Clinical trial results:
FINITE CHB – First investigation in stopping TDF treatment after long term virologic suppression in HBeAg-negative Chronic Hepatitis B

Summary

EudraCT number	2010-021925-12
Trial protocol	DE
Global end of trial date	23 August 2016

Results information

Result version number	v1 (current)
This version publication date	07 September 2017
First version publication date	07 September 2017

Trial information

Trial identification

Sponsor protocol code	GS-EU-174-0160

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01320943
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 Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@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	23 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 August 2016
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 evaluate hepatitis B surface antigen (HBsAg) loss and seroconversion in participants who stop tenofovir disoproxil fumarate (TDF) (Stop TDF arm) compared to participants who continue TDF (Continue TDF arm).
Only participants who already are on treatment with TDF monotherapy or TDF in combination with lamivudine or emtricitabine for at least 4 years and who achieved and maintained virologic suppression (< 400 copies/mL) for 3.5 or more years will be included in this study. One treatment arm will stop the TDF therapy while the other treatment arm will continue the TDF therapy. Participants in the Stop TDF arm will be monitored very closely with special focus on biochemical flares (especially alanine aminotransferase (ALT) increases) and virological relapses (Hepatitis B viral load increases). If any participant in the Stop TDF arm exceeds one or more predefined limits for such flares or relapses, TDF treatment will be reinstituted.

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	26 April 2011
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	Germany: 43
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	43
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 13 study sites in Germany. The first participant was screened on 26 April 2011.
The last study visit occurred on 23 August 2016.

Pre-assignment

Screening details:

65 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Stop TDF

Arm description:

Participants stopped tenofovir disoproxil fumarate monotherapy at baseline.

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

Dosage and administration details:

Participants stopped TDF monotherapy at baseline.

Arm title	Continue TDF

Arm description:

Participants continued TDF monotherapy

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

Dosage and administration details:

300 mg administered once daily

Number of subjects in period 1[1]	Stop TDF	Continue TDF
Started	21	21
Completed	20	20
Not completed	1	1
Physician decision	-	1
Lost to follow-up	1	-

Notes:

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

Justification: 1 participant who was enrolled but not treated is not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	Stop TDF
Reporting group description:	
Participants stopped tenofovir disoproxil fumarate monotherapy at baseline.	
Reporting group title	Continue TDF
Reporting group description:	
Participants continued TDF monotherapy	

Reporting group values	Stop TDF	Continue TDF	Total
Number of subjects	21	21	42
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	44.6	45	
standard deviation	± 10.51	± 7.06	-
Gender categorical Units: Subjects			
Female	3	6	9
Male	18	15	33
Race Units: Subjects			
Asian	1	1	2
Black or African American	1	0	1
White	18	19	37
Other	1	1	2
Hepatitis B Virus Surface Antigen Units: log10 IU/mL			
arithmetic mean	4.4	4.5	
standard deviation	± 0.71	± 0.35	-

End points

End points reporting groups

Reporting group title	Stop TDF
Reporting group description:	
Participants stopped tenofovir disoproxil fumarate monotherapy at baseline.	
Reporting group title	Continue TDF
Reporting group description:	
Participants continued TDF monotherapy	
Subject analysis set title	Restart TDF
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Stop TDF participants who restarted TDF therapy	

Primary: Proportion of Participants With HBsAg Loss at Week 144 in Both Study Arms

End point title	Proportion of Participants With HBsAg Loss at Week 144 in Both Study Arms
End point description:	
• HBsAg loss is defined as qualitative HBsAg result changing from positive at baseline (BL) to negative at any post-baseline visit. Proportions are based on a Kaplan-Meier estimate. • HBsAg Loss and Seroconversion Full Analysis Set: participants in the Full Analysis Set who had at least 1 post-BL HBsAg value and with HBsAg positive and HBsAb negative or missing at BL. • -999/ 999 = Not applicable (No participants in the Continue TDF group had HBsAg loss.)	
End point type	Primary
End point timeframe:	
Week 144	

End point values	Stop TDF	Continue TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Proportion of participants				
number (confidence interval 95%)	0.236 (0.095 to 0.516)	0 (-999 to 999)		

Statistical analyses

Statistical analysis title	HBsAg Loss – Stop TDF vs Continue TDF
Comparison groups	Stop TDF v Continue TDF
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022 [1]
Method	Logrank

