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	13 July 2023

Results information

Result version number	v2
This version publication date	28 October 2023
First version publication date	02 August 2019
Version creation reason	

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	13 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 July 2023
Was the trial ended prematurely?	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 384 final data for the main study (Global cohorts) and Week 48 interim data for China study. Additional data for the China study will be reported after the final analysis is completed.

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:

This study was conducted globally in multiple countries including China. As enrollment began later on clinicaltrials.gov, it has been separately registered. Global study has NCT identifier - NCT01940471 and China study has identifier - NCT02836249.

Evidence for comparator: -

Actual start date of recruitment	11 September 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	New Zealand: 17
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Hong Kong: 121
Country: Number of subjects enrolled	Taiwan: 83
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Canada: 83
Country: Number of subjects enrolled	China: 181

Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	India: 110
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Korea, Republic of: 173
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Turkey: 26
Worldwide total number of subjects	1056
EEA total number of subjects	74

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.

Pre-assignment

Screening details:

1396 participants were screened globally and 227 participants were screened in China.

Period 1

Period 1 title	Double-Blind Phase
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 (Global)

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 (Global)

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 (Global)	TDF 300 mg (Global)	TAF 25 mg (China)
Started	581	292	123
Completed	515	253	0
Not completed	66	39	123
HbsAg seroconversion	1	-	-
Withdrew Consent	31	18	-
Adverse Event	2	2	-
Protocol violation	-	1	-
Death	2	1	-
Protocol specified criteria for withdrawal	1	1	-
Pregnancy	9	2	2
Non-compliance with study drug	3	2	-
Still on Study	-	-	121
Lost to follow-up	8	6	-
Investigator's discretion	8	5	-
Lack of efficacy	1	1	-

Number of subjects in period 1[1]	TDF 300 mg (China)
Started	57
Completed	0
Not completed	57
HbsAg seroconversion	-
Withdrew Consent	1
Adverse Event	-
Protocol violation	-
Death	-
Protocol specified criteria for withdrawal	-
Pregnancy	-
Non-compliance with study drug	-
Still on Study	55
Lost to follow-up	1
Investigator's discretion	-
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: Global study: Two participants (1 each in TAF and TDF arms) were randomized but did not receive the treatment were not included in the analysis.
China study: One participant randomised to TDF arm, did not receive the treatment and was not included in the analysis.

Period 2

Period 2 title	Open-Label TAF Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TAF 25 mg to TAF 25 mg (Global)

Arm description:

After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to continue with Open-label (OL) TAF 25 mg for additional 288 or 240 weeks (up to Week 384), respectively. After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (treatment-free follow-up [TFFU]) for the assessment of safety.

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.

Arm title	TDF 300 mg to TAF 25 mg (Global)

Arm description:

After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to switch to OL TAF 25 mg for additional 288 or 240 weeks (up to Week 384), respectively. After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (TFFU) for the assessment of safety.

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

Number of subjects in period 2[2]	TAF 25 mg to TAF 25 mg (Global)	TDF 300 mg to TAF 25 mg (Global)
Started	514	253
Completed	422	213
Not completed	92	40
HbsAg seroconversion	1	-
Withdrew Consent	48	22
Adverse Event	5	1
Protocol specified criteria for withdrawal	5	4

Pregnancy	5	-
Non-compliance with study drug	4	1
Lost to follow-up	13	8
Investigator's discretion	9	4
Lack of efficacy	2	-

Notes:

[2] - 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: One participant randomised to TAF arm did not enter Open-label TAF extension Phase.

Baseline characteristics

Reporting groups	
Reporting group title	TAF 25 mg (Global)
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 (Global)
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 (Global)	TDF 300 mg (Global)	TAF 25 mg (China)
Number of subjects	581	292	123
Age categorical Units: Subjects			
< 50 years	493	234	114
> = 50 years	88	58	9
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			
< 50 years	50	891	
> = 50 years	7	162	
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 (Global)
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 (Global)
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 title	TAF 25 mg to TAF 25 mg (Global)
Reporting group description:	
After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to continue with Open-label (OL) TAF 25 mg for additional 288 or 240 weeks (up to Week 384), respectively. After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (treatment-free follow-up [TFFU]) for the assessment of safety.	
Reporting group title	TDF 300 mg to TAF 25 mg (Global)
Reporting group description:	
After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to switch to OL TAF 25 mg for additional 288 or 240 weeks (up to Week 384), respectively. After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (TFFU) for the assessment of safety.	

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 were treated as not achieving the endpoint.	
End point type	Primary
End point timeframe:	
Week 48	

End point values	TAF 25 mg (Global)	TDF 300 mg (Global)	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 (Global 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 (Global) v TDF 300 mg (Global)
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 (Global)	TDF 300 mg (Global)	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 (Global)	TDF 300 mg (Global)	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 (Global)	TDF 300 mg (Global)	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 (Global)	TDF 300 mg (Global)	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 (Global)	TDF 300 mg (Global)	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 information

Timeframe for reporting adverse events:

All-cause mortality: For Global cohorts: Randomization up to approximately 416 weeks. For China Cohorts: Randomization up to Week 48 Data cut.
Adverse events - For Global cohorts: First dose date up to Week 384. For China Cohorts: Up to Week 48 Data cut.

Adverse event reporting additional description:

All-cause mortality: Randomized Analysis Set: All participants randomized into the study.
Adverse events: Safety Analysis Set: Participants who received at least 1 dose of study drug in the respective period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Double-blind Phase: TAF 25 mg (Global)

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	Double-blind Phase: TDF 300 mg (Global)

Reporting group description:

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

Reporting group title	Open-label TAF Extension Phase:TAF 25 mg to TAF 25 mg (Global)

Reporting group description:

After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to continue with OL TAF 25 mg for additional 288 or 240 weeks (up to Week 384).
After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (TFFU) for the assessment of safety.

Reporting group title	Double-blind Phase: TDF 300 mg (China)

Reporting group description:

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

Reporting group title	Open-labelTAF Extension Phase:TDF 300 mg to TAF 25 mg (Global)

Reporting group description:

After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to switch to Open-label (OL) TAF 25 mg for additional 288 or 240 weeks (up to Week 384).
After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (TFFU) for the assessment of safety.

Reporting group title	Double-blind Phase: TAF 25 mg (China)

Reporting group description:

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

Serious adverse events	Double-blind Phase: TAF 25 mg (Global)	Double-blind Phase: TDF 300 mg (Global)	Open-label TAF Extension Phase:TAF 25 mg to TAF 25 mg (Global)
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 581 (7.57%)	20 / 292 (6.85%)	59 / 514 (11.48%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	2 / 514 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
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%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	2 / 581 (0.34%)	2 / 292 (0.68%)	2 / 514 (0.39%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Borderline mucinous tumour of ovary			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Gastric cancer			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 514 (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
Haemangioma of liver			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Meningioma			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
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 fibroma			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 514 (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 neoplasm			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
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%)	0 / 514 (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
Pregnancy, puerperium and perinatal			

conditions			
Ectopic pregnancy			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Abortion			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
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			
Chest pain			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Pyrexia			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	3 / 514 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suprapubic pain			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	2 / 581 (0.34%)	1 / 292 (0.34%)	0 / 514 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Heavy menstrual bleeding			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
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 / 514 (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
Pelvic adhesions			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Prostatomegaly			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis chronic			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Nasal septum deviation			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute psychosis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 581 (0.17%)	1 / 292 (0.34%)	0 / 514 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	2 / 514 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Spinal compression fracture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Limb crushing injury			
subjects affected / exposed	2 / 581 (0.34%)	0 / 292 (0.00%)	0 / 514 (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
Joint dislocation			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Facial bones fracture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Ligament injury			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Procedural haemorrhage			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Traumatic haematoma			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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 / 514 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Patent ductus arteriosus			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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			
Coronary artery disease			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	2 / 514 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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

Acute coronary syndrome			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	2 / 514 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 581 (0.34%)	0 / 292 (0.00%)	0 / 514 (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 / 514 (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%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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 / 514 (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
Ischaemic stroke			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Cerebrovascular disorder			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 514 (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 / 514 (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
Haemolytic anaemia			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Thrombocytopenia			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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			
Angle closure glaucoma			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Macular hole			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal hernia			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Anal fistula			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Abdominal pain lower			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Colitis ischaemic			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Duodenal ulcer			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Diarrhoea			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Ileus			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Oesophagitis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatomegaly			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Cholecystitis			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	1 / 514 (0.19%)
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%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 514 (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

Osteoarthritis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	2 / 514 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Spondylolisthesis			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Synovial cyst			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Osteonecrosis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Dengue fever			
subjects affected / exposed	1 / 581 (0.17%)	1 / 292 (0.34%)	0 / 514 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	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%)	3 / 514 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 514 (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
Chronic sinusitis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Covid-19			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	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 / 514 (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
Echinococciasis			

subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Hepatitis E			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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 / 514 (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
Otitis externa			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis tuberculous			
subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Osteomyelitis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Scrub typhus			

subjects affected / exposed	1 / 581 (0.17%)	0 / 292 (0.00%)	0 / 514 (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
Sinusitis			
subjects affected / exposed	0 / 581 (0.00%)	1 / 292 (0.34%)	0 / 514 (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
Tuberculosis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Sepsis			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	1 / 514 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-blind Phase: TDF 300 mg (China)	Open-labelTAF Extension Phase:TDF 300 mg to TAF 25 mg (Global)	Double-blind Phase: TAF 25 mg (China)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 57 (3.51%)	32 / 253 (12.65%)	5 / 123 (4.07%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Transitional cell carcinoma			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 57 (0.00%)	3 / 253 (1.19%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Borderline mucinous tumour of ovary			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Colon cancer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Gastric cancer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Gastrointestinal submucosal tumour			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Haemangioma of liver			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Hepatic cancer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Meningioma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Ovarian fibroma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Thymoma			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Renal neoplasm			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Thyroid neoplasm			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Abortion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 57 (0.00%)	2 / 253 (0.79%)	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
Pyrexia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Suprapubic pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Heavy menstrual bleeding			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Ovarian cyst			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Pelvic adhesions			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Prostatomegaly			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Bronchitis chronic			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Nasal septum deviation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Acute psychosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 253 (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

Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Ankle fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Hand fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Ligament rupture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Limb crushing injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Joint dislocation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Contusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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

Facial bones fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Ligament injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Ligament sprain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Procedural haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Meniscus injury			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Rib fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Traumatic haematoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 57 (1.75%)	0 / 253 (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
Congenital, familial and genetic disorders			
Patent ductus arteriosus			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Acute myocardial infarction			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Angina pectoris			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Acute coronary syndrome			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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

Ventricular fibrillation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Basilar artery occlusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Epilepsy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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 / 57 (0.00%)	0 / 253 (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
Ischaemic stroke			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Coma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Cerebrovascular disorder			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Cerebrovascular accident			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Syncope			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Haemolytic anaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Thrombocytopenia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Eye disorders			

Angle closure glaucoma			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Macular hole			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Retinal detachment			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Abdominal pain upper			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Abdominal hernia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Anal fistula			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Abdominal pain lower			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Colitis ischaemic			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Duodenal ulcer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Haemorrhoids			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Ileus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Proctitis			

subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Oesophagitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Hepatomegaly			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Cholecystitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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	0 / 57 (0.00%)	0 / 253 (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
Renal colic			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Stress urinary incontinence			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Endocrine disorders			

Cushing's syndrome			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Goitre			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	2 / 253 (0.79%)	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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Intervertebral disc degeneration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Osteoarthritis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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 stenosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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

Lumbar spinal stenosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Spondylolisthesis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Synovial cyst			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Osteonecrosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Infections and infestations			
Dengue fever			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Pneumonia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Appendicitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Diarrhoea infectious			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Chronic sinusitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Covid-19			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Anal abscess			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Echinococciasis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Gastroenteritis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Hepatitis E			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Periodontitis			

subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Otitis externa			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Pericarditis tuberculous			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Osteomyelitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Pneumonia bacterial			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Scrub typhus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Sinusitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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
Tuberculosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Sepsis			

subjects affected / exposed	0 / 57 (0.00%)	1 / 253 (0.40%)	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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 253 (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

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

Non-serious adverse events	Double-blind Phase: TAF 25 mg (Global)	Double-blind Phase: TDF 300 mg (Global)	Open-label TAF Extension Phase:TAF 25 mg to TAF 25 mg (Global)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	296 / 581 (50.95%)	146 / 292 (50.00%)	173 / 514 (33.66%)
Investigations			
Blood parathyroid hormone increased			
subjects affected / exposed	1 / 581 (0.17%)	1 / 292 (0.34%)	0 / 514 (0.00%)
occurrences (all)	3	1	0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 581 (0.00%)	0 / 292 (0.00%)	0 / 514 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 581 (2.41%)	6 / 292 (2.05%)	21 / 514 (4.09%)
occurrences (all)	14	6	21
Nervous system disorders			
Headache			
subjects affected / exposed	59 / 581 (10.15%)	30 / 292 (10.27%)	32 / 514 (6.23%)
occurrences (all)	89	39	62
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	36 / 581 (6.20%)	14 / 292 (4.79%)	6 / 514 (1.17%)
occurrences (all)	43	19	6
Gastrointestinal disorders			

Dyspepsia			
subjects affected / exposed	32 / 581 (5.51%)	16 / 292 (5.48%)	16 / 514 (3.11%)
occurrences (all)	37	19	16
Gastrooesophageal reflux disease			
subjects affected / exposed	19 / 581 (3.27%)	10 / 292 (3.42%)	17 / 514 (3.31%)
occurrences (all)	20	10	19
Diarrhoea			
subjects affected / exposed	35 / 581 (6.02%)	19 / 292 (6.51%)	13 / 514 (2.53%)
occurrences (all)	36	21	13
Nausea			
subjects affected / exposed	35 / 581 (6.02%)	15 / 292 (5.14%)	5 / 514 (0.97%)
occurrences (all)	37	17	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	48 / 581 (8.26%)	24 / 292 (8.22%)	15 / 514 (2.92%)
occurrences (all)	72	31	17
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	36 / 581 (6.20%)	22 / 292 (7.53%)	20 / 514 (3.89%)
occurrences (all)	42	23	22
Osteopenia			
subjects affected / exposed	3 / 581 (0.52%)	8 / 292 (2.74%)	8 / 514 (1.56%)
occurrences (all)	7	9	8
Arthralgia			
subjects affected / exposed	39 / 581 (6.71%)	22 / 292 (7.53%)	24 / 514 (4.67%)
occurrences (all)	42	23	25
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	71 / 581 (12.22%)	29 / 292 (9.93%)	33 / 514 (6.42%)
occurrences (all)	133	52	51
Upper respiratory tract infection			
subjects affected / exposed	70 / 581 (12.05%)	33 / 292 (11.30%)	32 / 514 (6.23%)
occurrences (all)	116	57	115
Urinary tract infection			
subjects affected / exposed	14 / 581 (2.41%)	10 / 292 (3.42%)	14 / 514 (2.72%)
occurrences (all)	19	14	16

Non-serious adverse events	Double-blind Phase: TDF 300 mg (China)	Open-labelTAF Extension Phase:TDF 300 mg to TAF 25 mg (Global)	Double-blind Phase: TAF 25 mg (China)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 57 (47.37%)	104 / 253 (41.11%)	50 / 123 (40.65%)
Investigations			
Blood parathyroid hormone increased			
subjects affected / exposed	4 / 57 (7.02%)	0 / 253 (0.00%)	6 / 123 (4.88%)
occurrences (all)	4	0	8
Creatinine renal clearance decreased			
subjects affected / exposed	3 / 57 (5.26%)	0 / 253 (0.00%)	2 / 123 (1.63%)
occurrences (all)	5	0	5
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 57 (1.75%)	15 / 253 (5.93%)	1 / 123 (0.81%)
occurrences (all)	1	15	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 57 (1.75%)	20 / 253 (7.91%)	1 / 123 (0.81%)
occurrences (all)	1	27	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 57 (1.75%)	5 / 253 (1.98%)	1 / 123 (0.81%)
occurrences (all)	1	5	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 57 (0.00%)	9 / 253 (3.56%)	0 / 123 (0.00%)
occurrences (all)	0	10	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 57 (0.00%)	13 / 253 (5.14%)	0 / 123 (0.00%)
occurrences (all)	0	13	0
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)	6 / 253 (2.37%)	3 / 123 (2.44%)
occurrences (all)	3	7	3
Nausea			
subjects affected / exposed	3 / 57 (5.26%)	2 / 253 (0.79%)	2 / 123 (1.63%)
occurrences (all)	4	2	2

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 57 (3.51%)	19 / 253 (7.51%)	1 / 123 (0.81%)
occurrences (all)	2	28	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 57 (1.75%)	12 / 253 (4.74%)	0 / 123 (0.00%)
occurrences (all)	1	14	0
Osteopenia			
subjects affected / exposed	3 / 57 (5.26%)	3 / 253 (1.19%)	0 / 123 (0.00%)
occurrences (all)	3	3	0
Arthralgia			
subjects affected / exposed	1 / 57 (1.75%)	15 / 253 (5.93%)	2 / 123 (1.63%)
occurrences (all)	1	17	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 57 (12.28%)	13 / 253 (5.14%)	27 / 123 (21.95%)
occurrences (all)	9	14	37
Upper respiratory tract infection			
subjects affected / exposed	5 / 57 (8.77%)	17 / 253 (6.72%)	17 / 123 (13.82%)
occurrences (all)	6	50	19
Urinary tract infection			
subjects affected / exposed	4 / 57 (7.02%)	10 / 253 (3.95%)	4 / 123 (3.25%)
occurrences (all)	5	14	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2013	All changes done per amendment#01 were prior to enrollment of any participant. • 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: