; FTC/TDF: n=116)	2.23 (± 0.052)	2.26 (± 0.376)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normal ALT at Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With Normal ALT at Weeks 48, 96, 144, 192, and 240

End point description:

Full Analysis Set, missing = failure method. Normal ALT was defined as having a value less than or equal to the ULN. The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69, and 35 U/L for males and 32 U/L for females aged ≥ 69.

End point type	Secondary

End point timeframe:

Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)				
Week 48	67.4	69.8		
Week 96	70.2	69.8		
Week 144	70.2	75.5		
Week 192	75.9	76.3		
Week 240	71.6	71.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Loss at Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With HBeAg Loss at Weeks 48, 96, 144, 192, and 240

End point description:

Participants in the Full Analysis Set who were HBeAg positive at baseline were analyzed using the missing = failure method. The percentage of participants who were HBeAg positive at baseline and who had HBeAg Loss at the given time point was summarized. Loss of HBeAg was defined as change of detectable HBeAg from positive to negative.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	68		
Units: percentage of participants				
number (not applicable)				
Week 48	9.2	5.9		
Week 96	15.4	13.2		
Week 144	23.1	17.6		
Week 192	21.5	14.7		
Week 240	24.6	19.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Seroconversion to Antibody Against HBeAg (Anti-HBe) at Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With Seroconversion to Antibody Against HBeAg (Anti-HBe) at Weeks 48, 96, 144, 192, and 240

End point description:

Participants in the Full Analysis Set who were HBeAg positive at baseline were analyzed using the missing = failure method. The percentage of participants who were HBeAg positive at baseline and who had seroconversion to anti-HBe at the given time point was summarized. Seroconversion to anti-HBe was defined as change of detectable antibody to HBeAg from negative to positive.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	68		
Units: percentage of participants				
number (not applicable)				
Week 48	6.2	4.4		
Week 96	10.8	10.3		
Week 144	12.3	11.8		
Week 192	10.8	10.3		
Week 240	12.3	10.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV Surface Antigen (HBsAg) Loss at

Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With HBV Surface Antigen (HBsAg) Loss at Weeks 48, 96, 144, 192, and 240

End point description:

Full Analysis Set, missing = failure method. The percentage of participants with HBsAg Loss at the given time point was summarized. Loss of HBsAg was defined as change of detectable HBsAg from positive to negative.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)				
Week 48	0	0.7		
Week 96	0	0.7		
Week 144	0.7	1.4		
Week 192	0.7	2.9		
Week 240	1.4	2.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Seroconversion to Antibody Against HBV Surface Antigen (Anti-HBs) at Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With Seroconversion to Antibody Against HBV Surface Antigen (Anti-HBs) at Weeks 48, 96, 144, 192, and 240

End point description:

Full Analysis Set, missing = failure method. The percentage of participants with seroconversion to anti-HBs at the given time point was summarized. Seroconversion to anti-HBs was defined as change of detectable antibody to HBsAg from negative to positive.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)				
Week 48	0	0		
Week 96	0	0		
Week 144	0	0.7		
Week 192	0	0.7		
Week 240	0	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virologic Breakthrough at Weeks 48, 96, 144, 192, and 240

End point title	Percentage of Participants With Virologic Breakthrough at Weeks 48, 96, 144, 192, and 240

End point description:

Full Analysis Set; the missing-equals-excluded method was used in which participants with missing data were excluded from the analysis. The percentage of participants with virologic breakthrough at the given time point was summarized. Virologic breakthrough was defined as having two consecutive 1.0 log10 or greater increases in serum HBV DNA from on-treatment nadir, or two consecutive HBV DNA values ≥ 400 copies/mL after being < 400 copies/mL.

End point type	Secondary

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage of participants				
number (not applicable)				
Week 48 (TDF: n=130; FTC/TDF: n=133)	0	0.8		
Week 96 (TDF: n=132; FTC/TDF: n=127)	0	0		
Week 144 (TDF: n=128; FTC/TDF: n=123)	0.8	0.8		
Week 192 (TDF: n=126; FTC/TDF: n=119)	0.8	0		
Week 240 (TDF: n=118; FTC/TDF: n=116)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in bone mineral density (BMD) of the spine at Weeks 24, 48, 72, 96, 144, 192, and 240

End point title	Percent change from baseline in bone mineral density (BMD) of the spine at Weeks 24, 48, 72, 96, 144, 192, and 240

End point description:

BMD is calculated as grams per cubic centimeter (g/cm^2); the mean (SD) percentage change is presented. Participants in the Safety Analysis Set (randomized and received at least 1 dose of study drug) with spine BMD measurements at the given time point were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Weeks 24, 48, 72, 96, 144, 192

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage change				
arithmetic mean (standard deviation)				
% Change at Week 24 (TDF: n=132; FTC/TDF: n=127)	-1.74 (± 2.867)	-1.83 (± 2.565)		
% Change at Week 48 (TDF: n=126; FTC/TDF: n=121)	-1.68 (± 3.094)	-1.73 (± 2.944)		
% Change at Week 72 (TDF: n=123; FTC/TDF: n=119)	-1.35 (± 3.337)	-1.95 (± 2.977)		
% Change at Week 96 (TDF: n=126; FTC/TDF: n=114)	-1.24 (± 3.761)	-1.72 (± 3.269)		
% Change at Week 144 (TDF: n=123; FTC/TDF: n=110)	-1.36 (± 3.81)	-1.63 (± 3.591)		
% Change at Week 192 (TDF: n=120; FTC/TDF: n=106)	-1.32 (± 4.237)	-1.6 (± 4.628)		
% Change at Week 240 (TDF: n=115; FTC/TDF: n=102)	-0.83 (± 4.49)	-1.15 (± 5.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in BMD of the hip at Weeks 24, 48, 72, 96, 144, 192, and 240

End point title	Percent change from baseline in BMD of the hip at Weeks 24, 48, 72, 96, 144, 192, and 240

End point description:

BMD is calculated as g/cm^2; the mean (SD) percentage change is presented. Participants in the Safety Analysis Set with hip BMD measurements at the given time point were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline; Weeks 24, 48, 72, 96, 144, 192, and 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: percentage change				
arithmetic mean (standard deviation)				
% Change at Week 24 (TDF: n=130; FTC/TDF: n=127)	-0.71 (± 1.724)	-0.59 (± 1.835)		
% Change at Week 48 (TDF: n=126; FTC/TDF: n=118)	-1.15 (± 2.12)	-1 (± 2.063)		
% Change at Week 72 (TDF: n=121; FTC/TDF: n=115)	-1.59 (± 2.507)	-1.61 (± 2.525)		
% Change at Week 96 (TDF: n=125; FTC/TDF: n=112)	-1.7 (± 2.617)	-1.77 (± 2.801)		
% Change at Week 144 (TDF: n=120; FTC/TDF: n=107)	-2.02 (± 3.03)	-1.91 (± 3.281)		
% Change at Week 192 (TDF: n=116; FTC/TDF: n=105)	-2.33 (± 3.19)	-2.41 (± 3.783)		
% Change at Week 240 (TDF: n=111; FTC/TDF: n=100)	-2.46 (± 3.191)	-2.63 (± 3.872)		

Statistical analyses

No statistical analyses for this end point

Secondary: Development of Drug-resistant Mutations (DRMs)

End point title	Development of Drug-resistant Mutations (DRMs)

End point description:

Full Analysis Set. The development of DRMs was summarized, either as development of new DRMs or enrichment of existing DRMs.

End point type	Secondary

End point timeframe:

Baseline to Week 240

End point values	Tenofovir DF	FTC/Tenofovir DF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: participants				
New tenofovir DF DRMs	0	0		
Enrichment of tenofovir DF DRMs	0	0		
New FTC DRMs	0	0		
Enrichment of FTC DRMs	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline through end of study drug treatment (average exposure 220 weeks) plus 7 days	
Adverse event reporting additional description:	
Safety Analysis Set: participants were randomized and received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Tenofovir DF
Reporting group description:	
Tenofovir DF once daily plus FTC/TDF placebo once daily	
Reporting group title	FTC/Tenofovir DF
Reporting group description:	
FTC/TDF once daily plus TDF placebo once daily	

Serious adverse events	Tenofovir DF	FTC/Tenofovir DF	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 141 (16.31%)	21 / 139 (15.11%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	2 / 141 (1.42%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenolymphoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal adenoma			

subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal neoplasm			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma cell myeloma			

subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 141 (0.71%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			

subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tympanic membrane perforation			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 141 (0.71%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	2 / 141 (1.42%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 141 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acarodermatitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone tuberculosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngotonsillitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tenofovir DF	FTC/Tenofovir DF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 141 (77.30%)	105 / 139 (75.54%)	
Investigations			
Creatinine renal clearance decreased			
subjects affected / exposed	2 / 141 (1.42%)	7 / 139 (5.04%)	
occurrences (all)	2	9	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 141 (4.96%)	9 / 139 (6.47%)	
occurrences (all)	7	11	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 141 (16.31%)	20 / 139 (14.39%)	
occurrences (all)	48	42	
Dizziness			
subjects affected / exposed	7 / 141 (4.96%)	8 / 139 (5.76%)	
occurrences (all)	7	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 141 (9.93%)	15 / 139 (10.79%)	
occurrences (all)	16	17	
Pyrexia			
subjects affected / exposed	8 / 141 (5.67%)	5 / 139 (3.60%)	
occurrences (all)	8	7	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	8 / 141 (5.67%)	3 / 139 (2.16%)	
occurrences (all)	9	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 141 (8.51%)	11 / 139 (7.91%)	
occurrences (all)	13	17	
Abdominal pain upper			
subjects affected / exposed	8 / 141 (5.67%)	12 / 139 (8.63%)	
occurrences (all)	9	14	
Diarrhoea			

subjects affected / exposed	13 / 141 (9.22%)	7 / 139 (5.04%)	
occurrences (all)	16	7	
Abdominal pain			
subjects affected / exposed	6 / 141 (4.26%)	7 / 139 (5.04%)	
occurrences (all)	7	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 141 (8.51%)	13 / 139 (9.35%)	
occurrences (all)	16	15	
Oropharyngeal pain			
subjects affected / exposed	12 / 141 (8.51%)	3 / 139 (2.16%)	
occurrences (all)	13	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 141 (7.09%)	18 / 139 (12.95%)	
occurrences (all)	12	22	
Back pain			
subjects affected / exposed	10 / 141 (7.09%)	15 / 139 (10.79%)	
occurrences (all)	12	17	
Myalgia			
subjects affected / exposed	7 / 141 (4.96%)	8 / 139 (5.76%)	
occurrences (all)	8	9	
Musculoskeletal pain			
subjects affected / exposed	5 / 141 (3.55%)	7 / 139 (5.04%)	
occurrences (all)	5	7	
Pain in extremity			
subjects affected / exposed	4 / 141 (2.84%)	8 / 139 (5.76%)	
occurrences (all)	4	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 141 (17.02%)	20 / 139 (14.39%)	
occurrences (all)	32	35	
Influenza			
subjects affected / exposed	14 / 141 (9.93%)	10 / 139 (7.19%)	
occurrences (all)	14	15	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2	7 / 139 (5.04%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2008	The Gilead Sciences, Inc. (GSI) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities was modified to be consistent with the toxicity grading scale used for every other GSI-sponsored chronic hepatitis B study in the adult TDF HBV program.
30 June 2008	The HBV DNA entry threshold was reduced from 10^5 copies/mL to 10^4 copies/mL to reflect the current standard of treatment for either switching or adding on to therapy in patients with resistance to current anti-HBV therapy. It was clarified that dual-energy x-ray absorptiometry (DXA) scans were only required at sites with such capabilities.
16 February 2009	The entry criteria for the lower threshold of HBV DNA was changed from ≥ 4 log10 copies/mL to ≥ 3 log10 IU/mL, as current treatment practices were such that this cutoff was used more often in a clinical setting to guide treatment change; exclusion criteria relating to laboratory values used to define hepatic decompensation were made less stringent to permit enrollment of compensated cirrhotics; the lower exclusionary limit for neutrophils was modified from ≥ 1500 IU/mL to ≥ 1000 IU/mL to permit inclusion of subjects with physiologically low counts.
24 October 2011	Analysis of the primary endpoint was modified to occur at Week 96 and was not to be conducted using group sequential testing annually (ie, every 48 weeks) beginning after the last subject reached Week 48; efficacy and safety analyses conducted after Week 96 were considered secondary analyses.

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/24929235

http://www.ncbi.nlm.nih.gov/pubmed/24861361

http://www.ncbi.nlm.nih.gov/pubmed/24368224