Notes:

[1] - Log-rank test statistic was used to compare the time to HBsAg loss between the two treatment arms

Secondary: Proportion of Participants With Seroconversion in Both Study Arms at Weeks 96 and 144

End point title	Proportion of Participants With Seroconversion in Both Study Arms at Weeks 96 and 144

End point description:

- HBsAg seroconversion is defined as qualitative HBsAb result changing from negative at baseline to positive at any postbaseline visit. Proportions are based on the Kaplan-Meier estimate.
- HBsAg Loss and Seroconversion Full Analysis Set: participants in the Full Analysis Set who had at least 1 post-baseline HBsAg value and with HBsAg positive and HBsAb negative or missing at baseline
- -999/ 999 = Not applicable (No participants in the Continue TDF arm achieved HBsAg seroconversion at Weeks 96 and 144)

End point type	Secondary

End point timeframe:

Weeks 96 and 144

End point values	Stop TDF	Continue TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Proportion of participants				
number (confidence interval 95%)				
HBsAg Seroconversion at Week 96	0.056 (0.008 to 0.334)	0 (-999 to 999)		
HBsAg Seroconversion at Week 144	0.203 (0.069 to 0.513)	0 (-999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quantitative HBsAg (IU/mL) in Both Study Arms

End point title	Change From Baseline in Quantitative HBsAg (IU/mL) in Both Study Arms

End point description:

- Participants in the Full Analysis Set (participants who were randomized to Stop TDF arm and had a baseline visit or who were randomized to Continue TDF arm and received at least 1 dose of study drug) with available data were analyzed.
- The analyses were summarized by 3 treatment subgroups: Stop TDF (TDF-Free), Restart TDF, and Continue TDF
- When participant randomized in the Stop TDF group restarted TDF therapy, that participant was considered part of the Restart TDF group from that point forward.
- 999 = Not Applicable (No participants were in the Restart TDF group at Weeks 2, 4, 6, 8 and 10.)
- 9999 = Not Applicable (HBsAg assessment in the Continue TDF arm was not performed at Weeks 2, 6, 8, 10, 16, 20, 28, 32, 40, and 44.)

End point type	Secondary

End point timeframe:

