Clinical trial results:
A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults

Summary

EudraCT number	2009-016758-42
Trial protocol	DE GB FR PT BE NL AT ES DK IT SE
Global end of trial date	18 September 2014

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-236-0103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01106586
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, clinical.trials@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, clinical.trials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of Stribild®, a single tablet regimen (STR) containing fixed doses of elvitegravir (EVG)/cobicistat (COBI [GS-9350])/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) versus ritonavir-boosted atazanavir (ATV/r) plus the standard of care nucleoside reverse transcriptase inhibitor (NRTI) backbone FTC/TDF. ATV/r + FTC/TDF was selected as the active comparator for this study as it is a preferred protease inhibitor-based regimen in guidelines for the treatment of HIV-1 infected, antiretroviral treatment-naive 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	06 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Australia: 62
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	Thailand: 11

Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 387
Country: Number of subjects enrolled	Mexico: 5
Worldwide total number of subjects	715
EEA total number of subjects	207

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)	709
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 146 sites in 16 countries. The first participant was screened on 06 April 2010. The last study visit occurred on 18 September 2014.

Pre-assignment

Screening details:

1017 subjects were screened.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Stribild

Arm description:

Stribild plus placebo to match ATV/r + FTC/TDF once daily for the duration of the study

Arm type	Experimental
Investigational medicinal product name	Stribild
Investigational medicinal product code	
Other name	EVG/COBI/FTC/TDF
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Stribild (elvitegravir [EVG] 150 mg/cobicistat [COBI] 150 mg/emtricitabine [FTC] 200 mg/tenofovir disoproxil fumarate [TDF] 300 mg) administered orally once daily

Investigational medicinal product name	ATV/r placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match ritonavir-boosted atazanavir (ATV/r) administered orally once daily

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

Dosage and administration details:

Placebo to match FTC plus TDF or FTC/TDF administered orally once daily

Arm title	ATV/r + FTC/TDF

Arm description:

ATV/r + FTC/TDF plus placebo to match Stribild once daily for the duration of the study

Arm type	Active comparator

Investigational medicinal product name	ATV/r
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ritonavir-boosted atazanavir (ATV/r 300/100 mg) administered orally once daily

Investigational medicinal product name	FTC + TDF
Investigational medicinal product code	
Other name	Emtriva®, Viread®, Truvada®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

FTC 200 mg plus TDF 300 mg administered either as FTC tablet plus TDF tablet or as FTC/TDF fixed dose combination tablet orally once daily.

Investigational medicinal product name	Stribild placebo
Investigational medicinal product code	
Other name	EVG/COBI/FTC/TDF
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Stribild administered orally once daily

Number of subjects in period 1[1]	Stribild	ATV/r + FTC/TDF
Started	353	355
Completed	68	70
Not completed	285	285
Participant joined other study	212	197
Adverse event, non-fatal	9	15
Protocol violation	1	-
Death	1	3
Pregnancy	2	2
Investigator's discretion	5	8
Withdrew consent	18	30
Lost to follow-up	24	20
Participant noncompliance	12	10
Lack of efficacy	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: 7 participants who were randomized but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	Stribild
Reporting group description:	
Stribild plus placebo to match ATV/r + FTC/TDF once daily for the duration of the study	
Reporting group title	ATV/r + FTC/TDF
Reporting group description:	
ATV/r + FTC/TDF plus placebo to match Stribild once daily for the duration of the study	

Reporting group values	Stribild	ATV/r + FTC/TDF	Total
Number of subjects	353	355	708
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	38	39	
standard deviation	± 10.5	± 9.8	-
Gender categorical Units: Subjects			
Female	29	39	68
Male	324	316	640
Race Units: Subjects			
American Indian or Alaska Native	2	3	5
Asian	17	17	34
Black or African Heritage	72	47	119
Native Hawaiian or Pacific Islander	1	2	3
White	250	277	527
Other	11	9	20
HIV Disease Status Units: Subjects			
Asymptomatic	285	293	578
Symptomatic HIV Infections	36	38	74
AIDS	32	24	56
Hepatitis B Virus (HBV) Infection Status Units: Subjects			
Negative	347	346	693
Positive	5	7	12
Indeterminate	0	1	1
Not done	1	1	2
Hepatitis C Virus (HCV) Infection Status Units: Subjects			
Negative	335	344	679
Positive	18	10	28
Indeterminate	0	0	0
Not done	0	1	1

HIV-1 RNA Category Units: Subjects			
≤ 100,000 copies/mL	203	214	417
> 100,000 copies/mL	150	141	291
CD4 Cell Count (/µL) Units: Subjects			
≤ 50 µL	12	5	17
51 to ≤ 200 µL	42	34	76
201 to ≤ 350 µL	122	124	246
351 to ≤ 500 µL	122	122	244
> 500 µL	55	70	125

End points

End points reporting groups

Reporting group title	Stribild
Reporting group description:	
Stribild plus placebo to match ATV/r + FTC/TDF once daily for the duration of the study	
Reporting group title	ATV/r + FTC/TDF
Reporting group description:	
ATV/r + FTC/TDF plus placebo to match Stribild once daily for the duration of the study	

Primary: The Percentage of Participants With Virologic Success Using the Food and Drug Administration (FDA)-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 Ribonucleic Acid (RNA) < 50 Copies/mL at Week 48

End point title	The Percentage of Participants With Virologic Success Using the Food and Drug Administration (FDA)-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 Ribonucleic Acid (RNA) < 50 Copies/mL at Week 48

End point description:

ITT analysis set: participants who were randomized into the study and received at least 1 dose of study drug.

To preserve the overall alpha level: 0.05, accounting for 2 interim analyses for Independent Data Monitoring Committee meetings, the 95.2% CI in the statistical analysis was computed using normal approximation stratified by baseline HIV-1 RNA (≤ 100,000 or > 100,000 copies/mL).

End point type	Primary
End point timeframe:	
Week 48	

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	355		
Units: percentage of participants				
number (not applicable)	89.5	86.8		

Statistical analyses

Statistical analysis title	Difference in response rates

Statistical analysis description:

The null hypothesis was that the Stribild group is at least 12% worse than the ATV/r + FTC/TDF group with respect to percentage of participants achieving HIV-1 RNA < 50 copies/mL (response rate as defined by the snapshot analysis algorithm) at Week 48; the alternative hypothesis was that the response rate in the Stribild group is less than 12% worse than that in the ATV/r + FTC/TDF Group.

Comparison groups	Stribild v ATV/r + FTC/TDF

Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in response rates
Point estimate	3
Confidence interval	
level	95.2 %
sides	2-sided
lower limit	-1.9
upper limit	7.8

Notes:

[1] - A total of 700 HIV-1 infected participants, randomized in a 1:1 ratio to 2 groups would achieve at least 95% power to establish noninferiority in Week 48 response (HIV-1 RNA < 50 copies/mL per the FDA-defined snapshot analysis) rate difference between the 2 groups. For sample size and power computation, it was assumed that both treatment groups have a response rate of 0.795, a noninferiority margin of 0.12, and that the significance level of the test is at a one-sided, 0.025 level.

Secondary: The Percentage of Participants With Virologic Success Using the FDA-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 RNA < 50 Copies/mL at Week 96

End point title	The Percentage of Participants With Virologic Success Using the FDA-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 RNA < 50 Copies/mL at Week 96
End point description:	
ITT Analysis Set	
End point type	Secondary
End point timeframe:	
Week 96	

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	355		
Units: percentage of participants				
number (not applicable)	83.3	82.3		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Participants With Virologic Success Using the FDA-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 RNA < 50 Copies/mL at Week 144

End point title	The Percentage of Participants With Virologic Success Using the FDA-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 RNA < 50 Copies/mL at Week 144
End point description:	
ITT Analysis Set	
End point type	Secondary

End point timeframe:

Week 144

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	355		
Units: percentage of participants				
number (not applicable)	77.6	74.6		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Participants With Virologic Success Using the FDA-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 RNA < 50 Copies/mL at Week 192

End point title	The Percentage of Participants With Virologic Success Using the FDA-Defined Snapshot Analysis as Determined by the Achievement of HIV-1 RNA < 50 Copies/mL at Week 192

End point description:

Week 192 modified intent-to-treat (MITT) Analysis Set: Participants in the ITT analysis set, excluding those who either 1) transferred to other Gilead-sponsored studies after completing their Week 144 Visit and before the lower limit of the Week 192 analysis window, or 2) prematurely discontinued study drug prior to the Week 144 Visit.

End point type	Secondary

End point timeframe:

Week 192

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	78		
Units: percentage of participants				
number (not applicable)	78.4	73.1		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 50 Copies/mL at Week 48 Using the FDA-defined Time to Loss of Virologic Response (TLOVR) Algorithm

End point title	The Percentage of Participants Achieving and Maintaining

	Confirmed HIV-1 RNA < 50 Copies/mL at Week 48 Using the FDA-defined Time to Loss of Virologic Response (TLOVR) Algorithm
End point description: ITT analysis set	
End point type	Secondary
End point timeframe: Week 48	

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	355		
Units: percentage of participants				
number (not applicable)	86.1	84.8		

Statistical analyses

No statistical analyses for this end point

Secondary: The Change From Baseline in Cluster Determinant 4 (CD4) Cell Count at Weeks 48, 96, 144, and 192

End point title	The Change From Baseline in Cluster Determinant 4 (CD4) Cell Count at Weeks 48, 96, 144, and 192
End point description: ITT analysis set. The missing = excluded (M = E) method was used in which participants with missing data were excluded from analysis. Change = value of the relevant time point minus the baseline value.	
End point type	Secondary
End point timeframe: Baseline; Weeks 48, 96, 144, and 192	

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	355		
Units: cells/µL				
arithmetic mean (standard deviation)				
Change at Wk 48 (Stribild, n=334; ATV/r, n=321)	207 (± 164.2)	211 (± 160.3)		
Change at Wk 96 (Stribild, n=317; ATV/r, n=315)	256 (± 166.8)	261 (± 188)		
Change at Wk 144 (Stribild, n=297; ATV/r, n=286)	280 (± 159.8)	293 (± 211.5)		
Change at Wk 192 (Stribild, n=69; ATV/r, n=72)	338 (± 186.8)	340 (± 224.2)		

Statistical analyses

No statistical analyses for this end point

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

End point title	The Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48

End point description:

ITT analysis set. The missing = failure (M = F) method was used in which all missing data were considered as failure (HIV-1 RNA ≥ 50 copies/mL).

End point type	Secondary

End point timeframe:

Week 48

End point values	Stribild	ATV/r + FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	355		
Units: percentage of participants				
number (not applicable)	91.5	88.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events are reported from baseline to the end of treatment (up to maximum of 216 weeks) plus 30 days	
Adverse event reporting additional description:	
Safety Analysis Set: participants who were randomized into the study and received at least 1 dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Stribild
Reporting group description:	
Stribild plus placebo to match ATV/r + FTC/TDF once daily for the duration of the study	
Reporting group title	ATV/r + FTC/TDF
Reporting group description:	
ATV/r + FTC/TDF plus placebo to match Stribild once daily for the duration of the study	

Serious adverse events	Stribild	ATV/r + FTC/TDF	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 353 (16.43%)	62 / 355 (17.46%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anogenital warts			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma stage II			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burkitt's lymphoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			

subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Treatment noncompliance			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 353 (0.85%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	2 / 353 (0.57%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			

subjects affected / exposed	1 / 353 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	2 / 353 (0.57%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive symptom			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic stress disorder			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance abuse			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 353 (0.57%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxicity to various agents			
subjects affected / exposed	1 / 353 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			

subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post concussion syndrome			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital ureteric anomaly			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 353 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 353 (0.57%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Critical illness polyneuropathy			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 353 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	2 / 353 (0.57%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc displacement			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neck pain			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 353 (0.28%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 353 (0.85%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 353 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 353 (0.57%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 353 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 353 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis cryptosporidial			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site infection			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphogranuloma venereum			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant syphilis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis enteroviral			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			

subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary syphilis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shigella infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 353 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Stribild	ATV/r + FTC/TDF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	326 / 353 (92.35%)	326 / 355 (91.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anorectal human papilloma virus infection			
subjects affected / exposed	21 / 353 (5.95%)	12 / 355 (3.38%)	
occurrences (all)	23	12	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 353 (6.80%)	12 / 355 (3.38%)	
occurrences (all)	24	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	60 / 353 (17.00%)	60 / 355 (16.90%)	
occurrences (all)	66	66	
Pyrexia			
subjects affected / exposed	23 / 353 (6.52%)	22 / 355 (6.20%)	
occurrences (all)	27	26	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	17 / 353 (4.82%)	19 / 355 (5.35%)	
occurrences (all)	19	21	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	38 / 353 (10.76%)	46 / 355 (12.96%)	
occurrences (all)	44	52	
Oropharyngeal pain			
subjects affected / exposed	19 / 353 (5.38%)	32 / 355 (9.01%)	
occurrences (all)	27	34	
Psychiatric disorders			
Depression			
subjects affected / exposed	47 / 353 (13.31%)	52 / 355 (14.65%)	
occurrences (all)	53	55	
Insomnia			
subjects affected / exposed	37 / 353 (10.48%)	36 / 355 (10.14%)	
occurrences (all)	42	39	
Anxiety			
subjects affected / exposed	22 / 353 (6.23%)	29 / 355 (8.17%)	
occurrences (all)	24	33	
Nervous system disorders			
Headache			
subjects affected / exposed	67 / 353 (18.98%)	55 / 355 (15.49%)	
occurrences (all)	81	67	
Dizziness			
subjects affected / exposed	25 / 353 (7.08%)	28 / 355 (7.89%)	
occurrences (all)	27	30	
Paraesthesia			
subjects affected / exposed	9 / 353 (2.55%)	21 / 355 (5.92%)	
occurrences (all)	11	22	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	23 / 353 (6.52%)	16 / 355 (4.51%)	
occurrences (all)	26	16	
Eye disorders			
Ocular icterus			
subjects affected / exposed	2 / 353 (0.57%)	52 / 355 (14.65%)	
occurrences (all)	2	62	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	99 / 353 (28.05%)	121 / 355 (34.08%)	
occurrences (all)	130	160	
Nausea			
subjects affected / exposed	80 / 353 (22.66%)	78 / 355 (21.97%)	
occurrences (all)	103	93	
Vomiting			
subjects affected / exposed	26 / 353 (7.37%)	35 / 355 (9.86%)	
occurrences (all)	36	41	
Abdominal pain			
subjects affected / exposed	25 / 353 (7.08%)	26 / 355 (7.32%)	
occurrences (all)	30	29	
Flatulence			
subjects affected / exposed	16 / 353 (4.53%)	32 / 355 (9.01%)	
occurrences (all)	17	34	
Constipation			
subjects affected / exposed	20 / 353 (5.67%)	14 / 355 (3.94%)	
occurrences (all)	22	15	
Dyspepsia			
subjects affected / exposed	13 / 353 (3.68%)	19 / 355 (5.35%)	
occurrences (all)	13	21	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 353 (0.00%)	34 / 355 (9.58%)	
occurrences (all)	0	40	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	30 / 353 (8.50%)	37 / 355 (10.42%)	
occurrences (all)	41	40	
Night sweats			
subjects affected / exposed	10 / 353 (2.83%)	18 / 355 (5.07%)	
occurrences (all)	12	18	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	46 / 353 (13.03%)	37 / 355 (10.42%)	
occurrences (all)	55	41	
Arthralgia			

subjects affected / exposed	35 / 353 (9.92%)	32 / 355 (9.01%)	
occurrences (all)	39	37	
Pain in extremity			
subjects affected / exposed	22 / 353 (6.23%)	21 / 355 (5.92%)	
occurrences (all)	25	25	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	86 / 353 (24.36%)	97 / 355 (27.32%)	
occurrences (all)	157	156	
Nasopharyngitis			
subjects affected / exposed	53 / 353 (15.01%)	57 / 355 (16.06%)	
occurrences (all)	70	91	
Bronchitis			
subjects affected / exposed	47 / 353 (13.31%)	42 / 355 (11.83%)	
occurrences (all)	59	52	
Sinusitis			
subjects affected / exposed	35 / 353 (9.92%)	38 / 355 (10.70%)	
occurrences (all)	41	52	
Syphilis			
subjects affected / exposed	27 / 353 (7.65%)	29 / 355 (8.17%)	
occurrences (all)	28	35	
Influenza			
subjects affected / exposed	31 / 353 (8.78%)	24 / 355 (6.76%)	
occurrences (all)	39	29	
Gastroenteritis			
subjects affected / exposed	18 / 353 (5.10%)	28 / 355 (7.89%)	
occurrences (all)	19	30	
Folliculitis			
subjects affected / exposed	19 / 353 (5.38%)	22 / 355 (6.20%)	
occurrences (all)	21	23	
Pharyngitis			
subjects affected / exposed	23 / 353 (6.52%)	18 / 355 (5.07%)	
occurrences (all)	27	19	
Urinary tract infection			
subjects affected / exposed	18 / 353 (5.10%)	20 / 355 (5.63%)	
occurrences (all)	21	29	

Chlamydial infection			
subjects affected / exposed	18 / 353 (5.10%)	17 / 355 (4.79%)	
occurrences (all)	21	20	
Herpes zoster			
subjects affected / exposed	15 / 353 (4.25%)	20 / 355 (5.63%)	
occurrences (all)	15	21	
Onychomycosis			
subjects affected / exposed	21 / 353 (5.95%)	13 / 355 (3.66%)	
occurrences (all)	23	13	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	21 / 353 (5.95%)	19 / 355 (5.35%)	
occurrences (all)	21	19	
Decreased appetite			
subjects affected / exposed	14 / 353 (3.97%)	19 / 355 (5.35%)	
occurrences (all)	16	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2010	Updated statistical objectives, endpoints, and methods based on feedback from the US FDA.
30 January 2012	Extended the blinded phase of the study from 96 weeks of treatment to 192 weeks of treatment.

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/22748590

http://www.ncbi.nlm.nih.gov/pubmed/23337366

http://www.ncbi.nlm.nih.gov/pubmed/24346640