Clinical trial results:
A Multicenter, Randomized, Double-Blind, Double-Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) Versus Raltegravir (RAL) Each Administered With a Background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults

Summary

EudraCT number	2007-004225-26
Trial protocol	DE GB NL BE ES IT PT FR
Global end of trial date	22 April 2015

Results information

Result version number	v1 (current)
This version publication date	07 May 2016
First version publication date	07 May 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-183-0145

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00708162
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	22 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to compare the safety, tolerability and efficacy of a regimen containing once-daily elvitegravir (EVG) versus twice-daily raltegravir (RAL) added to a background regimen (1 fully-active ritonavir (RTV)-boosted protease inhibitor (PI) plus 1 or 2 additional antiretroviral (ARV) agents) in HIV-1 infected, ARV treatment-experienced adults who had documented resistance, or at least six months experience prior to screening with two or more different classes of ARV agents.

Participants were randomized in a 1:1 ratio to receive EVG plus background regimen (Elvitegravir group), or raltegravir plus background regimen (Raltegravir group). Due to known drug interactions, participants in the Elvitegravir group who received RTV-boosted atazanavir (ATV) or RTV-boosted lopinavir (LPV) as part of their background regimen received elvitegravir at a lower dose (85 mg).

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:

The background regimen was constructed by the investigator based on viral resistance testing. The fully active PI was defined by phenotypic resistance analysis. For phenotypic susceptibility, fully active was defined as being below the lower clinical or biological cutoff. Participants were required to take their RTV dose based on the dosing schedule indicated in the prescribing information for the PI; no additional ritonavir was required to be taken with EVG. No other marketed PIs were allowed as part of the background regimen due to unknown drug interactions.

The second agent could have been one nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), etravirine, maraviroc, or T-20. However, the second agent must not have included an integrase inhibitor; the nonnucleoside reverse transcriptase inhibitors efavirenz, nevirapine, or delavirdine (due to unknown drug interactions); or the fixed-dose combination therapies Atripla® or Trizivir® (abacavir sulfate/lamivudine/zidovudine). The second agent may or may not have been fully active (except in Spain, where participants have to receive a fully active second agent, as requested by the Spanish regulatory agency).

If the M184V/I reverse transcriptase (RT) mutation was present on the screening genotype report and an NRTI was used as the second agent, then either FTC or LAM may have been added as a third agent in the background regimen to maintain the M184V/I mutation. In this situation only, the fixed-dose combination therapies Combivir®, Truvada®, or Epzicom/Kivexa® may have been prescribed as the combined second and third agents of the background regimen.

After Week 96, participants continued to take their blinded study drug and attended visits until treatment assignments were unblinded, at which point they were given the option to participate in an open-label EVG extension phase of the study.

Evidence for comparator: -

Actual start date of recruitment	19 June 2008
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	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 21
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 453
Country: Number of subjects enrolled	Mexico: 51
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Puerto Rico: 22
Worldwide total number of subjects	724
EEA total number of subjects	135

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	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in a total of 161 study sites in Australia, Europe, and North America. The first participant was screened on 19 June 2008. The last study visit occurred on 22 April 2015.

Pre-assignment

Screening details:

1335 participants were screened.

Period 1

Period 1 title	Randomized Phase
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	Elvitegravir

Arm description:

EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.

Arm type	Experimental
Investigational medicinal product name	Elvitegravir
Investigational medicinal product code	
Other name	Vitekta®, GS-9137
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

EVG 150 mg tablet administered orally once daily with food (85 mg if receiving RTV-boosted ATV or RTV-boosted LPV as part of the background regimen)

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

Dosage and administration details:

RAL placebo tablet administered twice daily

Arm title	Raltegravir

Arm description:

EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.

Arm type	Active comparator
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	Isentress®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RAL 400 tablet administered twice daily

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

Dosage and administration details:

EVG placebo tablet administered orally once daily with food

Number of subjects in period 1[1]	Elvitegravir	Raltegravir
Started	354	358
Completed	205	209
Not completed	149	149
Protocol violation	10	11
Adverse event, non-fatal	8	12
Death	2	9
Pregnancy	3	-
Lost to follow-up	34	34
Withdrew consent	31	22
Investigator's discretion	7	10
Participant noncompliance	40	32
Lack of efficacy	14	19

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 in the Elvitegravir group and 5 participants in the Raltegravir group who were randomized but not treated are not included in the subject disposition table.

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Elvitegravir

Arm description:

EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.

Arm type	Experimental
Investigational medicinal product name	Elvitegravir
Investigational medicinal product code	
Other name	Vitekta®, GS-9137
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:	
EVG 150 mg tablet administered orally once daily with food (85 mg if receiving RTV-boosted ATV or RTV-boosted LPV as part of the background regimen)	
Investigational medicinal product name	Raltegravir placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
RAL placebo tablet administered twice daily	
Arm title	Raltegravir
Arm description:	
RAL plus EVG placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	
Arm type	Active comparator
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	Isentress®
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
RAL 400 tablet administered twice daily	
Investigational medicinal product name	Elvitegravir placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
EVG placebo tablet administered orally once daily with food	

Number of subjects in period 2[2]	Elvitegravir	Raltegravir
Started	196	151
Completed	152	121
Not completed	44	30
Adverse event, non-fatal	1	2
Death	3	1
Unknown	1	-
Lost to follow-up	10	8
Withdrew consent	12	6
Investigator's discretion	3	2
Participant noncompliance	7	7
Lack of efficacy	7	4

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 9 participants in the Elvitegravir group and 58 participants in the Raltegravir group who completed the Randomized Phase did not continue to the Open-Label Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Elvitegravir
Reporting group description:	
EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	
Reporting group title	Raltegravir
Reporting group description:	
EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	

Reporting group values	Elvitegravir	Raltegravir	Total
Number of subjects	354	358	712
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	44	45	
standard deviation	± 9	± 9.1	-
Gender categorical Units: Subjects			
Female	60	67	127
Male	294	291	585
Ethnicity Units: Subjects			
Hispanic or Latino	81	74	155
Not Hispanic or Latino	272	283	555
Unknown or Not Reported	1	1	2
Race Units: Subjects			
White	210	227	437
Black or African American	128	119	247
Asian	9	5	14
American Indian or Alaska Native	3	3	6
Native Hawaiian or Other Pacific Islander	1	0	1
Other	3	4	7
HIV-1 RNA category Units: Subjects			
≤ 100,000 copies/mL	263	267	530
> 100,000 copies/mL	91	91	182
HIV Disease Status Units: Subjects			
Asymptomatic	172	175	347
Symptomatic HIV Infections	52	54	106
AIDS	126	125	251
Unknown	4	4	8

Type of PI in Background Regimen (Excluding Ritonavir)			
One participant in the Raltegravir group switched from darunavir to fosamprenavir at Day 5, and is counted only in the number receiving darunavir at baseline.			
Units: Subjects			
atazanavir	64	53	117
darunavir	202	206	408
fosamprenavir	14	20	34
lopinavir	68	72	140
tipranavir	6	7	13
Type of NRTI in Background Regimen			
Only participants who had an nucleoside reverse transcriptase inhibitor (NRTI) in their background regimen were reported.			
Units: Subjects			
tenofovir disoproxil fumarate	163	171	334
emtricitabine/tenofovir disoproxil fumarate	91	66	157
lamivudine	13	13	26
abacavir	6	15	21
abacavir/lamivudine	4	8	12
lamivudine/zidovudine	6	5	11
zidovudine	3	6	9
didanosine	1	7	8
emtricitabine	2	3	5
no NRTI in background regimen	65	64	129
Enfuvirtide (T-20) in background regimen			
Units: Subjects			
No	352	357	709
Yes	2	1	3
Etravirine in background regimen			
Units: Subjects			
No	309	303	612
Yes	45	55	100
Maraviroc in background regimen			
Units: Subjects			
No	330	340	670
Yes	24	18	42
Phenotypic Sensitivity Score			
Phenotypic sensitivity score (PSS) was calculated by summing up drug susceptibility values (1=sensitive; 0.5=partially sensitive; 0=resistance or reduced susceptibility) on all drugs in the baseline background regimen. For subjects naive to enfuvirtide (or maraviroc), a score of 1 was assigned for enfuvirtide (or maraviroc). Higher scores correspond to increased sensitivity.			
Units: Subjects			
1.0	5	4	9
1.5	23	28	51
2.0	309	313	622
2.5	2	1	3
3.0	14	10	24
3.5	0	1	1
No baseline PSS score	1	1	2
Chronic Hepatitis B (HBV) Infection Status			
Units: Subjects			

Indeterminant	1	0	1
Negative	333	342	675
Positive	17	13	30
No baseline HBV measurement	3	3	6
Chronic Hepatitis C (HCV) Infection Status Units: Subjects			
Indeterminant	2	2	4
Negative	305	298	603
Positive	44	55	99
No baseline HCV measurement	3	3	6
HIV-1 RNA Units: log10 copies/mL			
arithmetic mean	4.26	4.27	
standard deviation	± 0.969	± 0.943	-
Cluster of differentiation (CD4) Cell Count Units: cells/mm^3			
arithmetic mean	257.9	265.3	
standard deviation	± 204.31	± 207.04	-

End points

End points reporting groups

Reporting group title	Elvitegravir
Reporting group description:	
EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	
Reporting group title	Raltegravir
Reporting group description:	
EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	
Reporting group title	Elvitegravir
Reporting group description:	
EVG plus RAL placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	
Reporting group title	Raltegravir
Reporting group description:	
RAL plus EVG placebo plus background regimen in the Randomized Phase, followed by EVG plus background regimen in the Open-Label Phase.	

Primary: Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 50 Copies/mL at Week 48

End point title	Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 50 Copies/mL at Week 48
End point description:	
The percentage of participants achieving and maintaining confirmed HIV-1 RNA < 50 copies/mL at Week 48 was analyzed using the FDA-defined Time to Loss of Virologic Response (TLOVR) algorithm, which takes into account a patient's longitudinal viral load up to the predefined time point by considering patterns of suppression and rebounding.	
End point type	Primary
End point timeframe:	
Week 48	

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	59	57.8		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The planned sample size of 700 HIV-1 infected participants, (350 in each group) was estimated to provide at least 85% power to establish noninferiority in the percentage of participants achieving and maintaining confirmed HIV-1 RNA < 50 copies/mL through Week 48. For sample size and power

computation, it was assumed that both elvitegravir and raltegravir arms have a response rate of 0.74, that a noninferiority margin was 0.10, and that the significance level of the test was 1-sided 0.025 level.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in percentages
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	8.2

Notes:

[1] - Null hypothesis: the EVG group was at least 10% worse than the RAL group with respect to percentage of participants achieving and maintaining HIV-1 RNA < 50 copies/mL through Week 48; alternative hypothesis: the EVG group was less than 10% worse than the RAL group. The difference in percentages and its 95% confidence interval (CI) were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using Mantel-Haenszel (MH) proportions and normal approximation.

Secondary: Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 50 Copies/mL at Week 96

End point title	Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 50 Copies/mL at Week 96

End point description:

The percentage of participants achieving and maintaining confirmed HIV-1 RNA < 50 copies/mL at Week 96 was analyzed using the FDA-defined TLOVR algorithm, which takes into account a patient's longitudinal viral load up to the predefined time point by considering patterns of suppression and rebounding.

End point type	Secondary

End point timeframe:

Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	47.6	45		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

Null hypothesis: the EVG group was at least 10% worse than the RAL group with respect to percentage of participants achieving and maintaining HIV-1 RNA < 50 copies/mL through Week 48; alternative hypothesis: the EVG group was less than 10% worse than the RAL group. The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir

Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentages
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	9.9

Secondary: Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 400 Copies/mL at Week 48

End point title	Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 400 Copies/mL at Week 48

End point description:

The percentage of participants achieving and maintaining confirmed HIV-1 RNA < 400 copies/mL at Week 48 was analyzed using the FDA-defined TLOVR algorithm, which takes into account a patient's longitudinal viral load up to the predefined time point by considering patterns of suppression and rebounding.

End point type	Secondary

End point timeframe:

Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	68.1	67.2		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	The difference in percentages and its 95
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	7.7

Notes:

[2] - Comparative analysis

Secondary: Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 400 Copies/mL at Week 96

End point title	Percentage of Participants Achieving and Maintaining Confirmed HIV-1 RNA < 400 Copies/mL at Week 96

End point description:

The percentage of participants achieving and maintaining confirmed HIV-1 RNA < 400 copies/mL at Week 96 was analyzed using the FDA-defined TLOVR algorithm, which takes into account a patient's longitudinal viral load up to the predefined time point by considering patterns of suppression and rebounding.

End point type	Secondary

End point timeframe:

Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	57	56.1		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference in percentages
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	8.2

Notes:

[3] - Comparative analysis

Secondary: Virologic Response at Week 48 (HIV-1 RNA < 50 Copies/mL)

End point title	Virologic Response at Week 48 (HIV-1 RNA < 50 Copies/mL)

End point description:

Virologic response at Week 48 (percentage of participants with HIV-1 RNA < 50 copies/mL) was analyzed using the FDA-defined Snapshot algorithm, which defines a patient's virologic response status using the viral load along with study drug discontinuation status at the predefined time point within an allowed window of time.

End point type	Secondary

End point timeframe:

Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	59.8	57.5		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in percentages
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	9.3

Notes:

[4] - Comparative analysis

Secondary: Virologic Response at Week 96 (HIV-1 RNA < 50 Copies/mL)

End point title	Virologic Response at Week 96 (HIV-1 RNA < 50 Copies/mL)

End point description:

Virologic response at Week 96 (percentage of participants with HIV-1 RNA < 50 copies/mL) was analyzed using the FDA-defined Snapshot algorithm, which defines a patient's virologic response status using the viral load along with study drug discontinuation status at the predefined time point within an allowed window of time.

End point type	Secondary

End point timeframe:

Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	52.4	53		

Statistical analyses

Statistical analysis title	Difference in percentages
Statistical analysis description:	
The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.	
Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Difference in percentages
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	6.8

Notes:

[5] - Comparative analysis

Secondary: Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 50 Copies/mL) up to Week 48

End point title	Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 50 Copies/mL) up to Week 48
End point description:	
The percentage of participants with pure virologic failure (HIV-1 RNA cutoff at 50 copies/mL) up to Week 48 was estimated using the Kaplan-Meier method in the time to event analysis.	
End point type	Secondary
End point timeframe:	
Baseline to Week 48	

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (confidence interval 95%)	35 (29.8 to 39.8)	35 (29.8 to 39.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 50 Copies/mL) up to Week 96

End point title	Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 50 Copies/mL) up to Week 96

End point description:

The percentage of participants with pure virologic failure (HIV-1 RNA cutoff at 50 copies/mL) up to Week 96 was estimated using the Kaplan-Meier method in the time to event analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (confidence interval 95%)	45 (39.3 to 49.9)	46 (41.1 to 51.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 400 Copies/mL) up to Week 48

End point title	Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 400 Copies/mL) up to Week 48

End point description:

The percentage of participants with pure virologic failure (HIV-1 RNA cutoff at 400 copies/mL) up to Week 48 was estimated using the Kaplan-Meier method in the time to event analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (confidence interval 95%)	24 (19.5 to 28.5)	24 (19.7 to 28.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 400 Copies/mL) up to Week 96

End point title	Percentage of Participants With Pure Virologic Failure (HIV-1 RNA Cutoff at 400 Copies/mL) up to Week 96

End point description:

The percentage of participants with pure virologic failure (HIV-1 RNA cutoff at 400 copies/mL) up to Week 96 was estimated using the Kaplan-Meier method in the time to event analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (confidence interval 95%)	32 (26.7 to 36.7)	31 (26.1 to 36.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: 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 missing = failure method, where participants with missing data were considered as having failed to meet the criteria for evaluation.

End point type	Secondary

End point timeframe:

Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	61	60.7		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Difference in percentages
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	7.3

Notes:

[6] - Comparative analysis

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 missing = failure method.

End point type	Secondary

End point timeframe:

Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	53.6	56.4		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Difference in percentages
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	4.4

Notes:

[7] - Comparative analysis

Secondary: Percentage of Participants With HIV-1 RNA < 400 Copies/mL at Week 48

End point title	Percentage of Participants With HIV-1 RNA < 400 Copies/mL at Week 48

End point description:

The percentage of participants with HIV-1 RNA < 400 copies/mL at Week 48 was analyzed using the missing = failure method.

End point type	Secondary

End point timeframe:

Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	70.1	72.1		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Difference in percentages
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	4.7

Notes:

[8] - Comparative analysis

Secondary: Percentage of Participants With HIV-1 RNA < 400 Copies/mL at Week 96

End point title	Percentage of Participants With HIV-1 RNA < 400 Copies/mL at Week 96

End point description:

The percentage of participants with HIV-1 RNA < 400 copies/mL at Week 96 was analyzed using the missing = failure method.

End point type	Secondary

End point timeframe:

Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	351		
Units: percentage of participants				
number (not applicable)	61.3	63		

Statistical analyses

Statistical analysis title	Difference in percentages

Statistical analysis description:

The difference in percentages and its 95% CI were based on stratum-adjusted HIV-1 RNA level and the class of second agent (NRTI or other classes) using MH proportions and normal approximation.

Comparison groups	Elvitegravir v Raltegravir

Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Difference in percentages
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	5.5

Notes:

[9] - Comparative analysis

Secondary: Change From Baseline in HIV-1 RNA at Week 48

End point title	Change From Baseline in HIV-1 RNA at Week 48

End point description:

The change from baseline in log10 HIV-1 RNA (copies/mL) at Week 48 was analyzed. Participants with evaluable change data at Week 48 were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	291		
Units: log10 copies/mL				
arithmetic mean (standard deviation)	-2.17 (± 1.162)	-2.18 (± 1.178)		

Statistical analyses

Statistical analysis title	Difference in log10 copies/mL

Statistical analysis description:

The difference in least squares means (LSM) and its 95% CI were obtained using an analysis of variance model (ANOVA) adjusting for baseline HIV-1 RNA level and class of the second agent (NRTI or other classes).

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Difference in log10 copies/mL
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.19

Notes:

[10] - Comparative analysis

Secondary: Change From Baseline in HIV-1 RNA at Week 96

End point title	Change From Baseline in HIV-1 RNA at Week 96

End point description:

The change from baseline in log10 HIV-1 RNA (copies/mL) at Week 96 was analyzed. Participants with evaluable change data at Week 96 were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	238		
Units: log10 copies/mL				
arithmetic mean (standard deviation)	-2.26 (± 1.078)	-2.31 (± 1.068)		

Statistical analyses

Statistical analysis title	Difference in log10 copies/mL

Statistical analysis description:

The difference in LSM and its 95% CI were obtained using ANOVA adjusting for baseline HIV-1 RNA level and class of the second agent (NRTI or other classes).

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Difference in log10 copies/mL
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.22

Notes:

[11] - Comparative analysis

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:

The change from baseline in CD4 cell count (cells/mm^3) at Week 48 was analyzed. Participants with evaluable change data at Week 48 were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	282		
Units: cells/mm^3				
arithmetic mean (standard deviation)	138 (± 141.4)	147 (± 148.9)		

Statistical analyses

Statistical analysis title	Difference in cells/mm^3

Statistical analysis description:

The difference in LSM and its 95% CI were obtained using ANOVA adjusting for baseline HIV-1 RNA level and class of the second agent (NRTI or other classes).

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	549
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Difference in cells/mm^3
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33
upper limit	16

Notes:

[12] - Comparative analysis

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:

The change from baseline in CD4 cell count (cells/mm^3) at Week 96 was analyzed. Participants with evaluable change data at Week 96 were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 96

End point values	Elvitegravir	Raltegravir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	233		
Units: cells/mm^3				
arithmetic mean (standard deviation)	205 (± 191.5)	198 (± 162.2)		

Statistical analyses

Statistical analysis title	Difference in cells/mm^3

Statistical analysis description:

The difference in LSM and its 95% CI were obtained using ANOVA adjusting for baseline HIV-1 RNA level and class of the second agent (NRTI or other classes).

Comparison groups	Elvitegravir v Raltegravir
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Difference in cells/mm^3
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25
upper limit	39

Notes:

[13] - Comparative analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through end of study drug treatment (average exposure: 100 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	18.0

Reporting groups

Reporting group title	Elvitegravir

Reporting group description:

Adverse events in this reporting group are those experienced by participants in the Elvitegravir group during the Randomized Phase.

Reporting group title	Raltegravir

Reporting group description:

Adverse events in this reporting group are those experienced by participants in the Raltegravir group during the Randomized Phase.

Reporting group title	All Elvitegravir

Reporting group description:

Adverse events in this reporting group are those experienced by participants in the Elvitegravir group during both the Randomized Phase and Open-Label Phase, and those experienced by participants in the Raltegravir group following switch to EVG in the Open-Label Phase only.

Serious adverse events	Elvitegravir	Raltegravir	All Elvitegravir
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 354 (20.62%)	86 / 358 (24.02%)	127 / 505 (25.15%)
number of deaths (all causes)	5	10	9
number of deaths resulting from adverse events	0	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	2 / 354 (0.56%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kaposi's sarcoma			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal cancer recurrent			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lung cancer metastatic			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Oral papilloma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland neoplasm			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal cancer stage 0			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder adenocarcinoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hodgkin's disease stage IV			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Primary effusion lymphoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Queyrat erythroplasia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			

subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-cell lymphoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 354 (0.28%)	4 / 358 (1.12%)	4 / 505 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal syndrome			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 354 (0.56%)	1 / 358 (0.28%)	5 / 505 (0.99%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	2 / 354 (0.56%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary cavitation			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choking			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	3 / 354 (0.85%)	4 / 358 (1.12%)	4 / 505 (0.79%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance abuse			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute psychosis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol abuse			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Homicidal ideation			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 354 (0.56%)	2 / 358 (0.56%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lower limb fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thermal burn			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemical poisoning			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			

subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirenal haematoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fractured base			

subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic injury			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 354 (0.56%)	0 / 358 (0.00%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocardial infarction			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve prolapse			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	2 / 354 (0.56%)	0 / 358 (0.00%)	7 / 505 (1.39%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 354 (0.28%)	2 / 358 (0.56%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 354 (0.28%)	2 / 358 (0.56%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			

subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery dissection			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coombs positive haemolytic anaemia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Eye disorders			

Retinal detachment			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 354 (0.28%)	2 / 358 (0.56%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Colitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Small intestinal obstruction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anogenital dysplasia			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hepatitis			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis cholestatic			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Skin ulcer			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 354 (0.56%)	1 / 358 (0.28%)	5 / 505 (0.99%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 354 (0.00%)	2 / 358 (0.56%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular acidosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal vein thrombosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Basedow's disease			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cushing's syndrome			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fasciitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myositis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	12 / 354 (3.39%)	7 / 358 (1.96%)	15 / 505 (2.97%)
occurrences causally related to treatment / all	0 / 15	0 / 7	0 / 19
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Cellulitis			
subjects affected / exposed	5 / 354 (1.41%)	5 / 358 (1.40%)	8 / 505 (1.58%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 354 (0.56%)	4 / 358 (1.12%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 354 (0.56%)	0 / 358 (0.00%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Urosepsis			
subjects affected / exposed	1 / 354 (0.28%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	2 / 505 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Folliculitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital herpes			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurosyphilis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatitis B			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Breast abscess			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis bacterial			

subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural abscess			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis A			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle abscess			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotid abscess			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Spinal cord abscess			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			

subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	3 / 505 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 354 (0.28%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	0 / 354 (0.00%)	0 / 358 (0.00%)	1 / 505 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			

subjects affected / exposed	0 / 354 (0.00%)	1 / 358 (0.28%)	0 / 505 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Elvitegravir	Raltegravir	All Elvitegravir
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 354 (78.81%)	250 / 358 (69.83%)	294 / 505 (58.22%)
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 354 (3.95%)	26 / 358 (7.26%)	39 / 505 (7.72%)
occurrences (all)	14	28	41
Nervous system disorders			
Headache			
subjects affected / exposed	49 / 354 (13.84%)	37 / 358 (10.34%)	63 / 505 (12.48%)
occurrences (all)	58	49	87
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	39 / 354 (11.02%)	25 / 358 (6.98%)	55 / 505 (10.89%)
occurrences (all)	47	31	68
Pyrexia			
subjects affected / exposed	18 / 354 (5.08%)	19 / 358 (5.31%)	29 / 505 (5.74%)
occurrences (all)	19	22	33
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	120 / 354 (33.90%)	77 / 358 (21.51%)	158 / 505 (31.29%)
occurrences (all)	172	111	246
Nausea			
subjects affected / exposed	45 / 354 (12.71%)	41 / 358 (11.45%)	61 / 505 (12.08%)
occurrences (all)	53	53	74
Abdominal pain			
subjects affected / exposed	24 / 354 (6.78%)	18 / 358 (5.03%)	40 / 505 (7.92%)
occurrences (all)	28	21	45
Vomiting			

subjects affected / exposed	22 / 354 (6.21%)	28 / 358 (7.82%)	30 / 505 (5.94%)
occurrences (all)	24	30	35
Gastrooesophageal reflux disease			
subjects affected / exposed	14 / 354 (3.95%)	9 / 358 (2.51%)	28 / 505 (5.54%)
occurrences (all)	16	9	31
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 354 (11.58%)	47 / 358 (13.13%)	65 / 505 (12.87%)
occurrences (all)	42	61	71
Oropharyngeal pain			
subjects affected / exposed	18 / 354 (5.08%)	10 / 358 (2.79%)	24 / 505 (4.75%)
occurrences (all)	18	10	27
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	28 / 354 (7.91%)	29 / 358 (8.10%)	40 / 505 (7.92%)
occurrences (all)	31	38	46
Psychiatric disorders			
Depression			
subjects affected / exposed	33 / 354 (9.32%)	33 / 358 (9.22%)	49 / 505 (9.70%)
occurrences (all)	37	34	56
Insomnia			
subjects affected / exposed	26 / 354 (7.34%)	21 / 358 (5.87%)	42 / 505 (8.32%)
occurrences (all)	28	23	47
Anxiety			
subjects affected / exposed	16 / 354 (4.52%)	9 / 358 (2.51%)	33 / 505 (6.53%)
occurrences (all)	18	9	37
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	42 / 354 (11.86%)	36 / 358 (10.06%)	68 / 505 (13.47%)
occurrences (all)	47	47	78
Arthralgia			
subjects affected / exposed	30 / 354 (8.47%)	28 / 358 (7.82%)	57 / 505 (11.29%)
occurrences (all)	39	31	77
Pain in extremity			
subjects affected / exposed	28 / 354 (7.91%)	25 / 358 (6.98%)	48 / 505 (9.50%)
occurrences (all)	30	25	56

Muscle spasms			
subjects affected / exposed	18 / 354 (5.08%)	13 / 358 (3.63%)	28 / 505 (5.54%)
occurrences (all)	21	13	33
Myalgia			
subjects affected / exposed	14 / 354 (3.95%)	11 / 358 (3.07%)	26 / 505 (5.15%)
occurrences (all)	16	11	30
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	75 / 354 (21.19%)	59 / 358 (16.48%)	116 / 505 (22.97%)
occurrences (all)	124	100	218
Nasopharyngitis			
subjects affected / exposed	40 / 354 (11.30%)	32 / 358 (8.94%)	56 / 505 (11.09%)
occurrences (all)	62	41	94
Bronchitis			
subjects affected / exposed	34 / 354 (9.60%)	34 / 358 (9.50%)	57 / 505 (11.29%)
occurrences (all)	41	45	68
Urinary tract infection			
subjects affected / exposed	28 / 354 (7.91%)	35 / 358 (9.78%)	52 / 505 (10.30%)
occurrences (all)	40	47	74
Sinusitis			
subjects affected / exposed	28 / 354 (7.91%)	28 / 358 (7.82%)	48 / 505 (9.50%)
occurrences (all)	34	34	59
Influenza			
subjects affected / exposed	15 / 354 (4.24%)	10 / 358 (2.79%)	30 / 505 (5.94%)
occurrences (all)	17	10	33
Folliculitis			
subjects affected / exposed	18 / 354 (5.08%)	7 / 358 (1.96%)	25 / 505 (4.95%)
occurrences (all)	22	7	32
Gastroenteritis			
subjects affected / exposed	15 / 354 (4.24%)	7 / 358 (1.96%)	25 / 505 (4.95%)
occurrences (all)	17	7	32
Oral herpes			
subjects affected / exposed	15 / 354 (4.24%)	6 / 358 (1.68%)	26 / 505 (5.15%)
occurrences (all)	27	6	43
Metabolism and nutrition disorders			

Hypercholesterolaemia subjects affected / exposed occurrences (all)	12 / 354 (3.39%) 15	20 / 358 (5.59%) 27	26 / 505 (5.15%) 44

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2008	All references to "second single agent" were changed to "second agent;" the protocol was updated to include Asia as a region for site participation and to include Mexico as a participating country in North America; if the M184V/I RT mutation was present on the screening genotype report and a NRTI was used as the second agent, FTC or 3TC may have been prescribed as a third agent, or one of the fixed-dose combination therapies Combivir®, Truvada®, or Epzicom®/Kivexa® may have been prescribed as the combined second and third agents; the addition of adverse event (AE) monitoring recommendations when EVG/r and rifabutin were administered together; change in inclusion criteria, including hepatic transaminases criteria and the deletion of the prothrombin time criterion. The inclusion criterion of the upper limit of normal (ULN) for hepatic transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels was changed from ≤ 2.5 to ≤ 5; the malignant exclusion criterion was modified to include exclusion of a history of or ongoing malignancy (including untreated carcinoma in-situ) other than cutaneous Kaposi sarcoma (KS), basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma; the definition of virologic rebound was changed.
18 February 2009	The protocol was updated to reflect the unification of Studies GS-US-183-0144 and GS-US-183-0145; the inclusion criterion that subjects remain on their stable antiretroviral regimen until the baseline visit was modified to allow subjects to discontinue their regimen after screening and remain off therapy at the discretion of the investigator; the screening window was extended to 56 days; additional secondary efficacy endpoints were added; the malignancy exclusion criterion was further modified to clarify that subjects with a history of or ongoing malignancy, other than cutaneous KS, basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma, were not eligible and that subjects with biopsy-confirmed cutaneous KS were eligible; however, they must not have received any systemic therapy for KS within 30 days of baseline and were not anticipated to require systemic therapy during the study.
05 August 2009	The HIV-1 RNA reference assay changed from the Roche COBAS® AmpliPrep/COBAS TaqMan® HIV-1 Test, version 1.0 (referred to as the Taqman 1.0 assay) to the Roche COBAS AmpliPrep/COBAS Amplicor HIV-1 Monitor Ultrasensitive Test version 1.5 (referred to as the Amplicor Assay). This change, which resulted in the retesting of samples obtained after screening, was based on published data (Lima V, et al, JAIDS 2009;51(1):3-6) demonstrating that the Taqman 1.0 assay did not correlate well with the Amplicor assay at the critical threshold of HIV-1 RNA < 50 copies/mL.
06 July 2010	The study was extended to include an optional 144-week open-label extension; updated GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Urinalysis section
04 February 2011	At the request of the FDA, the blinded study was extended to 96 weeks of double-blind treatment prior to the open-label extension to collect longer-term blinded comparative safety and effectiveness data; incorporated the clarifications to Amendment 4 referenced in the Administrative Letter dated 26 October 2010; these included a change in Gilead's medical monitor, assessments for the Early Study Drugs Discontinuation Visit, and definition of HIV-related diseases.

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.

10 participants from a single study site were excluded from Intent-to-Treat (ITT) Analysis Set due to critical and multiple protocol violations (elvitegravir arm: n = 3; raltegravir arm: n = 7).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22015077