Clinical trial results:
A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Positive, Chronic Hepatitis B

Summary

EudraCT number	2013-000636-10
Trial protocol	IT GB DE ES PL BG
Global end of trial date	

Results information

Result version number	v1
This version publication date	02 August 2019
First version publication date	02 August 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-320-0110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01940471
WHO universal trial number (UTN)	-
Other trial identifiers	CTRI/2014/01/004329: CTRI, NCT02836249: ClinicalTrials.gov identifier (NCT number)

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	Interim
Date of interim/final analysis	23 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy, safety, and tolerability of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) in treatment-naive and treatment-experienced adults with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B virus (HBV) infection. Results presented include Week 48 interim data for the main study (non-China) and China study.

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	25 August 2013
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: 12
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	China: 181
Country: Number of subjects enrolled	Korea, Republic of: 173
Country: Number of subjects enrolled	Hong Kong: 121
Country: Number of subjects enrolled	India: 110
Country: Number of subjects enrolled	Canada: 83
Country: Number of subjects enrolled	Taiwan: 83
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	New Zealand: 17
Country: Number of subjects enrolled	Singapore: 9

Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Turkey: 26
Worldwide total number of subjects	1056
EEA total number of subjects	82

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)	1048
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in East Asia, Europe, North America, Australia, India, New Zealand, and China. The first participant was screened on 25 August 2013 (non-China) and 19 June 2015 (China). The last Week 48 study visit occurred on 06 November 2015 (non-China) and 15 December 2016 (China).

Pre-assignment

Screening details:

1473 participants were screened in non-China and 227 participants were screened in China.

Period 1

Period 1 title	Double-Blind Phase (overall period)
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	TAF 25 mg (non-China)

Arm description:

TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)

Arm type	Experimental
Investigational medicinal product name	Tenofovir alafenamide
Investigational medicinal product code	
Other name	TAF, Vemlidy®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg administered once daily

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

Dosage and administration details:

Administered once daily

Arm title	TDF 300 mg (non-China)

Arm description:

TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)

Arm type	Active comparator
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

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

Dosage and administration details:
Administered once daily

Arm title	TAF 25 mg (China)

Arm description:
TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks

Arm type	Experimental
Investigational medicinal product name	Tenofovir alafenamide
Investigational medicinal product code	
Other name	TAF, Vemlidy®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
25 mg administered once daily

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

Dosage and administration details:
Administered once daily

Arm title	TDF 300 mg (China)

Arm description:
TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks

Arm type	Active comparator
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

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

Dosage and administration details:
Administered once daily

Number of subjects in period 1[1]	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)
Started	581	292	123
Completed	14	8	0
Not completed	567	284	123
Withdrew Consent	13	7	-
Adverse Event	1	2	-
Protocol specified criteria for withdrawal	1	-	-
Death	1	-	-
Investigator's Discretion	5	-	-
Pregnancy	2	1	2
Non-compliance with study drug	1	1	-
Protocol Violation	-	1	-
Still on Study	539	270	121
Lost to follow-up	3	2	-
Lack of efficacy	1	-	-

Number of subjects in period 1[1]	TDF 300 mg (China)
Started	57
Completed	0
Not completed	57
Withdrew Consent	1
Adverse Event	-
Protocol specified criteria for withdrawal	-
Death	-
Investigator's Discretion	-
Pregnancy	-
Non-compliance with study drug	-
Protocol Violation	-
Still on Study	55
Lost to follow-up	1
Lack of efficacy	-

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: 3 participants (1 each in non-China groups and 1 in TDF China group) who were randomized but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	TAF 25 mg (non-China)
Reporting group description:	
TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)	
Reporting group title	TDF 300 mg (non-China)
Reporting group description:	
TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)	
Reporting group title	TAF 25 mg (China)
Reporting group description:	
TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks	
Reporting group title	TDF 300 mg (China)
Reporting group description:	
TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks	