Baseline to Week 144

End point values	Stop TDF	Continue TDF	Restart TDF	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	8	21	
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Wk2-StopTDF: N=21;ContinueTDF:N=21;RestartTDF:N	-0.03 (± 0.139)	9999 (± 9999)	999 (± 999)	
Wk4-StopTDF: N=20;ContinueTDF:N=20;RestartTDF:N	-0.03 (± 0.17)	-0.01 (± 0.105)	999 (± 999)	
Wk6-StopTDF: N=20;ContinueTDF:N=21;RestartTDF:N	-0.02 (± 0.192)	9999 (± 9999)	999 (± 999)	
Wk8-StopTDF: N=20;ContinueTDF:N=21;RestartTDF:N	0.04 (± 0.5)	9999 (± 9999)	999 (± 999)	
Wk10-StopTDF: N=20;ContinueTDF:N=21;RestartTDF:N	0.01 (± 0.556)	9999 (± 9999)	999 (± 999)	
Wk12-StopTDF: N=19;ContinueTDF:N=21;RestartTDF:N	-0.11 (± 0.621)	-0.02 (± 0.137)	-0.03 (± 999)	
Wk16-StopTDF: N=19;ContinueTDF:N=21;RestartTDF:N	-0.35 (± 0.741)	9999 (± 9999)	-0.73 (± 0.438)	
Wk20-StopTDF: N=18;ContinueTDF:N=21;RestartTDF:N	-0.48 (± 0.949)	9999 (± 9999)	-0.42 (± 999)	
Wk24-StopTDF: N=18;ContinueTDF:N=21;RestartTDF:N	-0.56 (± 1.029)	-0.07 (± 0.139)	-1.41 (± 1.211)	
Wk28-StopTDF: N=17;ContinueTDF:N=21;RestartTDF:N	-0.6 (± 0.969)	9999 (± 9999)	-0.88 (± 0.916)	
Wk32-StopTDF: N=16;ContinueTDF:N=21;RestartTDF:N	-0.77 (± 1.126)	9999 (± 9999)	-0.96 (± 1.211)	
Wk36-StopTDF: N=17;ContinueTDF:N=21;RestartTDF:N	-0.67 (± 1.151)	-0.08 (± 0.14)	-0.26 (± 0.461)	
Wk40-StopTDF: N=18;ContinueTDF:N=21;RestartTDF:N	-0.78 (± 1.198)	9999 (± 9999)	-0.97 (± 1.275)	
Wk44-StopTDF: N=17;ContinueTDF:N=21;RestartTDF:N	-0.87 (± 1.238)	9999 (± 9999)	-0.59 (± 999)	
Wk48-StopTDF: N=18;ContinueTDF:N=20;RestartTDF:N	-0.88 (± 1.314)	-0.11 (± 0.101)	-1.01 (± 1.295)	
Wk60-StopTDF: N=18;ContinueTDF:N=21;RestartTDF:N	-0.96 (± 1.353)	-0.1 (± 0.133)	-1.03 (± 1.236)	
Wk72-StopTDF: N=16;ContinueTDF:N=20;RestartTDF:N	-1.22 (± 1.478)	-0.14 (± 0.142)	-0.64 (± 1.085)	
Wk84-StopTDF: N=16;ContinueTDF:N=21;RestartTDF:N	-1.21 (± 1.555)	-0.16 (± 0.164)	-0.69 (± 1.084)	
Wk96-StopTDF: N=16;ContinueTDF:N=20;RestartTDF:N	-1.22 (± 1.53)	-0.17 (± 0.159)	-0.69 (± 1.031)	
Wk108-StopTDF:N=16;ContinueTDF:N=20;Rest	-1.43 (± 1.573)	-0.17 (± 0.145)	-0.69 (± 1.088)	
Wk120-StopTDF:N=14;ContinueTDF:N=20;Rest	-1.56 (± 1.752)	-0.2 (± 0.136)	-0.58 (± 0.87)	
Wk132-StopTDF:N=13;ContinueTDF:N=20;Rest	-1.74 (± 1.829)	-0.22 (± 0.172)	-0.52 (± 0.941)	
Wk144-StopTDF:N=13;ContinueTDF:N=20;Rest	-1.8 (± 1.796)	-0.22 (± 0.16)	-0.51 (± 0.861)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Who Restart TDF Therapy in the Stop TDF Arm (TDF-Free and Restart TDF)

End point title	Proportion of Participants Who Restart TDF Therapy in the Stop TDF Arm (TDF-Free and Restart TDF)[2]

End point description:

Full Analysis Set
• Proportions are based on the Kaplan-Meier estimate.

End point type	Secondary

End point timeframe:

Weeks 48, 96, and 144

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for Stop TDF arm (TDF-Free and Re-start TDF subgroups) only.

End point values	Stop TDF			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Proportion of participants				
number (confidence interval 95%)				
TDF Restart at Week 48	0.143 (0.048 to 0.38)			
TDF Restart at Week 96	0.238 (0.107 to 0.481)			
TDF Restart at Week 144	0.381 (0.212 to 0.619)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Viral Suppression in the Stop TDF Arm (TDF-Free and Restart TDF)

End point title	Percentage of Participants With Viral Suppression in the Stop TDF Arm (TDF-Free and Restart TDF)[3]

End point description:

• Viral suppression is defined as 2 consecutive assessments of HBV DNA < 400 copies/mL (69 IU/mL) through Week 144.
• Participants in the Full Analysis Set with available data were analyzed. When participant randomized in the Stop TDF group restarted TDF therapy, that participant was considered part of the Restart TDF group from that point forward.
• 1 participant restarted TDF during Week 72 and thus was reported in both Stop TDF and Restart TDF arms based on the TDF restart date.

End point type	Secondary

End point timeframe:

Baseline to Week 144

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for Stop TDF arm (TDF-Free and Re-start TDF subgroups) only.

End point values	Stop TDF	Restart TDF		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	8		
Units: Percentage of participants				
number (not applicable)				
Wk 2 (StopTDF: N=21; RestartTDF:N=0)	52.4	0		
Wk 4 (StopTDF: N=19; RestartTDF: N=0)	5.3	0		
Wk 6 (StopTDF: N=20; RestartTDF: N=0)	10	0		
Wk 8 (StopTDF: N=20; RestartTDF: N=0)	5	0		
Wk 10 (StopTDF: N=20; RestartTDF :N=0)	15	0		
Wk 12 (StopTDF: N=19; RestartTDF: N=1)	21.1	0		
Wk 16 (StopTDF: N=19; RestartTDF: N=2)	31.6	0		
Wk 20 (StopTDF: N=18; RestartTDF: N=2)	27.8	0		
Wk 24 (StopTDF: N=18; RestartTDF: N=2)	16.7	0		
Wk 28 (StopTDF: N=17; RestartTDF: N=3)	17.6	0		
Wk 32 (StopTDF: N=16; RestartTDF: N=3)	12.5	66.7		
Wk 36 (StopTDF: N=17; RestartTDF: N=2)	29.4	100		
Wk 40 (StopTDF: N=18; RestartTDF: N=3)	22.2	100		
Wk 44 (StopTDF: N=17; RestartTDF: N=1)	29.4	100		
Wk 48 (StopTDF: N=18; RestartTDF: N=3)	27.8	100		
Wk 60 (StopTDF: N=18; RestartTDF: N=3)	33.3	100		
Wk 72 (StopTDF: N=17; RestartTDF: N=5)	35.3	60		
Wk 84 (StopTDF: N=16; RestartTDF: N=5)	31.3	100		
Wk 96 (StopTDF: N=16; RestartTDF: N=5)	37.5	100		
Wk 108 (StopTDF :N=16; RestartTDF: N=5)	37.5	100		
Wk 120 (StopTDF: N=15; RestartTDF: N=7)	40	71.4		
Wk 132 (StopTDF: N=13; RestartTDF: N=7)	38.5	100		
Wk 144 (StopTDF: N=13; RestartTDF: N=8)	46.2	87.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Alanine Aminotransferase (ALT) > Upper Limit of the Normal Range in the Stop TDF Arm (TDF-Free and Restart TDF)

End point title	Percentage of Participants With Alanine Aminotransferase (ALT) > Upper Limit of the Normal Range in the Stop TDF Arm (TDF-Free and Restart TDF)[4]

End point description:

- Participants in the Full Analysis Set with available data were analyzed.
- Percentages are based on the number of subjects with non-missing laboratory test results at each visit.
- One participant restarted TDF during Weeks 72 and 120 and thus was reported in both the Stop TDF and Re-Start TDF groups based on the date of TDF restart.

End point type	Secondary

End point timeframe:

Baseline to Week 144

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for Stop TDF arm (TDF-Free and Re-start TDF subgroups) only.

End point values	Stop TDF	Restart TDF		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	8		
Units: Percentage of participants				
number (not applicable)				
Wk 2 (StopTDF: N=21; RestartTDF:N=0)	4.8	0		
Wk 4 (StopTDF: N=20; RestartTDF:N=0)	0	0		
Wk 6 (StopTDF: N=20; RestartTDF:N=0)	35	0		
Wk 8 (StopTDF: N=20; RestartTDF:N=0)	60	0		
Wk 10 (StopTDF: N=20; RestartTDF:N=0)	70	0		
Wk 12 (StopTDF: N=19; RestartTDF:N=2)	42.1	100		
Wk 16 (StopTDF: N=19; RestartTDF:N=2)	26.3	100		
Wk 20 (StopTDF: N=17; RestartTDF:N=2)	11.8	100		
Wk 24 (StopTDF: N=18; RestartTDF:N=2)	16.7	50		
Wk 28 (StopTDF: N=17; RestartTDF:N=3)	11.8	33.3		
Wk 32 (StopTDF: N=15; RestartTDF:N=3)	13.3	0		
Wk 36 (StopTDF: N=17; RestartTDF:N=2)	11.8	0		
Wk 40 (StopTDF: N=17; RestartTDF:N=3)	23.5	0		
Wk 44 (StopTDF: N=17; RestartTDF:N=1)	11.8	0		
Wk 48 (StopTDF: N=18; RestartTDF:N=3)	16.7	0		

Wk 60 (StopTDF: N=18; RestartTDF:N=3)	22.2	0		
Wk 72 (StopTDF: N=17; RestartTDF:N=5)	11.8	40		
Wk 84 (StopTDF: N=16; RestartTDF:N=5)	18.8	0		
Wk 96 (StopTDF: N=16; RestartTDF:N=5)	12.5	0		
Wk 108 (StopTDF: N=16; RestartTDF:N=5)	18.8	0		
Wk 120 (StopTDF: N=15; RestartTDF:N=7)	20	14.3		
Wk 132 (StopTDF: N=12; RestartTDF:N=7)	0	28.6		
Wk 144 (StopTDF: N=13; RestartTDF:N=8)	15.4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with HBsAg Loss at Week 96 in Both Study Arms

End point title	Proportion of Participants with HBsAg Loss at Week 96 in Both Study Arms

End point description:

• HBsAg loss is defined as qualitative HBsAg result changing from positive at baseline (BL) to negative at any postbaseline
visit. Proportions are based on a Kaplan-Meier estimate.
• HBsAg Loss and Seroconversion Full Analysis Set
• 999 = No participants in the Continue TDF group had HBsAg loss

End point type	Secondary

End point timeframe:

Week 96

End point values	Stop TDF	Continue TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Proportion of participants				
number (confidence interval 95%)	0.172 (0.058 to 0.446)	0 (-999 to 999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 144 weeks

Adverse event reporting additional description:

Safety Analysis Set: participants who were either randomized to Stop TDF and had a BL visit, or who were randomized to Continue TDF and received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Stop TDF (TDF-Free)

Reporting group description:

Participants stopped TDF monotherapy at baseline.
Adverse Events (AEs) reported are Termination Emergent. Termination-emergent events began on or after Study Day 1 for the Stop TDF group until last study day for subjects who did not restart TDF and prior to date of restart for subjects who restarted TDF.

Reporting group title	Restart TDF

Reporting group description:

Stop TDF participants who restarted TDF therapy. AEs reported are Termination Emergent. TDF-emergent events began on or after date of TDF restart until last dose day for subjects who restarted TDF in the Stop TDF group and on or after Study Day 1 until last dose day for subjects in the Continue TDF group.

Reporting group title	Continue TDF

Reporting group description:

AEs reported are Termination Emergent. TDF-emergent events began on or after date of TDF restart until last dose day for subjects who restarted TDF in the Stop TDF group and on or after Study Day 1 until last dose day for subjects in the Continue TDF group.

Serious adverse events	Stop TDF (TDF-Free)	Restart TDF	Continue TDF
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	1 / 8 (12.50%)	3 / 21 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			

subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 8 (0.00%)	0 / 21 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Surgical failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	0 / 21 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 8 (0.00%)	0 / 21 (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

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

Non-serious adverse events	Stop TDF (TDF-Free)	Restart TDF	Continue TDF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 21 (80.95%)	6 / 8 (75.00%)	16 / 21 (76.19%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Keratoacanthoma			
subjects affected / exposed	1 / 21 (4.76%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	4 / 21 (19.05%)
occurrences (all)	2	0	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 21 (19.05%)	2 / 8 (25.00%)	2 / 21 (9.52%)
occurrences (all)	4	2	2
Influenza like illness			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 21 (19.05%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	5	0	0

Aspartate aminotransferase increased			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 21 (23.81%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	7	1	6
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 21 (19.05%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	4	0	0
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	2 / 21 (9.52%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Dyspepsia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Gastritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Renal colic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Back pain			
subjects affected / exposed	4 / 21 (19.05%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	4	1	1
Musculoskeletal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Myalgia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	3	0	2
Gastroenteritis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	2
Nasopharyngitis			
subjects affected / exposed	11 / 21 (52.38%)	1 / 8 (12.50%)	6 / 21 (28.57%)
occurrences (all)	18	2	12
Sinusitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	1	3
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 8 (12.50%) 1	0 / 21 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2011	The calculation of creatinine clearance was changed from using ideal body weight to actual body weight
05 March 2012	• The following inclusion criterion was added: HBeAg-negative at TDF therapy start. • The inclusion criterion that defined duration of TDF monotherapy prior to screening was modified from "Receiving continuous TDF monotherapy treatment for at least 4 years prior to screening" to "Received continuous TDF therapy for at least 4 years (ie, TDF monotherapy or combination therapy TDF + lamivudine or TDF + emtricitabine). If TDF had been used in combination with lamivudine or emtricitabine, lamivudine or emtricitabine was must have been stopped at least 12 weeks prior to screening." • A clinicaltrials.gov identifier was added. • Safety reporting procedures were modified to comply with "Communication from the Commission – Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')" (2011/C 172/01)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported