



Clinical trial results:

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naïve Adults

Summary

EudraCT number	2012-004458-27
Trial protocol	BE AT IT SE NL GB DE PT ES
Global end of trial date	06 September 2017

Results information

Result version number	v1 (current)
This version publication date	07 September 2018
First version publication date	07 September 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-292-0104
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01780506
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA , United States, 94404
Public contact	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	Final
Date of interim/final analysis	06 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2014
Global end of trial reached?	Yes
Global end of trial date	06 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) fixed-dose combination (FDC) versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) FDC in HIV-1 positive, antiretroviral treatment-naïve adults.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 December 2012
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	Spain: 85
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 23
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	United States: 500
Country: Number of subjects enrolled	Thailand: 121
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	Puerto Rico: 6
Worldwide total number of subjects	872
EEA total number of subjects	137

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)	864
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and Asia. The first participant was screened on 26 December 2012. The last study visit occurred on 06 September 2017.

Pre-assignment

Screening details:

1105 participants were screened.

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	E/C/F/TAF

Arm description:

E/C/F/TAF plus E/C/F/TDF placebo for at least 144 weeks

Arm type	Experimental
Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Investigational medicinal product code	
Other name	E/C/F/TAF, Genvoya®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150/150/200/10 mg FDC tablet administered once daily

Investigational medicinal product name	E/C/F/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	E/C/F/TDF
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Arm description:

E/C/F/TDF plus E/C/F/TAF placebo for at least 144 weeks

Arm type	Active comparator
Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	E/C/F/TDF, Stribild®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150/150/200/300 mg FDC tablet administered once daily

Investigational medicinal product name	E/C/F/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]	E/C/F/TAF	E/C/F/TDF
Started	435	432
Completed	368	356
Not completed	67	76
Adverse event, serious fatal	1	1
Non- Compliance with Study Drug	4	3
Withdrew Consent	23	24
Adverse event, non-fatal	3	13
Death	1	2
Investigator's Discretion	5	2
Pregnancy	2	1
Protocol Violation	4	3
Lost to follow-up	23	26
Lack of efficacy	1	1

Notes:

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

Justification: 5 participants (E/C/F/TAF: N = 3; E/C/F/TDF: N = 2) who were randomized but not treated are not included in the subject disposition table.

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	E/C/F/TAF to E/C/F/TAF

Arm description:

After study unblinding, participants who completed 144 weeks of the study were given the option to receive open-label E/C/F/TAF FDC tablet until commercially available, or until Gilead Sciences terminated the study in that country.

Arm type	Experimental
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Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Investigational medicinal product code	
Other name	E/C/F/TAF, Genvoya®
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 150/150/200/10 mg FDC tablet administered once daily	
Arm title	E/C/F/TDF to E/C/F/TAF

Arm description:

After study unblinding, participants who completed 144 weeks of the study were given the option to receive open-label E/C/F/TAF FDC tablet until commercially available, or until Gilead Sciences terminated the study in that country.

Arm type	Experimental
Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Investigational medicinal product code	
Other name	E/C/F/TAF, Genvoya®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150/150/200/10 mg FDC tablet administered once daily

Number of subjects in period 2^[2]	E/C/F/TAF to E/C/F/TAF	E/C/F/TDF to E/C/F/TAF
Started	90	95
Completed	90	94
Not completed	0	1
Enrolled but not Treated	-	1

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: 539 participants (E/C/F/TAF: N = 278; E/C/F/TDF: N = 261) completed the Double-Blind Phase but did not enter the Open-Label Extension Phase.

Baseline characteristics

Reporting groups

Reporting group title	E/C/F/TAF
Reporting group description: E/C/F/TAF plus E/C/F/TDF placebo for at least 144 weeks	
Reporting group title	E/C/F/TDF
Reporting group description: E/C/F/TDF plus E/C/F/TAF placebo for at least 144 weeks	

Reporting group values	E/C/F/TAF	E/C/F/TDF	Total
Number of subjects	435	432	867
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	35 ± 10.0	36 ± 10.5	-
Gender categorical Units: Subjects			
Female	71	56	127
Male	364	376	740
Ethnicity Units: Subjects			
Hispanic or Latino	60	70	130
Not Hispanic or Latino	375	362	737
Race Units: Subjects			
American Indian or Alaska Native	4	5	9
Asian	76	77	153
Black	94	81	175
Native Hawaiian or Pacific Islander	1	3	4
White	250	255	505
Other	10	11	21
HIV-1 RNA Category Units: Subjects			
≤ 100,000 copies/mL	331	336	667
> 100,000 to ≤ 400,000 copies/mL	79	72	151
> 400,000 copies/mL	25	24	49
CD4 Cell Count Category Units: Subjects			
< 50 cells/μL	10	12	22
≥ 50 to < 200 cells/μL	48	41	89
≥ 200 to < 350 cells/μL	103	111	214
≥ 350 to < 500 cells/μL	122	135	257
≥ 500 cells/ μL	152	133	285
HIV Disease Status			

Units: Subjects			
Asymptomatic	402	406	808
Symptomatic HIV Infection	23	15	38
AIDS	9	10	19
Unknown	1	1	2
HIV-1 RNA (log10 copies/mL)			
Units: log10 copies/mL			
arithmetic mean	4.55	4.55	
standard deviation	± 0.682	± 0.674	-
CD4 Cell Count			
Units: cells/μL			
arithmetic mean	437	426	
standard deviation	± 223.7	± 212.3	-

End points

End points reporting groups

Reporting group title	E/C/F/TAF
Reporting group description: E/C/F/TAF plus E/C/F/TDF placebo for at least 144 weeks	
Reporting group title	E/C/F/TDF
Reporting group description: E/C/F/TDF plus E/C/F/TAF placebo for at least 144 weeks	
Reporting group title	E/C/F/TAF to E/C/F/TAF
Reporting group description: After study unblinding, participants who completed 144 weeks of the study were given the option to receive open-label E/C/F/TAF FDC tablet until commercially available, or until Gilead Sciences terminated the study in that country.	
Reporting group title	E/C/F/TDF to E/C/F/TAF
Reporting group description: After study unblinding, participants who completed 144 weeks of the study were given the option to receive open-label E/C/F/TAF FDC tablet until commercially available, or until Gilead Sciences terminated the study in that country.	

Primary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48
End point description: The percentage of participants achieving HIV-1 RNA < 50 copies/mL at Week 48 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set (participants who were randomized and received at least 1 dose of study drug) were analyzed.	
End point type	Primary
End point timeframe: Week 48	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	435	432		
Units: percentage of participants				
number (not applicable)	93.1	92.8		

Statistical analyses

Statistical analysis title	Statistical Analysis - E/C/F/TAF vs E/C/F/TDF
Statistical analysis description: Null hypothesis: the E/C/F/TAF group was $\geq 12\%$ worse than the E/C/F/TDF group with respect to the percentage of participants achieving HIV-1 RNA < 50 copies/mL at Week 48; alternative hypothesis: the E/C/F/TAF group was < 12% worse than the E/C/F/TDF group.	

Comparison groups	E/C/F/TAF v E/C/F/TDF
Number of subjects included in analysis	867
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.78 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentages
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4

Notes:

[1] - The difference in percentages and its 95.002% confidence interval (CI) were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline HIV-1 RNA and region stratum.

[2] - P-value was from the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HIV-1 RNA (\leq 100,000 or $>$ 100,000 copies/mL) and region (US vs ex-US).

Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 96 and 144

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Weeks 96 and 144
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End point description:

The percentage of participants achieving HIV-1 RNA < 50 copies/mL at Weeks 96 and 144 were analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Weeks 96 and 144

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	435	432		
Units: percentage of participants				
number (not applicable)				
Week 96	89.2	88.2		
Week 144	86.9	83.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA < 20 Copies/mL at Weeks 48, 96, and 144

End point title	Percentage of Participants With HIV-1 RNA < 20 Copies/mL at Weeks 48, 96, and 144
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End point description:

The percentage of participants achieving HIV-1 RNA < 20 copies/mL at Weeks 48, 96, and 144 were analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status.

End point type	Secondary
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End point timeframe:

Weeks 48, 96, and 144

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	435	432		
Units: percentage of participants				
number (not applicable)				
Week 48	86.4	87.3		
Week 96	84.4	83.6		
Week 144	84.6	80.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Count at Week 48

End point title	Change From Baseline in CD4+ Cell Count at Week 48
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End point description:

Participants in the Full Analysis Set with on-treatment data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 48

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	404		
Units: cells/ μ L				
arithmetic mean (standard deviation)	235 (\pm 183.1)	221 (\pm 178.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Count at Week 96

End point title	Change From Baseline in CD4+ Cell Count at Week 96
End point description: Participants in the Full Analysis Set with on-treatment data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 96	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	384		
Units: cells/ μ L				
arithmetic mean (standard deviation)	285 (\pm 203.0)	271 (\pm 208.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Count at Week 144

End point title	Change From Baseline in CD4+ Cell Count at Week 144
End point description: Participants in the Full Analysis Set with on-treatment data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 144	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	360		
Units: cells/ μ L				
arithmetic mean (standard deviation)	323 (\pm 213.1)	310 (\pm 207.2)		

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: Hip BMD was assessed by dual energy x-ray absorptiometry (DXA) scan. Participants in the Hip DXA	

Analysis Set (participants who were randomized and received at least 1 dose of study drugs and had nonmissing baseline hip BMD values) were analyzed. Participants were grouped according to the treatment they actually received. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.

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

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	394		
Units: percent change				
arithmetic mean (standard deviation)	-0.865 (\pm 3.2532)	-3.200 (\pm 3.1759)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Hip BMD at Week 96
End point description:	
Hip BMD was assessed by DXA scan. Participants in the Hip DXA Analysis Set were analyzed. Participants were grouped according to the treatment they actually received. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.	
End point type	Secondary
End point timeframe:	
Baseline; Week 96	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	365		
Units: percent change				
arithmetic mean (standard deviation)	-0.951 (\pm 3.8633)	-3.515 (\pm 3.9451)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Hip BMD at Week 144
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End point description:

Hip BMD was assessed by DXA scan. Participants in the Hip DXA Analysis Set were analyzed. Participants were grouped according to the treatment they actually received. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.

End point type	Secondary
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End point timeframe:

Baseline; Week 144

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	354		
Units: percent change				
arithmetic mean (standard deviation)	-0.826 (\pm 4.6786)	-3.475 (\pm 4.1551)		

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
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End point description:

Spine BMD was assessed by DXA scan. Participants in the Spine DXA Analysis Set (participants who were randomized and received at least 1 dose of study drugs and had nonmissing baseline spine BMD values) were analyzed. Participants were grouped according to the treatment they actually received. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.

End point type	Secondary
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End point timeframe:

Baseline; Week 48

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	396		
Units: percent change				
arithmetic mean (standard deviation)	-1.337 (\pm 3.0715)	-2.956 (\pm 3.3524)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Spine BMD at Week 96
End point description:	
Spine BMD was assessed by DXA scan. Participants in the Spine DXA Analysis Set were analyzed. Participants were grouped according to the treatment they actually received. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.	
End point type	Secondary
End point timeframe:	
Baseline; Week 96	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	367		
Units: percent change				
arithmetic mean (standard deviation)	-0.907 (\pm 4.0039)	-3.053 (\pm 3.9539)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Spine BMD at Week 144
End point description:	
Spine BMD was assessed by DXA scan. Participants in the Spine DXA Analysis Set were analyzed. Participants were grouped according to the treatment they actually received. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.	
End point type	Secondary
End point timeframe:	
Baseline; Week 144	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	352		
Units: percent change				
arithmetic mean (standard deviation)	-0.809 (\pm 4.5041)	-3.023 (\pm 4.3122)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Creatinine at Week 48

End point title	Change From Baseline in Serum Creatinine at Week 48
End point description: Participants in the Safety Analysis Set were analyzed. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.	
End point type	Secondary
End point timeframe: Baseline; Week 48	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	415	406		
Units: mg/dL				
arithmetic mean (standard deviation)	0.08 (± 0.110)	0.11 (± 0.116)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Creatinine at Week 96

End point title	Change From Baseline in Serum Creatinine at Week 96
End point description: Participants in the Safety Analysis Set were analyzed. The missing-equals-excluded approach was used, where participants with missing data were excluded from the analysis.	
End point type	Secondary
End point timeframe: Baseline; Week 96	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	386		
Units: mg/dL				
arithmetic mean (standard deviation)	0.05 (± 0.109)	0.07 (± 0.132)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Creatinine at Week 144

End point title	Change From Baseline in Serum Creatinine at Week 144
End point description: Participants in the Safety Analysis Set were analyzed. The missing-equals-excluded approach was used,	

where participants with missing data were excluded from the analysis.

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

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	362		
Units: mg/dL				
arithmetic mean (standard deviation)	0.04 (± 0.115)	0.08 (± 0.133)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Treatment-emergent Proteinuria Through Week 48

End point title	Percentage of Participants Experiencing Treatment-emergent Proteinuria Through Week 48
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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. The worst postbaseline value is presented for each participant. Participants in the Safety Analysis Set with at least 1 postbaseline urine protein value were analyzed.

End point type	Secondary
End point timeframe:	
Up to 48 weeks	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	431		
Units: percentage of participants				
number (not applicable)				
Grade 1	25.8	32.3		
Grade 2	4.6	4.9		
Grade 3	0	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Treatment-emergent

Proteinuria Through Week 96

End point title	Percentage of Participants Experiencing Treatment-emergent Proteinuria Through Week 96
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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. The worst postbaseline value is presented for each participant. Participants in the Safety Analysis Set with at least 1 postbaseline urine protein value were analyzed.

End point type	Secondary
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End point timeframe:

Up to 96 weeks

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	431		
Units: percentage of participants				
number (not applicable)				
Grade 1	28.8	33.9		
Grade 2	5.1	5.8		
Grade 3	0.2	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Treatment-emergent Proteinuria Through Week 144

End point title	Percentage of Participants Experiencing Treatment-emergent Proteinuria Through Week 144
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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. The worst postbaseline value is presented for each participant. Participants in the Safety Analysis Set with at least 1 postbaseline urine protein value were analyzed.

End point type	Secondary
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End point timeframe:

Up to 144 weeks

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	431		
Units: percentage of participants				
number (not applicable)				
Grade 1	31.3	37.1		
Grade 2	6.0	7.0		

Grade 3	0.2	0.2		
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine Retinol Binding Protein (RBP) to Creatinine Ratio at Week 48

End point title	Percent Change From Baseline in Urine Retinol Binding Protein (RBP) to Creatinine Ratio at Week 48
End point description: Urine RBP is a renal biomarker which is used to detect drug-induced kidney injury. Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 48	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	403		
Units: percent change				
median (inter-quartile range (Q1-Q3))	6.9 (-23.3 to 42.1)	51.2 (3.3 to 127.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine RBP to Creatinine Ratio at Week 96

End point title	Percent Change From Baseline in Urine RBP to Creatinine Ratio at Week 96
End point description: Urine RBP is a renal biomarker which is used to detect drug-induced kidney injury. Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 96	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	382		
Units: percent change				
median (inter-quartile range (Q1-Q3))	11.3 (-20.3 to 61.5)	75.0 (9.9 to 182.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine RBP to Creatinine Ratio at Week 144

End point title	Percent Change From Baseline in Urine RBP to Creatinine Ratio at Week 144
End point description: Urine RBP is a renal biomarker which is used to detect drug-induced kidney injury. Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 144	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	355		
Units: percent change				
median (inter-quartile range (Q1-Q3))	37.4 (-6.0 to 87.3)	106.9 (38.0 to 254.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 48

End point title	Percent Change From Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 48
End point description: Urine Beta-2-microglobulin is a renal biomarker which is used to detect drug-induced kidney injury. Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 48	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	407	397		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-32.8 (-58.7 to 1.3)	18.0 (-28.8 to 171.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 96

End point title	Percent Change From Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 96
End point description: Urine Beta-2-microglobulin is a renal biomarker which is used to detect drug-induced kidney injury. Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary
End point timeframe: Baseline; Week 96	

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	390	378		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-33.5 (-60.0 to 2.0)	32.5 (-27.8 to 205.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 144

End point title	Percent Change From Baseline in Urine Beta-2-microglobulin to Creatinine Ratio at Week 144
End point description: Urine Beta-2-microglobulin is a renal biomarker which is used to detect drug-induced kidney injury. Participants in the Safety Analysis Set with available data were analyzed.	
End point type	Secondary

End point timeframe:

Baseline; Week 144

End point values	E/C/F/TAF	E/C/F/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	351		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-24.6 (-57.5 to 13.3)	60.4 (-10.4 to 318.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-Blind Phase: Up to a maximum of 194.1 weeks plus 30 days;

Open-Label Phase: Up to a maximum of 48.3 weeks plus 30 days

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Double-Blind: E/C/F/TAF
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Reporting group description:

Adverse events reported in this group occurred during the Double-Blind Phase in participants who received E/C/F/TAF (150/150/200/10 mg) FDC tablet plus E/C/F/TDF placebo tablet administered orally once daily for 144 weeks.

Reporting group title	Double-Blind: E/C/F/TDF
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Reporting group description:

Adverse events reported in this group occurred during the Double-Blind Phase in participants who received E/C/F/TDF (150/150/200/300 mg) FDC tablet plus E/C/F/TAF placebo tablet administered orally once daily for 144 weeks.

Reporting group title	Open-Label: E/C/F/TAF to E/C/F/TAF
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Reporting group description:

Adverse events reported in this group occurred during the Open-Label Extension Phase in participants who switched from the Double-Blind E/C/F/TAF group to receive E/C/F/TAF (150/150/200/10 mg) FDC tablet until commercially available or until Gilead Sciences terminated the study in that country.

Reporting group title	Open-Label: E/C/F/TDF to E/C/F/TAF
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Reporting group description:

Adverse events reported in this group occurred during the Open-Label Extension Phase in participants who switched from the Double-Blind E/C/F/TAF group to receive E/C/F/TAF (150/150/200/10 mg) FDC tablet until commercially available or until Gilead Sciences terminated the study in that country.

Serious adverse events	Double-Blind: E/C/F/TAF	Double-Blind: E/C/F/TDF	Open-Label: E/C/F/TAF to E/C/F/TAF
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 435 (16.78%)	65 / 432 (15.05%)	0 / 90 (0.00%)
number of deaths (all causes)	2	2	0
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	2 / 435 (0.46%)	3 / 432 (0.69%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal squamous cell carcinoma			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Anogenital warts			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Burkitt's lymphoma			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Castleman's disease			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Cervix carcinoma			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Hodgkin's disease			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Laryngeal squamous cell carcinoma			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Pleomorphic adenoma			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Hypovolaemic shock			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Alcohol detoxification			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Death			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Incarcerated hernia			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Pyrexia			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Scrotal pain			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Bronchospasm			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Dyspnoea			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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 embolism			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Sleep apnoea syndrome			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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			
Suicidal ideation			
subjects affected / exposed	4 / 435 (0.92%)	2 / 432 (0.46%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 435 (0.23%)	2 / 432 (0.46%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol abuse			
subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Major depression			

subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Bipolar disorder			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Completed suicide			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Depression			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Drug use disorder			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Homicidal ideation			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Schizoaffective disorder			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Substance use disorder			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Substance-induced mood disorder			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 435 (0.46%)	0 / 432 (0.00%)	0 / 90 (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
Ankle fracture			
subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Alcohol poisoning			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Cartilage injury			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Facial bones fracture			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Fall			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Foot fracture			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Head injury			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Humerus fracture			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Injury			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Kidney contusion			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Laceration			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Liver contusion			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Lower limb fracture			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Meniscus injury			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Radius fracture			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Rib fracture			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Scrotal haematoma			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Stab wound			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Toxicity to various agents			

subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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 arthritis			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Ulna fracture			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Uterine perforation			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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			
Acute myocardial infarction			
subjects affected / exposed	2 / 435 (0.46%)	1 / 432 (0.23%)	0 / 90 (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
Tachycardia			
subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Cardiac arrest			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Cardiac failure congestive			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Cerebral infarction			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Migraine			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Paraesthesia			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Vascular headache			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Leukocytosis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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	2 / 435 (0.46%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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

Rectal haemorrhage			
subjects affected / exposed	0 / 435 (0.00%)	2 / 432 (0.46%)	0 / 90 (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
Alcoholic pancreatitis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Anal fissure			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Food poisoning			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Haemorrhoids			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Intestinal obstruction			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Proctitis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Nephrotic syndrome			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Post infection glomerulonephritis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 435 (0.46%)	0 / 432 (0.00%)	0 / 90 (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
Prognathism			

subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Retrognathia			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Rotator cuff syndrome			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	8 / 435 (1.84%)	3 / 432 (0.69%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 435 (0.00%)	3 / 432 (0.69%)	0 / 90 (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
Cellulitis			
subjects affected / exposed	0 / 435 (0.00%)	3 / 432 (0.69%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	3 / 435 (0.69%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatitis C			

subjects affected / exposed	2 / 435 (0.46%)	0 / 432 (0.00%)	0 / 90 (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
Perirectal abscess			
subjects affected / exposed	1 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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 / 435 (0.23%)	1 / 432 (0.23%)	0 / 90 (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
Staphylococcal skin infection			
subjects affected / exposed	2 / 435 (0.46%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Abscess limb			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Appendicitis perforated			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Bacterial sepsis			

subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Bronchitis			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Campylobacter infection			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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 of male external genital organ			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Dengue fever			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Epididymitis			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Eye infection syphilitic			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Hepatitis C			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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 syphilitic			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Herpes zoster disseminated			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Infected skin ulcer			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Mycobacterium avium complex infection			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Neurosyphilis			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Penile abscess			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Psoas abscess			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Pyelonephritis			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Secondary syphilis			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Septic shock			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Shigella infection			
subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Soft tissue infection			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Streptococcal bacteraemia			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Tonsillitis			

subjects affected / exposed	0 / 435 (0.00%)	1 / 432 (0.23%)	0 / 90 (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
Tooth abscess			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (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
Viral infection			
subjects affected / exposed	1 / 435 (0.23%)	0 / 432 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label: E/C/F/TDF to E/C/F/TAF		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 94 (1.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal squamous cell carcinoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anogenital warts			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Burkitt's lymphoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Castleman's disease			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hodgkin's disease			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleomorphic adenoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic shock			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Alcohol detoxification			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incarcerated hernia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scrotal pain			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol abuse			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug use disorder			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Homicidal ideation			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Schizoaffective disorder			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Substance use disorder			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Substance-induced mood disorder			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol poisoning			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cartilage injury			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kidney contusion			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver contusion			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scrotal haematoma			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stab wound			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Traumatic arthritis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine perforation			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure congestive subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Nervous system disorders			
Brain injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Cerebral infarction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Haemorrhage intracranial subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Haemorrhagic transformation stroke subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Headache subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Migraine subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Paraesthesia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 94 (0.00%) 0 / 0 0 / 0		
Syncope			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular headache			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Rectal haemorrhage				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alcoholic pancreatitis				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Food poisoning				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post infection glomerulonephritis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prognathism			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retrognathia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tenosynovitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute hepatitis C			

subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal skin infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal wall abscess				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical mycobacterial lower respiratory tract infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				

subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis of male external genital organ				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue fever				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye infection syphilitic				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis C				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis syphilitic				

subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster disseminated				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected skin ulcer				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mycobacterium avium complex infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurosyphilis				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Penile abscess				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psoas abscess				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Secondary syphilis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shigella infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Streptococcal bacteraemia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-Blind: E/C/F/TAF	Double-Blind: E/C/F/TDF	Open-Label: E/C/F/TAF to E/C/F/TAF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	380 / 435 (87.36%)	375 / 432 (86.81%)	16 / 90 (17.78%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	29 / 435 (6.67%)	29 / 432 (6.71%)	0 / 90 (0.00%)
occurrences (all)	34	32	0
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 435 (5.29%)	23 / 432 (5.32%)	0 / 90 (0.00%)
occurrences (all)	23	23	0
Nervous system disorders			
Headache			
subjects affected / exposed	69 / 435 (15.86%)	63 / 432 (14.58%)	0 / 90 (0.00%)
occurrences (all)	85	76	0
Dizziness			

subjects affected / exposed occurrences (all)	30 / 435 (6.90%) 30	25 / 432 (5.79%) 27	0 / 90 (0.00%) 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	49 / 435 (11.26%)	47 / 432 (10.88%)	0 / 90 (0.00%)
occurrences (all)	57	52	0
Pyrexia			
subjects affected / exposed	29 / 435 (6.67%)	31 / 432 (7.18%)	0 / 90 (0.00%)
occurrences (all)	31	39	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	112 / 435 (25.75%)	105 / 432 (24.31%)	1 / 90 (1.11%)
occurrences (all)	140	130	1
Nausea			
subjects affected / exposed	73 / 435 (16.78%)	84 / 432 (19.44%)	2 / 90 (2.22%)
occurrences (all)	87	99	2
Vomiting			
subjects affected / exposed	39 / 435 (8.97%)	26 / 432 (6.02%)	0 / 90 (0.00%)
occurrences (all)	50	32	0
Abdominal pain			
subjects affected / exposed	30 / 435 (6.90%)	24 / 432 (5.56%)	0 / 90 (0.00%)
occurrences (all)	32	25	0
Flatulence			
subjects affected / exposed	18 / 435 (4.14%)	29 / 432 (6.71%)	0 / 90 (0.00%)
occurrences (all)	19	30	0
Haemorrhoids			
subjects affected / exposed	20 / 435 (4.60%)	23 / 432 (5.32%)	0 / 90 (0.00%)
occurrences (all)	20	24	0
Gastrooesophageal reflux disease			
subjects affected / exposed	23 / 435 (5.29%)	20 / 432 (4.63%)	0 / 90 (0.00%)
occurrences (all)	23	21	0
Constipation			
subjects affected / exposed	15 / 435 (3.45%)	23 / 432 (5.32%)	0 / 90 (0.00%)
occurrences (all)	19	25	0
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	58 / 435 (13.33%) 73	56 / 432 (12.96%) 69	4 / 90 (4.44%) 4
Oropharyngeal pain subjects affected / exposed occurrences (all)	34 / 435 (7.82%) 41	25 / 432 (5.79%) 26	0 / 90 (0.00%) 0
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	37 / 435 (8.51%) 44	27 / 432 (6.25%) 28	1 / 90 (1.11%) 1
Acne subjects affected / exposed occurrences (all)	24 / 435 (5.52%) 25	9 / 432 (2.08%) 9	1 / 90 (1.11%) 1
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	45 / 435 (10.34%) 45	35 / 432 (8.10%) 39	0 / 90 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	37 / 435 (8.51%) 39	35 / 432 (8.10%) 36	0 / 90 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	32 / 435 (7.36%) 34	25 / 432 (5.79%) 28	0 / 90 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	50 / 435 (11.49%) 58	61 / 432 (14.12%) 70	0 / 90 (0.00%) 0
Osteopenia subjects affected / exposed occurrences (all)	41 / 435 (9.43%) 41	57 / 432 (13.19%) 57	0 / 90 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	46 / 435 (10.57%) 47	36 / 432 (8.33%) 38	0 / 90 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	34 / 435 (7.82%) 35	26 / 432 (6.02%) 30	0 / 90 (0.00%) 0

Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	92 / 435 (21.15%)	95 / 432 (21.99%)	3 / 90 (3.33%)
occurrences (all)	123	148	3
Viral upper respiratory tract infection			
subjects affected / exposed	69 / 435 (15.86%)	64 / 432 (14.81%)	2 / 90 (2.22%)
occurrences (all)	91	104	2
Syphilis			
subjects affected / exposed	55 / 435 (12.64%)	56 / 432 (12.96%)	4 / 90 (4.44%)
occurrences (all)	65	62	4
Bronchitis			
subjects affected / exposed	41 / 435 (9.43%)	29 / 432 (6.71%)	0 / 90 (0.00%)
occurrences (all)	49	37	0
Sinusitis			
subjects affected / exposed	43 / 435 (9.89%)	25 / 432 (5.79%)	0 / 90 (0.00%)
occurrences (all)	60	32	0
Influenza			
subjects affected / exposed	28 / 435 (6.44%)	32 / 432 (7.41%)	0 / 90 (0.00%)
occurrences (all)	34	36	0
Gastroenteritis			
subjects affected / exposed	28 / 435 (6.44%)	25 / 432 (5.79%)	0 / 90 (0.00%)
occurrences (all)	30	29	0
Pharyngitis			
subjects affected / exposed	26 / 435 (5.98%)	23 / 432 (5.32%)	1 / 90 (1.11%)
occurrences (all)	30	31	2
Gonorrhoea			
subjects affected / exposed	22 / 435 (5.06%)	20 / 432 (4.63%)	0 / 90 (0.00%)
occurrences (all)	28	21	0
Chlamydial infection			
subjects affected / exposed	19 / 435 (4.37%)	22 / 432 (5.09%)	0 / 90 (0.00%)
occurrences (all)	24	26	0
Folliculitis			
subjects affected / exposed	26 / 435 (5.98%)	14 / 432 (3.24%)	0 / 90 (0.00%)
occurrences (all)	28	14	0

Non-serious adverse events	Open-Label: E/C/F/TDF to E/C/F/TAF		
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Total subjects affected by non-serious adverse events subjects affected / exposed	14 / 94 (14.89%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Anogenital warts subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0 0 / 94 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0 1 / 94 (1.06%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain	1 / 94 (1.06%) 1 0 / 94 (0.00%) 0 0 / 94 (0.00%) 0		

subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Acne			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Anxiety			

subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Osteopenia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Syphilis			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Gastroenteritis			

subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences (all)	1		
Gonorrhoea			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences (all)	2		
Chlamydial infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2013	<ul style="list-style-type: none">• Updated the inclusion criteria to remove treatment during pregnancy as an allowable exception to previous ART experience• Updated the exclusion criteria to exclude subjects with positive hepatitis B surface antigen• Removed the wording "in the AM" for all fasting urine and blood tests• Updated the Management of Virologic Failure• Updated serious adverse event (SAE) reporting procedure to include both paper and electronic reporting procedures• Clarified management of subjects with eGFR_{CG} < 50 mL/min
10 December 2013	<ul style="list-style-type: none">• Clarified management of HIV-1 genotype/phenotype resistance testing and corrected the dual-energy x-ray absorptiometry (DXA) window at the ESDD visit• The prior and concomitant medication table was updated based on current company core data sheets for EVG, COBI, and STB• Guidance for management of potential posterior uveitis cases was added• Updated safety analysis section and added treatment-emergent proteinuria and urine retinol binding protein (RBP) to creatinine ratio and beta-2-microglobulin to creatinine ratio• Updated Appendix 6 of the protocol with the most current Resistance Mutations by Antiretroviral Class table
18 December 2014	<ul style="list-style-type: none">• Extended the blinded phase of the study from 96 weeks to 144 weeks of treatment• Added language from Country Specific Addendum for UK to incorporate country specific end of study information into protocol• Updated the study procedures section to remove assessment of the EQ-5D-3L questionnaire post Week 96 and at early study drug discontinuation (ESDD) visits post Week 96• Concomitant medication table was updated based on current company core data sheet for E/C/F/TAF• A new electronic case report form (eCRF) was added to assess fracture risk at baseline• Removed blood collection for bone biomarkers post Week 96• Updated criteria for plasma storage sample used for future testing to match Appendix 2 of the protocol• Added collection of bone and renal biomarkers at Week 96• Revised potential posterior uveitis information to align with the revised E/C/F/TAF Investigator Brochure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25890673>

<http://www.ncbi.nlm.nih.gov/pubmed/28282300>

<http://www.ncbi.nlm.nih.gov/pubmed/28076335>

<http://www.ncbi.nlm.nih.gov/pubmed/26892863>

<http://www.ncbi.nlm.nih.gov/pubmed/27742226>

<http://www.ncbi.nlm.nih.gov/pubmed/26829661>