Reporting group values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)
Number of subjects	581	292	123
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	38	38	34
standard deviation	± 11.0	± 11.7	± 9.4
Gender categorical Units: Subjects			
Female	210	103	35
Male	371	189	88
Race Units: Subjects			
Asian	482	232	123
Black or African American	2	3	0
Native Hawaiian or Pacific Islander	1	3	0
White	96	53	0
Other	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	4	2	0
Not Hispanic or Latino	573	289	123
Not Permitted	4	1	0
Plasma HBV DNA Level Units: Subjects			
< 8 log10 IU/mL	309	150	74
≥ 8 log10 IU/mL	272	142	49
Oral antiviral (OAV) Treatment Status Units: Subjects			

Treatment Experienced	151	77	45
Treatment Naive	430	215	78
Proteinuria by Urinalysis (dipstick)			
Urine protein was measured using the dipstick method. Grade 0 = Absent; Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe			
Units: Subjects			
Grade 0	538	259	117
Grade 1	40	31	6
Grade 2	3	2	0
Grade 3	0	0	0
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	442	210	109
CT	112	69	12
TT	23	10	2
Missing	4	3	0
HBV DNA Units: log10 IU/mL			
arithmetic mean	7.6	7.6	7.2
standard deviation	± 1.34	± 1.41	± 1.65

Reporting group values	TDF 300 mg (China)	Total	
Number of subjects	57	1053	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36		
standard deviation	± 9.5	-	
Gender categorical Units: Subjects			
Female	13	361	
Male	44	692	
Race Units: Subjects			
Asian	57	894	
Black or African American	0	5	
Native Hawaiian or Pacific Islander	0	4	
White	0	149	
Other	0	1	
Ethnicity Units: Subjects			
Hispanic or Latino	0	6	
Not Hispanic or Latino	57	1042	
Not Permitted	0	5	
Plasma HBV DNA Level Units: Subjects			
< 8 log10 IU/mL	36	569	
≥ 8 log10 IU/mL	21	484	

Oral antiviral (OAV) Treatment Status Units: Subjects			
Treatment Experienced	18	291	
Treatment Naive	39	762	
Proteinuria by Urinalysis (dipstick)			
Urine protein was measured using the dipstick method. Grade 0 = Absent; Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe			
Units: Subjects			
Grade 0	54	968	
Grade 1	2	79	
Grade 2	1	6	
Grade 3	0	0	
IL28b Status			
The CC, CT, and TT alleles are different forms of the IL28b gene.			
Units: Subjects			
CC	52	813	
CT	5	198	
TT	0	35	
Missing	0	7	
HBV DNA Units: log10 IU/mL			
arithmetic mean	7.2		
standard deviation	± 1.48	-	

End points

End points reporting groups

Reporting group title	TAF 25 mg (non-China)
Reporting group description:	
TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)	
Reporting group title	TDF 300 mg (non-China)
Reporting group description:	
TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)	
Reporting group title	TAF 25 mg (China)
Reporting group description:	
TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks	
Reporting group title	TDF 300 mg (China)
Reporting group description:	
TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks	

Primary: Percentage of Participants With Hepatitis B Virus (HBV) DNA < 29 IU/mL (Missing = Failure)

End point title	Percentage of Participants With Hepatitis B Virus (HBV) DNA < 29 IU/mL (Missing = Failure)
End point description:	
Full Analysis Set included participants who were randomized into the study and received at least 1 dose of study drugs. Participants were analyzed according to the treatment to which they were randomized. A Missing = Failure approach was employed for the efficacy endpoints, in which all missing data will be treated as not achieving the endpoint.	
End point type	Primary
End point timeframe:	
Week 48	

End point values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)	TDF 300 mg (China)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	581	292	123	57
Units: percentage of participants				
number (not applicable)	63.9	66.8	61.0	68.4

Statistical analyses

Statistical analysis title	Statistical Analysis (non-China only)
Statistical analysis description:	
The null hypothesis was that the TAF group is at least 10% worse than the TDF group with respect to the proportion of participants with HBV DNA < 29 IU/mL at Week 48. The alternative hypothesis was that the TAF group is less than 10% worse than the TDF group with respect to the proportion of participants with HBV DNA < 29 IU/mL at Week 48. Noninferiority was assessed using a 95% confidence interval (CI) approach, with a noninferiority margin of 10%.	

Comparison groups	TAF 25 mg (non-China) v TDF 300 mg (non-China)
Number of subjects included in analysis	873
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in proportions
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	2.6

Notes:

[1] - Sample sizes of 288 and 576 participants in the TDF and TAF groups, respectively, were planned to give 84% power to rule out the noninferiority margin of 10% at a 1-sided significance level of 0.025. This sample size based on the assumption that the expected difference (TAF − TDF) in the proportion of participants with HBV DNA < 29 IU/mL was 0 and the proportion of participants with HBV DNA < 29 IU/mL in the TDF group was 69%. Missing data were treated as not achieving the primary endpoint.

Secondary: Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion to Antibody Against Hepatitis B e Antigen (Anti-HBe) at Week 48

End point title	Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion to Antibody Against Hepatitis B e Antigen (Anti-HBe) at Week 48

End point description:

Serologically Evaluable Full Analysis Set included participants who were randomized, had received at least 1 dose of study drug, and were HBeAg positive and anti-HBe negative or had a value missing value at baseline. Participants were analyzed according to their randomized treatment group. For the Missing = Failure approach, all missing data were treated as no HBeAg seroconversion.

End point type	Secondary

End point timeframe:

Week 48

End point values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)	TDF 300 mg (China)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	565	285	118	57
Units: percentage of participants				
number (not applicable)	10.3	8.1	11.0	8.8

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Participants in the Hip Dual-Energy X-ray Absorptiometry (DXA) Analysis Set (participants who were randomized, received at least 1 dose of study drugs, and had nonmissing baseline hip BMD values) with available data were analyzed. Participants were analyzed according to the treatment they actually

received. Missing data were excluded from analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)	TDF 300 mg (China)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	537	271	53	31
Units: percentage change				
arithmetic mean (standard deviation)	-0.100 (± 2.2912)	-1.715 (± 2.5723)	0.624 (± 2.2731)	-1.507 (± 2.4193)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Participants in the Spine DXA Analysis Set (participants who were randomized, received at least 1 dose of study drugs, and had nonmissing baseline spine BMD values) with available data were analyzed. Participants were analyzed according to the treatment they actually received. Missing data were excluded from analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)	TDF 300 mg (China)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	543	274	54	31
Units: percent change				
arithmetic mean (standard deviation)	-0.417 (± 2.9343)	-2.294 (± 3.1331)	0.683 (± 3.3281)	-2.169 (± 3.4503)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 48 in Serum Creatinine

End point title	Change From Baseline at Week 48 in Serum Creatinine

End point description:

Participants in the Safety Analysis Set (participants who were randomized into the study and received at least 1 dose of study drug) with available data were analyzed. Participants were analyzed according to the treatment they actually received.
Missing data were excluded from analysis.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)	TDF 300 mg (China)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	553	283	121	55
Units: mg/dL				
arithmetic mean (standard deviation)	0.009 (± 0.1238)	0.026 (± 0.0948)	-0.003 (± 0.0701)	0.016 (± 0.0920)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With Treatment-emergent Proteinuria by Urinalysis (Dipstick) Through Week 48

End point title	Percentage of Participants With Treatment-emergent Proteinuria by Urinalysis (Dipstick) Through Week 48

End point description:

Grades 1 (mild), 2 (moderate), and 3 (severe) were the highest treatment-emergent postbaseline grades for urine protein using the dipstick method. Participants in the Safety Analysis Set with at least 1 postbaseline urine protein value were analyzed.

End point type	Other pre-specified

End point timeframe:

Up to 48 weeks

End point values	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)	TDF 300 mg (China)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	577	286	123	57
Units: percentage of participants				
number (not applicable)				
Grade 1	23.9	17.8	24.4	22.8
Grade 2	3.5	4.5	0.8	3.5
Grade 3	0	0.3	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to the Week 48 Data Cut

Adverse event reporting additional description:

Safety Analysis Set included participants who were randomized into the study and received at least 1 dose of study drug. Participants were analyzed according to the treatment they actually received during the double-blinded phase. MedDRA version 18.0 was used for non-China participants and MedDRA version 19.1 was used for China participants.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0, 19.1

Reporting groups

Reporting group title	TAF 25 mg (non-China)

Reporting group description:

TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)

Reporting group title	TDF 300 mg (non-China)

Reporting group description:

TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3)

Reporting group title	TAF 25 mg (China)

Reporting group description:

TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks

Reporting group title	TDF 300 mg (China)

Reporting group description:

TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks

Serious adverse events	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 581 (3.79%)	12 / 292 (4.11%)	5 / 123 (4.07%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 581 (0.00%)	2 / 292 (0.68%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal submucosal tumour			

subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Thymoma			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 123 (0.81%)
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			
Pyrexia			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			

subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Nasal septum deviation			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Ligament rupture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Limb crushing injury			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Lower limb fracture			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Spinal compression fracture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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

Subarachnoid haemorrhage			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 123 (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			
Angina pectoris			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 581 (0.34%)	0 / 292 (0.00%)	0 / 123 (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
Basilar artery occlusion			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Epilepsy			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Optic neuritis			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Syncope			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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 upper			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Intervertebral disc degeneration			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Spondylolisthesis			

subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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 / 581 (0.17%)	0 / 292 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Cellulitis			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Dengue fever			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 123 (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
Diarrhoea infectious			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Periodontitis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Pneumonia			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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
Scrub typhus			

subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 123 (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	TDF 300 mg (China)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 57 (3.51%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal submucosal tumour			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thymoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal septum deviation			
subjects affected / exposed	0 / 57 (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	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb crushing injury				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basilar artery occlusion				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Optic neuritis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	0 / 57 (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 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diarrhoea infectious				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periodontitis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Scrub typhus				
subjects affected / exposed	0 / 57 (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	TAF 25 mg (non-China)	TDF 300 mg (non-China)	TAF 25 mg (China)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 581 (37.01%)	101 / 292 (34.59%)	28 / 123 (22.76%)
Investigations			
Blood parathyroid hormone increased			
subjects affected / exposed	1 / 581 (0.17%)	1 / 292 (0.34%)	6 / 123 (4.88%)
occurrences (all)	3	1	8
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	2 / 123 (1.63%)
occurrences (all)	0	0	5
Nervous system disorders			
Headache			
subjects affected / exposed	42 / 581 (7.23%)	22 / 292 (7.53%)	1 / 123 (0.81%)
occurrences (all)	59	26	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	33 / 581 (5.68%)	14 / 292 (4.79%)	1 / 123 (0.81%)
occurrences (all)	39	19	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 581 (4.65%)	15 / 292 (5.14%)	3 / 123 (2.44%)
occurrences (all)	27	17	3
Nausea			
subjects affected / exposed	28 / 581 (4.82%)	13 / 292 (4.45%)	2 / 123 (1.63%)
occurrences (all)	30	15	2
Abdominal pain upper			
subjects affected / exposed	19 / 581 (3.27%)	15 / 292 (5.14%)	2 / 123 (1.63%)
occurrences (all)	22	16	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 581 (6.37%)	19 / 292 (6.51%)	1 / 123 (0.81%)
occurrences (all)	55	19	1
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	1 / 581 (0.17%)	2 / 292 (0.68%)	0 / 123 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	56 / 581 (9.64%)	16 / 292 (5.48%)	27 / 123 (21.95%)
occurrences (all)	80	27	37
Upper respiratory tract infection			
subjects affected / exposed	51 / 581 (8.78%)	22 / 292 (7.53%)	17 / 123 (13.82%)
occurrences (all)	65	28	19
Urinary tract infection			
subjects affected / exposed	9 / 581 (1.55%)	10 / 292 (3.42%)	4 / 123 (3.25%)
occurrences (all)	14	12	7

Non-serious adverse events	TDF 300 mg (China)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 57 (49.12%)		
Investigations			

Blood parathyroid hormone increased subjects affected / exposed occurrences (all) Creatinine renal clearance decreased subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4 3 / 57 (5.26%) 5		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 3 3 / 57 (5.26%) 4 2 / 57 (3.51%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2		
Musculoskeletal and connective tissue disorders Osteopenia subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 9		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6		
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2013	• Extended the double-blind phase from 48 to 96 weeks and added Week 96 evaluations to other secondary objectives, as applicable • Changed the primary efficacy endpoint of proportion of subjects with HBV DNA levels at Week 48 from below 69 IU/mL to below 29 IU/mL • Replaced eGFR with serum creatinine as a key secondary safety objective • Extended duration of ophthalmologic substudy to 144 weeks, with additional ophthalmologic assessment at Weeks 72, 96, and 144 • Clarified and revised study entry criteria • Updated statistical section to reflect changes in objectives and to better define analyses of key secondary efficacy and safety endpoints • Revised the number of subjects for PK substudy from 30 subjects to approximately 16 subjects • Added section for Management of Potential Posterior Uveitis Cases and section for Multiplicity Adjustments
04 December 2013	• Lowered the entry criteria for estimated glomerular filtration rate (eGFR) from ≥ 60 mL/min to ≥ 50 mL/min • Clarified and revised study entry criteria • Added clarification regarding subjects who elected an evening study drug dosing schedule: such individuals were no longer required to undergo in-clinic dosing and population PK blood draws at the Week 4 and 12 visits • Updated statistical analysis methods for key secondary endpoints to align with the TAF HIV Phase 3 development program • Added cystatin C to the baseline assessments to accommodate the revision to toxicity management for possible nephrotoxicity • Updated information about the drug formulation for TDF, the comparator, to include the formulation used in developing markets • Updated information on the management of potential nephrotoxicity • Added reflex testing for HEV in the event of an ALT elevation
20 February 2015	This protocol change was only applicable for China: • Added the number of subjects to be enrolled in China • Specified that the dual-energy x-ray absorptiometry (DXA) scan procedure at all protocol-specified visits would be performed only at sites that have the capability • Added statement that fracture risk assessment at the baseline visit was intended for sites with DXA capability only • Added hepatitis E virus (HEV) testing as a reflex test for subjects who discontinued study drug and had confirmed ALT elevation • Updated the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities to reconcile with the scale that was employed in the global program via an administrative letter
05 February 2016	• Extended the blinded period of the study to Week 144 (from Week 96). • Extended the open label period of the study to Week 384 (from Week 144). • Updated the last study visit date of treatment from Week 144/Early Discontinuation (ED) to Week 384/ED. • Added 10 study visits (Week 168, 192, 216, 240, 264, 288, 312, 336, 360, and 384/ED) to be conducted during the additional 5 years of the study. • Revised visit Week numbers to accommodate extension of blinded and open label periods of the study. • Clarified when open label study drug is to be dispensed to participants who rollover to open-label TAF treatment following Amendment 1 or 2, and under Amendment 3. • Clarified visit windows for analysis timepoints (Weeks 48, 96, and 144) to be in alignment with DXA windows. • Added hepatic ultrasound for surveillance of hepatocellular carcinoma every 24 weeks from visit Week 96 to Week 384/ED.

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.

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: