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

Summary

EudraCT number	2009-016759-22
Trial protocol	DE BE NL FR PT GB AT ES DK IT SE
Global end of trial date	17 April 2015

Results information

Result version number	v1 (current)
This version publication date	01 May 2016
First version publication date	01 May 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-216-0114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01108510
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, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the safety and efficacy of a regimen containing cobicistat-boosted atazanavir (ATV+COBI) plus emtricitabine/tenofovir disoproxil fumarate (Truvada®; FTC/TDF) fixed-dose combination (FDC) versus ritonavir-boosted atazanavir (ATV+RTV) plus FTC/TDF FDC in HIV-1 infected, antiretroviral treatment-naive adults.

Participants were randomized in a 1:1 ratio. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Protection of trial subjects:

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

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 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	United States: 248
Country: Number of subjects enrolled	Thailand: 66
Country: Number of subjects enrolled	Dominican Republic: 58
Country: Number of subjects enrolled	Canada: 44
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Mexico: 35
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Austria: 18

Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	698
EEA total number of subjects	182

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)	694
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in a total of 144 study sites in Asia, Australia, Europe, and South and North America. The first participant was screened on 26 April 2010. The last study visit occurred on 17 April 2015.

Pre-assignment

Screening details:

867 participants 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	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ATV+COBI+FTC/TDF

Arm description:

COBI + RTV placebo + ATV + FTC/TDF once daily

Arm type	Experimental
Investigational medicinal product name	Cobicistat
Investigational medicinal product code	
Other name	Tybost®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cobicitat (COBI) (150 mg) once daily

Investigational medicinal product name	Atazanavir
Investigational medicinal product code	
Other name	Reyataz®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atazanavir (ATV) (300 mg) once daily

Investigational medicinal product name	Emtricitabine/tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Truvada®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) (200/300 mg) FDC once daily

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

Dosage and administration details: Ritonavir placebo once daily	

Arm title	ATV+RTV+FTC/TDF
Arm description: RTV + COBI placebo + ATV + FTC/TDF once daily	
Arm type	Active comparator
Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Ritonavir (RTV) (100 mg) once daily	
Investigational medicinal product name	Atazanavir
Investigational medicinal product code	
Other name	Reyataz®
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Atazanavir (ATV) (300 mg) once daily	
Investigational medicinal product name	Emtricitabine/tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	Truvada®
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) (200/300 mg) FDC once daily	
Investigational medicinal product name	Cobicistat placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Cobicitat placebo once daily	

Number of subjects in period 1[1]	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF
Started	344	348
Completed	70	81
Not completed	274	267
Withdrew Consent	21	15
Adverse event, non-fatal	26	19
Participant Noncompliance	5	7

Death	1	1
Investigator's Discretion	12	10
Pregnancy	-	3
Joined Another Gilead-sponsored Study	186	195
Lost to follow-up	20	17
Lack of efficacy	3	-

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 in the ATV+COBI+FTC/TDF group and 1 participant in the ATV+RTV+FTC/TDF group who were randomized but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	ATV+COBI+FTC/TDF
Reporting group description: COBI + RTV placebo + ATV + FTC/TDF once daily	
Reporting group title	ATV+RTV+FTC/TDF
Reporting group description: RTV + COBI placebo + ATV + FTC/TDF once daily	

Reporting group values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF	Total
Number of subjects	344	348	692
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	37	38	
standard deviation	± 9.8	± 9.6	-
Gender, Male/Female Units: participants			
Female	57	61	118
Male	287	287	574
Ethnicity Units: Subjects			
Hispanic or Latino	97	92	189
Not Hispanic or Latino	245	253	498
Unknown or Not Reported	2	3	5
Race Units: Subjects			
American Indian or Alaska Native	1	2	3
Asian	44	37	81
Black or African Heritage	65	63	128
Native Hawaiian or Pacific Islander	1	1	2
White	198	215	413
Not Permitted	2	3	5
Other	33	27	60
HIV-1 RNA Category Units: Subjects			
≤ 100,000 copies/mL	212	205	417
> 100,000 copies/mL	132	143	275
CD4 Cell Count Category Units: Subjects			
≤ 50 cells/µL	11	12	23
51 to ≤ 200 cells/µL	49	45	94
201 to ≤ 350 cells/µL	114	126	240
351 to ≤ 500 cells/µL	123	117	240
> 500 cells/µL	47	48	95

HIV Disease Status Units: Subjects			
Asymptomatic	285	292	577
Symptomatic HIV Infections	31	32	63
AIDS	28	24	52
Hepatitis B Surface Antigen Status Units: Subjects			
Positive	16	9	25
Negative	328	339	667
Hepatitis C Antibody Status Units: Subjects			
Positive	21	16	37
Negative	323	331	654
Indeterminate	0	1	1
HIV-1 RNA Units: log10 copies/mL			
arithmetic mean	4.81	4.84	
standard deviation	± 0.585	± 0.594	-
Cluster of differentiation (CD4) Cell Count Units: cells/µL			
arithmetic mean	353	351	
standard deviation	± 170.5	± 175.5	-

End points

End points reporting groups

Reporting group title	ATV+COBI+FTC/TDF
Reporting group description: COBI + RTV placebo + ATV + FTC/TDF once daily	
Reporting group title	ATV+RTV+FTC/TDF
Reporting group description: RTV + COBI placebo + ATV + FTC/TDF once daily	

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 with HIV-1 RNA < 50 copies/mL at Week 48 was analyzed using the snapshot algorithm, which defines a participant's virologic response status using only the viral load at the prespecified time point within an allowed window of time, along with study drug discontinuation status.

Intent-to-Treat (ITT) Analysis Set: participants who were randomized and received at least one dose of study drug

End point type	Primary
End point timeframe: Week 48	

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	348		
Units: percentage of participants				
number (not applicable)	85.2	87.4		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

700 planned subjects had 95% power to evaluate noninferiority assuming a response rate of 79.5% for both arms and a noninferiority margin of 12%. Null hypothesis: ATV+COBI+FTC/TDF group was at least 12% worse than the ATV+RTV+FTC/TDF group; alternative hypothesis: ATV+COBI+FTC/TDF group was less than 12% worse than the ATV+RTV+FTC/TDF group. ATV+COBI+FTC/TDF was noninferior if the lower bound of the 2-sided 95.2% confidence interval (CI) (COBI group - RTV group) was > -12%.

Comparison groups	ATV+RTV+FTC/TDF v ATV+COBI+FTC/TDF

Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in percentages
Point estimate	-2.2
Confidence interval	
level	95.2 %
sides	2-sided
lower limit	-7.4
upper limit	3

Notes:

[1] - Difference in percentages of success and its 95.2% confidence interval (CI) were calculated based on baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel (MH) proportion.

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

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 96

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 96 was analyzed using the snapshot algorithm.

ITT Analysis Set

End point type	Secondary

End point timeframe:

Week 96

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	348		
Units: percentage of participants				
number (not applicable)	77.9	79.3		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The null hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was at least 12% worse than the response rate in ATV+RTV+FTC/TDF group; the alternative hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was less than 12% worse than that in the ATV+RTV+FTC/TDF group.

Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in percentages
Point estimate	-1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	4.7

Notes:

[2] - Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

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

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 144

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 144 was analyzed using the snapshot algorithm.

ITT Analysis Set

End point type	Secondary

End point timeframe:

Week 144

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	348		
Units: percentage of participants				
number (not applicable)	72.1	74.1		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The null hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was at least 12% worse than the response rate in ATV+RTV+FTC/TDF group; the alternative hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was less than 12% worse than that in the ATV+RTV+FTC/TDF group.

Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in percentages
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	4.5

Notes:

[3] - Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 192

End point title	Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 192

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 192 was analyzed using the snapshot algorithm.

Week 192 Modified ITT Analysis Set: includes 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	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	69		
Units: percentage of participants				
number (not applicable)	71.6	79.7		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The null hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was at least 12% worse than the response rate in ATV+RTV+FTC/TDF group; the alternative hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was less than 12% worse than that in the ATV+RTV+FTC/TDF group.

Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in percentages
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.2
upper limit	6.3

Notes:

[4] - Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

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

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

End point description:

Participants in the ITT Analysis Set with available change data at Week 48 were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	313	324		
Units: cells/µL				
arithmetic mean (standard deviation)	213 (± 151)	219 (± 150.4)		

Statistical analyses

Statistical analysis title	Difference in least squares mean (LSM)
Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	637
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.67 [6]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	18

Notes:

[5] - Comparative analysis

[6] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

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 ITT Analysis Set with available change data at Week 96 were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	311		
Units: cells/µL				
arithmetic mean (standard deviation)	277 (± 176.8)	287 (± 181.5)		

Statistical analyses

Statistical analysis title	Difference in LSM
Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	611
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.51 [8]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38
upper limit	19

Notes:

[7] - Comparative analysis

[8] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

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 ITT Analysis Set with available change data at Week 144 were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline to Week 144	

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	275	288		
Units: cells/µL				
arithmetic mean (standard deviation)	310 (± 188)	332 (± 199.8)		

Statistical analyses

Statistical analysis title	Difference in LSM
Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.18 [10]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	-22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54
upper limit	10

Notes:

[9] - Comparative analysis

[10] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

Secondary: Change From Baseline in CD4 Cell Count at Week 192

End point title	Change From Baseline in CD4 Cell Count at Week 192
End point description:	
Participants in the ITT Analysis Set with available change data at Week 192 were analyzed.	
End point type	Secondary
End point timeframe:	
Baseline to Week 192	

End point values	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	83		
Units: cells/µL				
arithmetic mean (standard deviation)	350 (± 191.3)	343 (± 190.7)		

Statistical analyses

Statistical analysis title	Difference in LSM
Comparison groups	ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.84 [12]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-55
upper limit	67

Notes:

[11] - Comparative analysis

[12] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline through end of study drug treatment (average exposure: ATV+COBI+FTC/TDF group = 141.3 weeks; ATV+RTV+FTC/TDF group = 143.0 weeks) plus 30 days	
Adverse event reporting additional description:	
Safety Analysis Set: participants who were randomized and received at least one dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	ATV+COBI+FTC/TDF
Reporting group description:	
COBI + RTV placebo + ATV + FTC/TDF once daily	
Reporting group title	ATV+RTV+FTC/TDF
Reporting group description:	
RTV + COBI placebo + ATV + FTC/TDF once daily	

Serious adverse events	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 344 (18.60%)	50 / 348 (14.37%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 344 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anogenital warts			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (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 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			

subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 344 (0.58%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 344 (0.87%)	3 / 348 (0.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 344 (0.87%)	3 / 348 (0.86%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (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			
Immune reconstitution inflammatory syndrome			

subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	2 / 344 (0.58%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Priapism			
subjects affected / exposed	0 / 344 (0.00%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colpocele			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 344 (0.58%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (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 / 344 (0.87%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	0 / 344 (0.00%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	2 / 344 (0.58%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma scale abnormal			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count increased			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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 / 344 (0.29%)	0 / 348 (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	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Overdose			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (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 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 344 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			

subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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			
Anaemia			
subjects affected / exposed	1 / 344 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	2 / 344 (0.58%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal mass			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (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	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitic rash			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 344 (0.29%)	4 / 348 (1.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	2 / 344 (0.58%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fanconi syndrome acquired			
subjects affected / exposed	1 / 344 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Cellulitis			
subjects affected / exposed	2 / 344 (0.58%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 344 (0.29%)	3 / 348 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 344 (0.58%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 344 (0.58%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	4 / 344 (1.16%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 344 (0.29%)	2 / 348 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	3 / 344 (0.87%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 344 (0.58%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	1 / 344 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chancroid			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis shigella			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital abscess			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gonorrhoea			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis toxoplasmal			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			

subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (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	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
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	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 344 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 344 (0.58%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 344 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 344 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ATV+COBI+FTC/TDF	ATV+RTV+FTC/TDF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	311 / 344 (90.41%)	312 / 348 (89.66%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	24 / 344 (6.98%)	16 / 348 (4.60%)	
occurrences (all)	26	18	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 344 (5.23%)	23 / 348 (6.61%)	
occurrences (all)	18	29	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 344 (11.05%)	34 / 348 (9.77%)	
occurrences (all)	41	36	
Pyrexia			
subjects affected / exposed	36 / 344 (10.47%)	30 / 348 (8.62%)	
occurrences (all)	43	38	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 344 (10.47%)	29 / 348 (8.33%)	
occurrences (all)	42	35	
Nasal congestion			
subjects affected / exposed	15 / 344 (4.36%)	29 / 348 (8.33%)	
occurrences (all)	16	32	
Oropharyngeal pain			
subjects affected / exposed	20 / 344 (5.81%)	24 / 348 (6.90%)	
occurrences (all)	22	31	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	26 / 344 (7.56%)	29 / 348 (8.33%)	
occurrences (all)	29	30	
Depression			
subjects affected / exposed	25 / 344 (7.27%)	28 / 348 (8.05%)	
occurrences (all)	30	29	
Anxiety			

subjects affected / exposed	19 / 344 (5.52%)	16 / 348 (4.60%)	
occurrences (all)	19	18	
Nervous system disorders			
Headache			
subjects affected / exposed	57 / 344 (16.57%)	73 / 348 (20.98%)	
occurrences (all)	75	111	
Dizziness			
subjects affected / exposed	32 / 344 (9.30%)	28 / 348 (8.05%)	
occurrences (all)	36	32	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	18 / 344 (5.23%)	26 / 348 (7.47%)	
occurrences (all)	21	30	
Eye disorders			
Ocular icterus			
subjects affected / exposed	69 / 344 (20.06%)	79 / 348 (22.70%)	
occurrences (all)	81	88	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	76 / 344 (22.09%)	96 / 348 (27.59%)	
occurrences (all)	105	117	
Nausea			
subjects affected / exposed	66 / 344 (19.19%)	66 / 348 (18.97%)	
occurrences (all)	79	77	
Vomiting			
subjects affected / exposed	34 / 344 (9.88%)	25 / 348 (7.18%)	
occurrences (all)	40	28	
Abdominal pain			
subjects affected / exposed	22 / 344 (6.40%)	26 / 348 (7.47%)	
occurrences (all)	22	28	
Haemorrhoids			
subjects affected / exposed	23 / 344 (6.69%)	21 / 348 (6.03%)	
occurrences (all)	24	21	
Abdominal pain upper			
subjects affected / exposed	19 / 344 (5.52%)	23 / 348 (6.61%)	
occurrences (all)	25	27	
Flatulence			

subjects affected / exposed	28 / 344 (8.14%)	10 / 348 (2.87%)	
occurrences (all)	29	10	
Dyspepsia			
subjects affected / exposed	15 / 344 (4.36%)	21 / 348 (6.03%)	
occurrences (all)	16	26	
Abdominal distension			
subjects affected / exposed	16 / 344 (4.65%)	19 / 348 (5.46%)	
occurrences (all)	18	19	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	76 / 344 (22.09%)	61 / 348 (17.53%)	
occurrences (all)	94	68	
Hyperbilirubinaemia			
subjects affected / exposed	42 / 344 (12.21%)	39 / 348 (11.21%)	
occurrences (all)	74	68	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	26 / 344 (7.56%)	31 / 348 (8.91%)	
occurrences (all)	30	32	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	34 / 344 (9.88%)	42 / 348 (12.07%)	
occurrences (all)	42	52	
Arthralgia			
subjects affected / exposed	19 / 344 (5.52%)	19 / 348 (5.46%)	
occurrences (all)	23	20	
Myalgia			
subjects affected / exposed	18 / 344 (5.23%)	20 / 348 (5.75%)	
occurrences (all)	18	24	
Pain in extremity			
subjects affected / exposed	18 / 344 (5.23%)	15 / 348 (4.31%)	
occurrences (all)	22	17	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	59 / 344 (17.15%)	79 / 348 (22.70%)	
occurrences (all)	108	148	

Upper respiratory tract infection			
subjects affected / exposed	67 / 344 (19.48%)	65 / 348 (18.68%)	
occurrences (all)	99	77	
Bronchitis			
subjects affected / exposed	33 / 344 (9.59%)	33 / 348 (9.48%)	
occurrences (all)	38	44	
Sinusitis			
subjects affected / exposed	28 / 344 (8.14%)	28 / 348 (8.05%)	
occurrences (all)	41	33	
Urinary tract infection			
subjects affected / exposed	25 / 344 (7.27%)	25 / 348 (7.18%)	
occurrences (all)	41	36	
Syphilis			
subjects affected / exposed	23 / 344 (6.69%)	26 / 348 (7.47%)	
occurrences (all)	26	32	
Influenza			
subjects affected / exposed	25 / 344 (7.27%)	19 / 348 (5.46%)	
occurrences (all)	26	23	
Pharyngitis			
subjects affected / exposed	17 / 344 (4.94%)	27 / 348 (7.76%)	
occurrences (all)	19	31	
Oral candidiasis			
subjects affected / exposed	21 / 344 (6.10%)	19 / 348 (5.46%)	
occurrences (all)	29	26	
Gastroenteritis			
subjects affected / exposed	12 / 344 (3.49%)	20 / 348 (5.75%)	
occurrences (all)	13	21	
Tinea pedis			
subjects affected / exposed	18 / 344 (5.23%)	11 / 348 (3.16%)	
occurrences (all)	19	12	
Folliculitis			
subjects affected / exposed	18 / 344 (5.23%)	7 / 348 (2.01%)	
occurrences (all)	23	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2010	The first exclusion criterion was revised to clarify that subjects with an AIDS-defining diagnosis of a CD4-positive T lymphocyte count < 200/µL or a CD4-positive T lymphocyte count < 14% of the total lymphocyte count within 30 days prior to screening were not excluded from participation in the study.
03 February 2012	Extended the blinded phase of the study from 96 weeks of treatment to 192 weeks of treatment; updated the introduction section of the protocol to reflect updated treatment guidelines, new information gathered from ongoing studies, and safety information included in the third edition of the COBI investigator's brochure; added additional testing for plasma storage samples and urine storage samples collected at baseline and at Weeks 2, 4, 24, and 48; updated the analysis schedule due to the extension of the blinded phase of study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23532097

http://www.ncbi.nlm.nih.gov/pubmed/26181707