Clinical trial results:
A Multipart, Open-label Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir With and Without Dasabuvir Coadministered With and Without Ribavirin in Adults With Genotype 1 or 4 Chronic Hepatitis C Virus Infection and Human Immunodeficiency Virus, Type 1 Coinfection (TURQUOISE-I)

Summary

EudraCT number	2012-005143-24
Trial protocol	GB ES
Global end of trial date	25 October 2016

Results information

Result version number	v1 (current)
This version publication date	21 September 2017
First version publication date	21 September 2017

Trial information

Trial identification

Sponsor protocol code	M14-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01939197
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Rolando Viani, MD, AbbVie, rolando.viani@abbvie.com
Scientific contact	Rolando Viani, MD, AbbVie, rolando.viani@abbvie.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	25 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to assess the safety of ABT-450/r/ABT-267 with and without ABT-333 coadministered with and without ribavirin (RBV) for 12 and 24 weeks in hepatitis C virus (HCV) genotype (GT)1- or GT4-infected subjects with human immunodeficiency virus 1 (HIV-1) coinfection and to evaluate the percentage of subjects achieving sustained virologic response 12 (SVR12; HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] 12 weeks following treatment). These objectives were assessed separately within each part of the study. For Part 1a, the 12- and 24-week treatment arms were assessed separately; for Part 1b, the darunavir (DRV) once and twice daily (QD/BID) arms were assessed separately and in combination; for Part 2, the GT 1-infected subjects were assessed separately from the GT 4-infected subjects, and the percentage of GT1-infected subjects achieving SVR12 was compared to a threshold based on the historical SVR12 rate of sofosbuvir (SOF) plus RBV.

Protection of trial subjects:

Participant and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	United States: 142
Worldwide total number of subjects	318
EEA total number of subjects	121

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)	307
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part 2 was not designed to test different treatments on the same subject population. Rather, the arms in Part 2 represent subpopulations with different baseline characteristics (hepatitis C virus [HCV] genotype, cirrhotic status and prior HCV therapy experience). Arms F and G were randomized to a regimen without and with RBV,
respectively.

Pre-assignment

Screening details:

In Part 2, participants in Arms E, F, H, I, J all had GT1 infection and received 1 consistent treatment regimen based on label recommendations; they were therefore combined and named the "GT1 Analysis Group."

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1a: Arm A

Arm description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 was taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

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

Dosage and administration details:

RBV had weight-based dosing of 1,000 or 1,200 mg total daily dose divided BID per local label. For subjects with a screening creatinine clearance (CrCl) < 50 mL/min, RBV was given as alternating daily doses of 200 mg and 400 mg.

Arm title	Part 1a: Arm B

Arm description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 was taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

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

Dosage and administration details:

RBV had weight-based dosing of 1,000 or 1,200 mg total daily dose divided BID per local label. For subjects with a screening CrCl < 50 mL/min, RBV was given as alternating daily doses of 200 mg and 400 mg.

Arm title	Part 1b: Arm C

Arm description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir once-daily

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 was taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

Investigational medicinal product name	ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

RBV had weight-based dosing of 1,000 or 1,200 mg total daily dose divided BID per local label. For subjects with a screening CrCl < 50 mL/min, RBV was given as alternating daily doses of 200 mg and 400 mg.

Arm title	Part 1b: Arm D

Arm description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir twice-daily

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 was taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

Arm title	Part 2: GT1 Analysis Group

Arm description:

Subjects with HCV GT1a or GT1b at screening in Arms E, F, H, I, J (no subjects enrolled in Arm H).
Arm E: ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily.
Arm F: ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily.
Arm I: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm J: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily.

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 was taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

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

Dosage and administration details:

RBV had weight-based dosing of 1,000 or 1,200 mg total daily dose divided BID per local label. For subjects with a screening CrCl < 50 mL/min, RBV was given as alternating daily doses of 200 mg and 400 mg.

Arm title	Part 2: Arm G

Arm description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

Investigational medicinal product name	ABT-333
Investigational medicinal product code	ABT-333
Other name	dasabuvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 was taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

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

Dosage and administration details:

RBV had weight-based dosing of 1,000 or 1,200 mg total daily dose divided BID per local label. For subjects with a screening CrCl < 50 mL/min, RBV was given as alternating daily doses of 200 mg and 400 mg.

Arm title	GT4 Analysis Group

Arm description:

Subjects with HCV GT4 at screening in Arms K and L (no subjects enrolled in Arm L).
Arm K: ABT-450/r/ABT-267 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily, dolutegravir once-daily or twice-daily, darunavir once-daily.

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	ABT-450/r/ABT-267
Other name	ombitasvir/paritaprevir/ritonavir, ombitasvir also known as ABT-267, paritaprevir also known as ABT-450
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450/r/ABT-267 was taken orally as 2 tablets QD in the morning, which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

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

Dosage and administration details:

RBV had weight-based dosing of 1,000 or 1,200 mg total daily dose divided BID per local label. For subjects with a screening CrCl < 50 mL/min, RBV was given as alternating daily doses of 200 mg and 400 mg.

Number of subjects in period 1	Part 1a: Arm A	Part 1a: Arm B	Part 1b: Arm C
Started	31	32	10
Completed	30	31	10
Not completed	1	1	0
Consent withdrawn by subject	1	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Part 1b: Arm D	Part 2: GT1 Analysis Group	Part 2: Arm G
Started	12	200	5
Completed	11	196	4
Not completed	1	4	1
Consent withdrawn by subject	-	1	-
Lost to follow-up	1	3	1

Number of subjects in period 1	GT4 Analysis Group
Started	28
Completed	26
Not completed	2
Consent withdrawn by subject	-
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Part 1a: Arm A
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily	
Reporting group title	Part 1a: Arm B
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily	
Reporting group title	Part 1b: Arm C
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir once-daily	
Reporting group title	Part 1b: Arm D
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir twice-daily	
Reporting group title	Part 2: GT1 Analysis Group
Reporting group description:	
Subjects with HCV GT1a or GT1b at screening in Arms E, F, H, I, J (no subjects enrolled in Arm H). Arm E: ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm F: ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm I: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm J: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily.	
Reporting group title	Part 2: Arm G
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily	
Reporting group title	GT4 Analysis Group
Reporting group description:	
Subjects with HCV GT4 at screening in Arms K and L (no subjects enrolled in Arm L). Arm K: ABT-450/r/ABT-267 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily, dolutegravir once-daily or twice-daily, darunavir once-daily.	

Reporting group values	Part 1a: Arm A	Part 1a: Arm B	Part 1b: Arm C
Number of subjects	31	32	10
Age categorical Units: Subjects			
< 55 years	23	20	5
≥ 55 years	8	12	5
Gender categorical Units: Subjects			
Female	2	3	2
Male	29	29	8

Reporting group values	Part 1b: Arm D	Part 2: GT1 Analysis Group	Part 2: Arm G

Number of subjects	12	200	5
Age categorical Units: Subjects			
< 55 years	8	145	2
≥ 55 years	4	55	3
Gender categorical Units: Subjects			
Female	3	44	1
Male	9	156	4

Reporting group values	GT4 Analysis Group	Total	
Number of subjects	28	318	
Age categorical Units: Subjects			
< 55 years	24	227	
≥ 55 years	4	91	
Gender categorical Units: Subjects			
Female	2	57	
Male	26	261	

End points

End points reporting groups

Reporting group title	Part 1a: Arm A
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily	
Reporting group title	Part 1a: Arm B
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily	
Reporting group title	Part 1b: Arm C
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir once-daily	
Reporting group title	Part 1b: Arm D
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir twice-daily	
Reporting group title	Part 2: GT1 Analysis Group
Reporting group description:	
Subjects with HCV GT1a or GT1b at screening in Arms E, F, H, I, J (no subjects enrolled in Arm H). Arm E: ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm F: ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm I: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily. Arm J: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily.	
Reporting group title	Part 2: Arm G
Reporting group description:	
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily	
Reporting group title	GT4 Analysis Group
Reporting group description:	
Subjects with HCV GT4 at screening in Arms K and L (no subjects enrolled in Arm L). Arm K: ABT-450/r/ABT-267 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily, dolutegravir once-daily or twice-daily, darunavir once-daily.	
Subject analysis set title	Part 1b: Total
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Arm C: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir once-daily Arm D: ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir twice-daily	
Subject analysis set title	Part 2: Arm F
Subject analysis set type	Full analysis
Subject analysis set description:	
ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir oncedaily, raltegravir twice-daily	
Subject analysis set title	Part 2: Arm K
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ABT-450/r/ABT-267 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily, dolutegravir once-daily or twice-daily, darunavir once-	

daily

Subject analysis set title	Part 2: Arm E
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir oncedaily, raltegravir twice-daily

Subject analysis set title	Part 2: Arm I
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily

Subject analysis set title	Part 2: Arm J
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily

Primary: Percentage of Subjects in GT1 Analysis Group 1 in Part 2 Achieving SVR12

End point title	Percentage of Subjects in GT1 Analysis Group 1 in Part 2 Achieving SVR12[1][2]

End point description:

SVR12 is defined as plasma HCV RNA < LLOQ 12 weeks after the last dose of study drug without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. The 95% confidence interval (CI) is calculated using the Wilson score method for binomial distribution.

The primary efficacy endpoint was the non-inferiority of the percentage of subjects in the GT1 Analysis Group in Part 2 achieving SVR12 compared to the historical SVR12 rate for sofosbuvir plus ribavirin (a non-inferiority threshold of the lower bound of the 95% CI of 74%).

Intent-to-treat (ITT) population: Part 2 randomized or enrolled participants who received at least 1 dose of study drug. Imputation applied; participants with missing HCV RNA data after imputation were counted as failures. The primary efficacy endpoint analysis was based on subjects in the GT 1 Analysis Group in Part 2 containing Arms E, F, H, I, and J.

End point type	Primary

End point timeframe:

12 weeks after the last actual dose of study drug

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics and 95% confidence interval are presented per protocol.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for GT1 Analysis Group in Part 2 subjects only per protocol.

End point values	Part 2: GT1 Analysis Group			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: percentage of subjects				
number (confidence interval 95%)	97 (93.6 to 98.6)			

Attachments (see zip file)	primary endpoint stat analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1a Achieving SVR12

End point title	Percentage of Subjects in Part 1a Achieving SVR12[3]

End point description:

SVR12 is defined as plasma HCV RNA < LLOQ 12 weeks after the last dose of study drug without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. The 95% CI is calculated using the Wilson score method for binomial distribution.

ITT population: Part 1a randomized subjects who received at least 1 dose of study drug. Imputation applied; participants with missing HCV RNA data after imputation were counted as failures.

End point type	Secondary

End point timeframe:

12 weeks after last dose of study drug

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1a subjects only per protocol.

End point values	Part 1a: Arm A	Part 1a: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: percentage of subjects				
number (confidence interval 95%)	93.5 (79.3 to 98.2)	90.6 (75.8 to 96.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1a: Arm A v Part 1a: Arm B
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Secondary: Percentage of Subjects in Part 1b Achieving SVR12

End point title	Percentage of Subjects in Part 1b Achieving SVR12[4]

End point description:

SVR12 is defined as plasma HCV RNA < LLOQ 12 weeks after the last dose of study drug without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. The 95% CI is calculated using the Wilson score method for binomial distribution.

ITT population: Part 1b randomized subjects who received at least 1 dose of study drug. Imputation applied; subjects with missing HCV RNA data after imputation were counted as failures.

The Fisher exact test was performed as prespecified on the SAP but the p-value couldn’t be calculated because SVR12 rates in both arms were 100%, hence the p-value appeared as "not available."

End point type	Secondary

End point timeframe:

12 weeks after last dose of study drug

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1b subjects only per protocol.

End point values	Part 1b: Arm C	Part 1b: Arm D	Part 1b: Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	12	22	
Units: percentage of subjects				
number (confidence interval 95%)	100 (72.2 to 100)	100 (75.8 to 100)	100 (85.1 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Arm F and Arm G of Part 2 Achieving SVR12

End point title	Percentage of Subjects in Arm F and Arm G of Part 2 Achieving SVR12[5]

End point description:

SVR12 is defined as plasma HCV RNA < LLOQ 12 weeks after the last dose of study drug without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. The 95% CI is calculated using the Wilson score method for binomial distribution.

ITT population: Part 2 randomized or enrolled subjects who received at least 1 dose of study drug. Imputation applied; subjects with missing HCV RNA data after imputation were counted as failures.

End point type	Secondary

End point timeframe:

12 weeks after last dose of study drug

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 2 subjects only per protocol.

End point values	Part 2: Arm G	Part 2: Arm F		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	4		
Units: percentage of subjects				
number (confidence interval 95%)	80 (37.6 to 96.4)	75 (30.1 to 95.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With GT4 HCV in Part 2 Achieving SVR12, by Arm and Overall

End point title	Percentage of Subjects With GT4 HCV in Part 2 Achieving SVR12, by Arm and Overall[6]

End point description:

SVR12 is defined as plasma HCV RNA < LLOQ 12 weeks after the last dose of study drug without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. The 95% CI is calculated using the Wilson score method for binomial distribution.

ITT population: Part 2 randomized or enrolled subjects who received at least 1 dose of study drug. Imputation applied; subjects with missing HCV RNA data after imputation were counted as failures.

End point type	Secondary

End point timeframe:

12 weeks after last dose of study drug

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 2 subjects only per protocol.

End point values	GT4 Analysis Group	Part 2: Arm K		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	28	28		
Units: percentage of subjects				
number (confidence interval 95%)	96.4 (82.3 to 99.4)	96.4 (82.3 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1a With On-Treatment HCV Virologic Failure During the Treatment Period

End point title	Percentage of Subjects in Part 1a With On-Treatment HCV Virologic Failure During the Treatment Period[7]

End point description:

Percentage of subjects with on-treatment HCV virologic failure during the treatment period for each arm in Part 1a. Virologic failure is defined as confirmed quantifiable HCV RNA among participants with previously unquantifiable HCV RNA during treatment.

ITT population: Part 1a randomized subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

up to 12 or 24 weeks, based on treatment duration

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1a subjects only per protocol.

End point values	Part 1a: Arm A	Part 1a: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 11)	3.1 (0.6 to 15.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1b With On-Treatment HCV Virologic Failure During the Treatment Period

End point title	Percentage of Subjects in Part 1b With On-Treatment HCV Virologic Failure During the Treatment Period[8]

End point description:

Percentage of subjects with on-treatment HCV virologic failure during the treatment period for each arm and overall in Part 1b. Virologic failure is defined as confirmed quantifiable HCV RNA among participants with previously unquantifiable HCV RNA during treatment.

ITT population: Part 1b randomized subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

up to 12 weeks

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1b subjects only per protocol.

End point values	Part 1b: Arm C	Part 1b: Arm D	Part 1b: Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	12	22	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 27.8)	0 (0 to 24.2)	0 (0 to 14.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 2 With On-Treatment HCV Virologic Failure During the Treatment Period

End point title	Percentage of Subjects in Part 2 With On-Treatment HCV Virologic Failure During the Treatment Period[9]

End point description:

Percentage of subjects with on-treatment HCV virologic failure during the treatment period for arms in Part 2. Virologic failure is defined as confirmed quantifiable HCV RNA among participants with previously unquantifiable HCV RNA during treatment.

ITT population: Part 2 randomized or enrolled subjects in the GT1 analysis group (and its composing arms) and GT4 analysis group who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

up to 12 or 24 weeks, based on treatment duration

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 2 subjects only per protocol.

End point values	Part 2: GT1 Analysis Group	GT4 Analysis Group	Part 2: Arm F	Part 2: Arm K
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	200	28	4	28
Units: percentage of subjects				
number (confidence interval 95%)	0.5 (0.1 to 2.8)	0 (0 to 12.1)	25 (4.6 to 69.9)	0 (0 to 12.1)

End point values	Part 2: Arm E	Part 2: Arm I	Part 2: Arm J	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	135	19	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 8.4)	0 (0 to 2.8)	0 (0 to 16.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1a With Relapse12

End point title	Percentage of Subjects in Part 1a With Relapse12[10]

End point description:

Percentage of subjects who experienced Relapse12 among participants who completed treatment with HCV RNA < LLOQ at final treatment visit and had at least one post-treatment HCV RNA value. Relapse12 is defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR12 assessment time point) for a participant with HCV RNA < LLOQ at final treatment visit who completed treatment and had post-treatment data. Completion of treatment is defined as study drug duration ≥ 77 days for Arm C and Arm D. The 95% CI is calculated using Wilson score method for the binomial distribution.

ITT population: all Part 1a randomized subjects who received at least 1 dose of study drug and who completed treatment with HCV RNA < LLOQ at final treatment visit and had at least one post-treatment HCV RNA value.

End point type	Secondary

End point timeframe:

up to 12 or 24 weeks, based on treatment duration

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1a subjects only per protocol.

End point values	Part 1a: Arm A	Part 1a: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	31		
Units: percentage of subjects				
number (confidence interval 95%)	3.3 (0.6 to 16.7)	0 (0 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1b With Relapse12 for Each Arm and Overall

End point title	Percentage of Subjects in Part 1b With Relapse12 for Each Arm and Overall[11]

End point description:

Percentage of subjects who experienced Relapse12 among participants who completed treatment with HCV RNA < LLOQ at final treatment visit and had at least one post-treatment HCV RNA value. Relapse12 is defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR12 assessment time point) for a subject with HCV RNA < LLOQ at final treatment visit who completed treatment and had post-treatment data. Completion of treatment is defined as study drug duration ≥ 77 days for Arm C and Arm D. The 95% CI is calculated using Wilson score method for the binomial distribution.

ITT population: all Part 1b randomized subjects who received at least 1 dose of study drug and who completed treatment with HCV RNA < LLOQ at final treatment visit and had at least one post-treatment HCV RNA value.

End point type	Secondary

End point timeframe:

up to 12 or 24 weeks, based on treatment duration

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1b subjects only per protocol.

End point values	Part 1b: Arm C	Part 1b: Arm D	Part 1b: Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	12	22	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 27.8)	0 (0 to 24.2)	0 (0 to 14.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 2 With Relapse12

End point title	Percentage of Subjects in Part 2 With Relapse12[12]

End point description:

Percentage of subjects who experienced Relapse12 among those who completed treatment with HCV

RNA <LLOQ at final treatment visit and had ≥1 post-treatment HCV RNA value. Relapse12=confirmed HCV RNA ≥LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR12 window) for a subject with HCV RNA <LLOQ at final treatment visit who completed treatment and had post-treatment data, excluding reinfection. Completion of treatment=study drug duration ≥77 days for subjects who received 12 weeks of treatment and ≥154 days for subjects who received 24 weeks of treatment. HCV reinfection=confirmed HCV RNA ≥LLOQ after end of treatment in a subject who had HCV RNA <LLOQ at final treatment visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis. The 95% CI is calculated using Wilson score method for the binomial distribution. ITT population.

End point type	Secondary

End point timeframe:

up to 12 or 24 weeks based on treatment duration

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 2 subjects only per protocol.

End point values	Part 2: GT1 Analysis Group	GT4 Analysis Group	Part 2: Arm F	Part 2: Arm K
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	192[13]	27[14]	3[15]	27[16]
Units: percentage of subjects				
number (confidence interval 95%)	0.5 (0.1 to 2.9)	0 (0 to 12.5)	0 (0 to 56.1)	0 (0 to 12.5)

Notes:

[13] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value
[14] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value
[15] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value
[16] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value

End point values	Part 2: Arm E	Part 2: Arm I	Part 2: Arm J	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42[17]	131[18]	16[19]	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 8.4)	0.8 (0.1 to 4.2)	0 (0 to 19.4)	

Notes:

[17] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value
[18] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value
[19] - completed treatment w/ HCV RNA <LLOQ at final treatment visit & had ≥1 post-treatment HCV RNA value

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1a With Plasma HIV-1 RNA Suppression at End of Treatment and 12 Weeks Post-Treatment

End point title	Percentage of Subjects in Part 1a With Plasma HIV-1 RNA Suppression at End of Treatment and 12 Weeks Post-Treatment[20]

End point description:

HIV virologic success was defined as HIV-1 RNA suppression (HIV-1 RNA value < 40 copies/mL).

ITT population: Part 1a randomized subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment: HIV Week 12 window for 12-weeks of treatment (Treatment Day 71 - 98) or HIV Week 24 window (Treatment Day 155 - 182) for 24-weeks of treatment. Post-Treatment Week 12 (PTW12): HIV PTW12 window (Post-Treatment Day 57 - 126)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1a subjects only per protocol.

End point values	Part 1a: Arm A	Part 1a: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: percentage of subjects				
number (confidence interval 95%)				
End of Treatment	93.5 (79.3 to 98.2)	90.6 (75.8 to 96.8)		
Post-Treatment Week 12	96.8 (83.8 to 99.4)	93.8 (79.9 to 98.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 1b With Plasma HIV-1 RNA Suppression at End of Treatment and 12 Weeks Post-Treatment

End point title	Percentage of Subjects in Part 1b With Plasma HIV-1 RNA Suppression at End of Treatment and 12 Weeks Post-Treatment[21]

End point description:

HIV virologic success was defined as HIV-1 RNA suppression (HIV-1 RNA value < 40 copies/mL).

ITT population: Part 1b randomized subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment: HIV Week 12 window (Treatment Day 78 - 98). PTW12: HIV PTW12 window (Post-Treatment Day 57 - 126)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 1b subjects only per protocol.

End point values	Part 1b: Arm C	Part 1b: Arm D	Part 1b: Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	12	22	
Units: percentage of subjects				
number (confidence interval 95%)				
End of Treatment	100 (72.2 to 100)	83.3 (55.2 to 95.3)	90.9 (72.2 to 97.5)	

Post-Treatment Week 12	100 (72.2 to 100)	75 (46.8 to 91.1)	86.4 (66.7 to 95.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Part 2 With Plasma HIV-1 RNA Suppression at End of Treatment and 12 Weeks Post-Treatment

End point title	Percentage of Subjects in Part 2 With Plasma HIV-1 RNA Suppression at End of Treatment and 12 Weeks Post-Treatment[22]

End point description:

HIV virologic success was defined as HIV-1 RNA suppression (HIV-1 RNA value < 40 copies/mL).

ITT population: Part 2 randomized or enrolled subjects in the GT1 analysis group (and its composing arms) and GT4 analysis group who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

End of treatment: HIV Week 12 window for 12-weeks of treatment (Treatment Day 71 - 98) or HIV Week 24 window (Treatment Day 155 - 182) for 24-weeks of treatment. PTW12: HIV PTW12 window (Post-Treatment Day 57 - 126)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is presented for Part 2 subjects only per protocol.

End point values	Part 2: GT1 Analysis Group	GT4 Analysis Group	Part 2: Arm F	Part 2: Arm K
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	200	28	4	28
Units: percentage of subjects				
number (confidence interval 95%)				
End of Treatment	89 (83.9 to 92.6)	85.7 (68.5 to 94.3)	100 (51 to 100)	85.7 (68.5 to 94.3)
Post-Treatment Week 12	93 (88.6 to 95.8)	92.9 (77.4 to 98)	100 (51 to 100)	92.9 (77.4 to 98)

End point values	Part 2: Arm E	Part 2: Arm I	Part 2: Arm J	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	135	19	
Units: percentage of subjects				
number (confidence interval 95%)				
End of Treatment	90.5 (77.9 to 96.2)	89.6 (83.3 to 93.7)	78.9 (56.7 to 91.5)	
Post-Treatment Week 12	97.6 (87.7 to 99.6)	91.9 (86 to 95.4)	89.5 (68.6 to 97.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Protocol-related treatment-emergent adverse events (TEAEs) were collected from the first dose of study drug through end of treatment Week 12 and Week 24; serious TEAEs were collected from the first dose of study drug until post-treatment Day 30.

Adverse event reporting additional description:

A protocol-related event is defined as any event with onset or worsening reported by a participant from the first dose of study drug until 30 days have elapsed following discontinuation of study drug administration. Events were collected whether elicited or spontaneously reported by the subject.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Part 1a: Arm A

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily

Reporting group title	Part 1a: Arm B

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving atazanavir once-daily or raltegravir twice-daily

Reporting group title	Part 1b: Arm C

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir once-daily

Reporting group title	Part 1b: Arm D

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving darunavir twice-daily

Reporting group title	Part 2: Arm E

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir oncedaily, raltegravir twice-daily

Reporting group title	Part 2: Arm F

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 for 12 weeks for subjects receiving any of the following: atazanavir oncedaily, raltegravir twice-daily

Reporting group title	Part 2: Arm G

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily

Reporting group title	Part 2: Arm I

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily

Reporting group title	Part 2: Arm J

Reporting group description:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 24 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily

Reporting group title	Part 2: Arm K

Reporting group description:

ABT-450/r/ABT-267 coadministered with RBV for 12 weeks for subjects receiving any of the following: atazanavir once-daily, raltegravir twice-daily, dolutegravir once-daily or twice-daily, darunavir once-daily

Serious adverse events	Part 1a: Arm A	Part 1a: Arm B	Part 1b: Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
OVERDOSE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ANGINA UNSTABLE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PERFORATION			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG DEPENDENCE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
URETEROLITHIASIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1b: Arm D	Part 2: Arm E	Part 2: Arm F
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
OVERDOSE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ANGINA UNSTABLE			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (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
PERICARDITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PERFORATION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG DEPENDENCE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
URETEROLITHIASIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Arm G	Part 2: Arm I	Part 2: Arm J
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	6 / 135 (4.44%)	2 / 19 (10.53%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
OVERDOSE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (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			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (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			
ANGINA UNSTABLE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
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 disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PERFORATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (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			
DEPRESSION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG DEPENDENCE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
URETEROLITHIASIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
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			
APPENDICITIS			

subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (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
INFLUENZA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Arm K		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
OVERDOSE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ANGINA UNSTABLE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PERICARDITIS			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COLITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RECTAL PERFORATION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DRUG DEPENDENCE			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
URETEROLITHIASIS			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INFLUENZA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Part 1a: Arm A	Part 1a: Arm B	Part 1b: Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 31 (90.32%)	28 / 32 (87.50%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANOGENITAL WARTS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
SKIN PAPILLOMA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vascular disorders			
DIASTOLIC HYPOTENSION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
HAEMATOMA			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
HOT FLUSH			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
HYPERTENSION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
THROMBOPHLEBITIS SUPERFICIAL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
CHEST DISCOMFORT			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
CHEST PAIN			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
CHILLS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
EARLY SATIETY			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
FATIGUE			
subjects affected / exposed	18 / 31 (58.06%)	12 / 32 (37.50%)	5 / 10 (50.00%)
occurrences (all)	20	17	5
FEELING ABNORMAL			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
FEELING JITTERY			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PAIN			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PYREXIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
TEMPERATURE INTOLERANCE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
TENDERNESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
VESSEL PUNCTURE SITE BRUISE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Social circumstances			
MENOPAUSE			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
BREAST MASS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
ERECTILE DYSFUNCTION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
GENITAL RASH			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
COUGH			
subjects affected / exposed	2 / 31 (6.45%)	5 / 32 (15.63%)	2 / 10 (20.00%)
occurrences (all)	2	6	3
DYSPNOEA			
subjects affected / exposed	1 / 31 (3.23%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
EPISTAXIS			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
NASAL CONGESTION			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
NASAL DRYNESS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
OROPHARYNGEAL PAIN			

subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
RESPIRATORY TRACT CONGESTION			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
RHINORRHOEA			
subjects affected / exposed	3 / 31 (9.68%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
ABNORMAL DREAMS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
AFFECT LABILITY			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
AGITATION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
ANXIETY			
subjects affected / exposed	0 / 31 (0.00%)	3 / 32 (9.38%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
CONFUSIONAL STATE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
DEPRESSED MOOD			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
DEPRESSION			
subjects affected / exposed	0 / 31 (0.00%)	3 / 32 (9.38%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
INSOMNIA			
subjects affected / exposed	5 / 31 (16.13%)	7 / 32 (21.88%)	1 / 10 (10.00%)
occurrences (all)	6	11	1

IRRITABILITY			
subjects affected / exposed	3 / 31 (9.68%)	3 / 32 (9.38%)	3 / 10 (30.00%)
occurrences (all)	3	4	3
LIBIDO INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
MIDDLE INSOMNIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
NERVOUSNESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
NIGHTMARE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
RESTLESSNESS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
SLEEP DISORDER			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
STRESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
WITHDRAWAL SYNDROME			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
BLOOD CREATINE PHOSPHOKINASE INCREASED			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
BLOOD POTASSIUM INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
CREATININE RENAL CLEARANCE DECREASED			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
HAEMOGLOBIN DECREASED			
subjects affected / exposed	3 / 31 (9.68%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
WEIGHT DECREASED			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
WEIGHT INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
ANIMAL BITE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
ANKLE FRACTURE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
ARTHROPOD BITE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
CONTUSION			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
EXCORIATION			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
FALL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
MENISCUS INJURY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
MUSCLE STRAIN			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
SKIN ABRASION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
DISTURBANCE IN ATTENTION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
DIZZINESS			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
DIZZINESS EXERTIONAL			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
DYSGEUSIA			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
HEADACHE			
subjects affected / exposed	6 / 31 (19.35%)	4 / 32 (12.50%)	2 / 10 (20.00%)
occurrences (all)	6	4	2
HYPOAESTHESIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
LETHARGY			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
MEMORY IMPAIRMENT			
subjects affected / exposed	0 / 31 (0.00%)	3 / 32 (9.38%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
NEURALGIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
NEUROPATHY PERIPHERAL			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
PARAESTHESIA			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
PRESYNCOPE			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
SCIATICA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
SINUS HEADACHE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
SOMNOLENCE			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
SYNCOPE			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 31 (3.23%)	3 / 32 (9.38%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
LYMPHADENOPATHY			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
BLEPHAROSPASM			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DRY EYE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
EYE DISCHARGE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
EYE PRURITUS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
EYELID HAEMATOMA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
EYELID PTOSIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
MYDRIASIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
OCULAR DISCOMFORT			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
OCULAR HYPERAEMIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
OCULAR ICTERUS			
subjects affected / exposed	5 / 31 (16.13%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	5	1	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
ABDOMINAL PAIN			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
APHTHOUS ULCER			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
BARRETT'S OESOPHAGUS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
CONSTIPATION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
DIARRHOEA			
subjects affected / exposed	1 / 31 (3.23%)	4 / 32 (12.50%)	1 / 10 (10.00%)
occurrences (all)	1	4	1
DIVERTICULUM			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

DRY MOUTH			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
DYSPEPSIA			
subjects affected / exposed	1 / 31 (3.23%)	3 / 32 (9.38%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
DYSPHAGIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
FAECES PALE			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
FAECES SOFT			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
FLATULENCE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
GASTRITIS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
GASTROINTESTINAL SOUNDS ABNORMAL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
GINGIVAL BLEEDING			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
MOUTH ULCERATION			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
NAUSEA			
subjects affected / exposed	5 / 31 (16.13%)	6 / 32 (18.75%)	2 / 10 (20.00%)
occurrences (all)	5	8	3
ORAL PAIN			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
STOMATITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
TOOTHACHE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
VOMITING			
subjects affected / exposed	1 / 31 (3.23%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	3	7	0
Hepatobiliary disorders			
GALLBLADDER POLYP			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
HYPERBILIRUBINAEMIA			
subjects affected / exposed	4 / 31 (12.90%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
JAUNDICE			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
COLD SWEAT			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
DERMATITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
DRUG ERUPTION			

subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
DRY SKIN			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
ECZEMA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
ERYTHEMA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
PRURITUS			
subjects affected / exposed	6 / 31 (19.35%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	6	2	0
PRURITUS GENERALISED			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
RASH			
subjects affected / exposed	1 / 31 (3.23%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
RASH MACULAR			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
RASH PAPULAR			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
RASH PRURITIC			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
RASH VESICULAR			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
SKIN EXFOLIATION			

subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
SKIN FISSURES			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
SKIN LESION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
CHROMATURIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PROTEINURIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
HYPOGONADISM MALE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	1 / 10 (10.00%)
occurrences (all)	2	1	3
ARTHRITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
BACK PAIN			
subjects affected / exposed	1 / 31 (3.23%)	3 / 32 (9.38%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
COSTOCHONDRITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
FLANK PAIN			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
JOINT STIFFNESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
JOINT SWELLING			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
MUSCLE FATIGUE			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
MUSCLE SPASMS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
MUSCLE TIGHTNESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
MYALGIA			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
NECK PAIN			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PERIARTHRITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
TENDONITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			

ACUTE SINUSITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
BRONCHITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
CELLULITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
CHLAMYDIAL INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
EAR INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
ERYSIPELAS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
GASTROENTERITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
GINGIVITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
HERPES ZOSTER			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
HERPES ZOSTER DISSEMINATED			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
HERPES ZOSTER OTICUS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

INFLUENZA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
ORAL HERPES			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
PARONYCHIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
PERTUSSIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
PYELONEPHRITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
PYURIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
RHINITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
SECONDARY SYPHILIS			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
SINUSITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

TINEA VERSICOLOUR			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
TONSILLITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
TOOTH ABSCESS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 31 (12.90%)	5 / 32 (15.63%)	1 / 10 (10.00%)
occurrences (all)	4	5	1
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 31 (3.23%)	2 / 32 (6.25%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
GOUT			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
HYPOKALAEMIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 1b: Arm D	Part 2: Arm E	Part 2: Arm F
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)	26 / 42 (61.90%)	3 / 4 (75.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANOGENITAL WARTS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SKIN PAPILLOMA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
DIASTOLIC HYPOTENSION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HAEMATOMA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HOT FLUSH			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HYPERTENSION			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
THROMBOPHLEBITIS SUPERFICIAL			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
CHEST DISCOMFORT			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
CHEST PAIN			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

CHILLS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EARLY SATIETY			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
FATIGUE			
subjects affected / exposed	4 / 12 (33.33%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	5	2	0
FEELING ABNORMAL			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
FEELING JITTERY			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
PAIN			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PYREXIA			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
TEMPERATURE INTOLERANCE			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
TENDERNESS			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

VESSEL PUNCTURE SITE BRUISE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Social circumstances			
MENOPAUSE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
BREAST MASS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
ERECTILE DYSFUNCTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GENITAL RASH			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
COUGH			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
DYSPNOEA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EPISTAXIS			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NASAL CONGESTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NASAL DRYNESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
RESPIRATORY TRACT CONGESTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RHINORRHOEA			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
ABNORMAL DREAMS			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
AFFECT LABILITY			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
AGITATION			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
ANXIETY			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

DEPRESSED MOOD			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DEPRESSION			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
INSOMNIA			
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
IRRITABILITY			
subjects affected / exposed	2 / 12 (16.67%)	0 / 42 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
LIBIDO INCREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MIDDLE INSOMNIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NERVOUSNESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NIGHTMARE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RESTLESSNESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SLEEP DISORDER			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
STRESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
WITHDRAWAL SYNDROME			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BLOOD POTASSIUM INCREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
CREATININE RENAL CLEARANCE DECREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HAEMOGLOBIN DECREASED			
subjects affected / exposed	4 / 12 (33.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
WEIGHT DECREASED			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
WEIGHT INCREASED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
ANIMAL BITE			
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
ANKLE FRACTURE			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
ARTHROPOD BITE			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
CONTUSION			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
EXCORIATION			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
FALL			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MENISCUS INJURY			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MUSCLE STRAIN			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SKIN ABRASION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DISTURBANCE IN ATTENTION			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DIZZINESS			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
DIZZINESS EXERTIONAL			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DYSGEUSIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HEADACHE			
subjects affected / exposed	1 / 12 (8.33%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
HYPOAESTHESIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
LETHARGY			
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
MEMORY IMPAIRMENT			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
NEURALGIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
PARAESTHESIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PRESYNCOPE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SCIATICA			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SINUS HEADACHE			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
SOMNOLENCE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SYNCOPE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 12 (16.67%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
LYMPHADENOPATHY			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
BLEPHAROSPASM			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DRY EYE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EYE DISCHARGE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EYE PRURITUS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EYELID HAEMATOMA			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EYELID PTOSIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MYDRIASIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
OCULAR DISCOMFORT			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
OCULAR HYPERAEMIA			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
OCULAR ICTERUS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
ABDOMINAL PAIN			
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
APHTHOUS ULCER			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BARRETT'S OESOPHAGUS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

CONSTIPATION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DIARRHOEA			
subjects affected / exposed	2 / 12 (16.67%)	4 / 42 (9.52%)	1 / 4 (25.00%)
occurrences (all)	2	4	1
DIVERTICULUM			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DRY MOUTH			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DYSPEPSIA			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
DYSPHAGIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
FAECES PALE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
FAECES SOFT			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
FLATULENCE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GASTRITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GASTROINTESTINAL SOUNDS ABNORMAL			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MOUTH ULCERATION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NAUSEA			
subjects affected / exposed	2 / 12 (16.67%)	3 / 42 (7.14%)	1 / 4 (25.00%)
occurrences (all)	2	3	1
ORAL PAIN			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
STOMATITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
TOOTHACHE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
VOMITING			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
GALLBLADDER POLYP			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HYPERBILIRUBINAEMIA			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
JAUNDICE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
COLD SWEAT			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DERMATITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DRUG ERUPTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DRY SKIN			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
ECZEMA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
ERYTHEMA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
PRURITUS			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	1 / 4 (25.00%)
occurrences (all)	1	1	2
PRURITUS GENERALISED			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
RASH			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
RASH MACULAR			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RASH PAPULAR			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RASH PRURITIC			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RASH VESICULAR			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SKIN EXFOLIATION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SKIN FISSURES			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SKIN LESION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
CHROMATURIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PROTEINURIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
HYPOGONADISM MALE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
ARTHRITIS			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BACK PAIN			
subjects affected / exposed	1 / 12 (8.33%)	2 / 42 (4.76%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
COSTOCHONDRITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
FLANK PAIN			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
JOINT STIFFNESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
JOINT SWELLING			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MUSCLE FATIGUE			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MUSCLE SPASMS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MUSCLE TIGHTNESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MYALGIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NECK PAIN			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
PERIARTHRITIS			

subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
TENDONITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
ACUTE SINUSITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BRONCHITIS			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
CELLULITIS			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
CHLAMYDIAL INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
EAR INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
ERYSIPELAS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GASTROENTERITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GINGIVITIS			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

HERPES ZOSTER			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
HERPES ZOSTER DISSEMINATED			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HERPES ZOSTER OTICUS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
INFLUENZA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
ORAL HERPES			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PARONYCHIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PERTUSSIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PYELONEPHRITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
PYURIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
RHINITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

SECONDARY SYPHILIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SINUSITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
TINEA VERSICOLOUR			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
TONSILLITIS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
TOOTH ABSCESS			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	0 / 4 (0.00%)
occurrences (all)	0	4	0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 12 (16.67%)	3 / 42 (7.14%)	0 / 4 (0.00%)
occurrences (all)	2	3	0
GOUT			
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
HYPOKALAEMIA			

subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 12 (0.00%)	0 / 42 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2: Arm G	Part 2: Arm I	Part 2: Arm J
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	112 / 135 (82.96%)	18 / 19 (94.74%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANOGENITAL WARTS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SKIN PAPILLOMA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
DIASTOLIC HYPOTENSION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
HAEMATOMA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
HOT FLUSH			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
HYPERTENSION			
subjects affected / exposed	0 / 5 (0.00%)	4 / 135 (2.96%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
THROMBOPHLEBITIS SUPERFICIAL			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

ASTHENIA			
subjects affected / exposed	0 / 5 (0.00%)	13 / 135 (9.63%)	2 / 19 (10.53%)
occurrences (all)	0	14	2
CHEST DISCOMFORT			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
CHEST PAIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
CHILLS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
EARLY SATIETY			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
FATIGUE			
subjects affected / exposed	0 / 5 (0.00%)	40 / 135 (29.63%)	6 / 19 (31.58%)
occurrences (all)	0	42	8
FEELING ABNORMAL			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
FEELING JITTERY			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
PAIN			
subjects affected / exposed	1 / 5 (20.00%)	4 / 135 (2.96%)	0 / 19 (0.00%)
occurrences (all)	1	4	0
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

PYREXIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
TEMPERATURE INTOLERANCE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
TENDERNESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
VESSEL PUNCTURE SITE BRUISE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Social circumstances			
MENOPAUSE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
BREAST MASS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
ERECTILE DYSFUNCTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
GENITAL RASH			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
COUGH			

subjects affected / exposed	0 / 5 (0.00%)	7 / 135 (5.19%)	1 / 19 (5.26%)
occurrences (all)	0	8	1
DYSPNOEA			
subjects affected / exposed	0 / 5 (0.00%)	8 / 135 (5.93%)	2 / 19 (10.53%)
occurrences (all)	0	9	2
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 5 (20.00%)	6 / 135 (4.44%)	1 / 19 (5.26%)
occurrences (all)	1	6	1
EPISTAXIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
NASAL CONGESTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
NASAL DRYNESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
RESPIRATORY TRACT CONGESTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
RHINORRHOEA			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
ABNORMAL DREAMS			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
AFFECT LABILITY			
subjects affected / exposed	0 / 5 (0.00%)	4 / 135 (2.96%)	1 / 19 (5.26%)
occurrences (all)	0	4	2

AGITATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
ANXIETY			
subjects affected / exposed	0 / 5 (0.00%)	11 / 135 (8.15%)	1 / 19 (5.26%)
occurrences (all)	0	11	1
CONFUSIONAL STATE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
DEPRESSED MOOD			
subjects affected / exposed	1 / 5 (20.00%)	4 / 135 (2.96%)	0 / 19 (0.00%)
occurrences (all)	1	4	0
DEPRESSION			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
INSOMNIA			
subjects affected / exposed	1 / 5 (20.00%)	25 / 135 (18.52%)	2 / 19 (10.53%)
occurrences (all)	1	26	2
IRRITABILITY			
subjects affected / exposed	0 / 5 (0.00%)	7 / 135 (5.19%)	2 / 19 (10.53%)
occurrences (all)	0	7	2
LIBIDO INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
MIDDLE INSOMNIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
NERVOUSNESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
NIGHTMARE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
RESTLESSNESS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0

SLEEP DISORDER			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
STRESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
WITHDRAWAL SYNDROME			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
BLOOD POTASSIUM INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
CREATININE RENAL CLEARANCE DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	13 / 135 (9.63%)	6 / 19 (31.58%)
occurrences (all)	0	15	6
WEIGHT DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
WEIGHT INCREASED			

subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
ANIMAL BITE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
ANKLE FRACTURE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
ARTHROPOD BITE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
CONTUSION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
EXCORIATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
FALL			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
MENISCUS INJURY			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
MUSCLE STRAIN			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SKIN ABRASION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

TACHYCARDIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nervous system disorders			
DISTURBANCE IN ATTENTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
DIZZINESS			
subjects affected / exposed	0 / 5 (0.00%)	10 / 135 (7.41%)	2 / 19 (10.53%)
occurrences (all)	0	11	2
DIZZINESS EXERTIONAL			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
DYSGEUSIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
HEADACHE			
subjects affected / exposed	1 / 5 (20.00%)	22 / 135 (16.30%)	4 / 19 (21.05%)
occurrences (all)	1	27	4
HYPOAESTHESIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
LETHARGY			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
MEMORY IMPAIRMENT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
NEURALGIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
NEUROPATHY PERIPHERAL			

subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
PARAESTHESIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
PRESYNCOPE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SCIATICA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SINUS HEADACHE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SOMNOLENCE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SYNCOPE			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 5 (20.00%)	6 / 135 (4.44%)	1 / 19 (5.26%)
occurrences (all)	1	7	1
LYMPHADENOPATHY			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
BLEPHAROSPASM			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
DRY EYE			

subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
EYE DISCHARGE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
EYE PRURITUS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
EYELID HAEMATOMA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
EYELID PTOSIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
MYDRIASIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
OCULAR DISCOMFORT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
OCULAR HYPERAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
OCULAR ICTERUS			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
ABDOMINAL PAIN			
subjects affected / exposed	0 / 5 (0.00%)	3 / 135 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	3	1

ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 5 (0.00%)	5 / 135 (3.70%)	0 / 19 (0.00%)
occurrences (all)	0	6	0
APHTHOUS ULCER			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
BARRETT'S OESOPHAGUS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
CONSTIPATION			
subjects affected / exposed	0 / 5 (0.00%)	7 / 135 (5.19%)	2 / 19 (10.53%)
occurrences (all)	0	7	2
DIARRHOEA			
subjects affected / exposed	0 / 5 (0.00%)	26 / 135 (19.26%)	1 / 19 (5.26%)
occurrences (all)	0	35	1
DIVERTICULUM			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
DRY MOUTH			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
DYSPEPSIA			
subjects affected / exposed	0 / 5 (0.00%)	10 / 135 (7.41%)	0 / 19 (0.00%)
occurrences (all)	0	11	0
DYSPHAGIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
FAECES PALE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
FAECES SOFT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
FLATULENCE			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	3	0

GASTRITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
GASTROINTESTINAL SOUNDS ABNORMAL			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 5 (20.00%)	2 / 135 (1.48%)	1 / 19 (5.26%)
occurrences (all)	1	2	1
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
MOUTH ULCERATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
NAUSEA			
subjects affected / exposed	0 / 5 (0.00%)	34 / 135 (25.19%)	4 / 19 (21.05%)
occurrences (all)	0	41	4
ORAL PAIN			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
STOMATITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
TOOTHACHE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
VOMITING			
subjects affected / exposed	0 / 5 (0.00%)	11 / 135 (8.15%)	1 / 19 (5.26%)
occurrences (all)	0	19	1
Hepatobiliary disorders			

GALLBLADDER POLYP			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
HYPERBILIRUBINAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	4 / 135 (2.96%)	1 / 19 (5.26%)
occurrences (all)	0	9	1
JAUNDICE			
subjects affected / exposed	0 / 5 (0.00%)	7 / 135 (5.19%)	0 / 19 (0.00%)
occurrences (all)	0	7	0
Skin and subcutaneous tissue disorders			
COLD SWEAT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
DERMATITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
DRUG ERUPTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
DRY SKIN			
subjects affected / exposed	0 / 5 (0.00%)	4 / 135 (2.96%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
ECZEMA			
subjects affected / exposed	0 / 5 (0.00%)	4 / 135 (2.96%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
ERYTHEMA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	0 / 5 (0.00%)	18 / 135 (13.33%)	2 / 19 (10.53%)
occurrences (all)	0	20	2
PRURITUS GENERALISED			

subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
RASH			
subjects affected / exposed	0 / 5 (0.00%)	6 / 135 (4.44%)	2 / 19 (10.53%)
occurrences (all)	0	7	2
RASH MACULAR			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
RASH PAPULAR			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
RASH PRURITIC			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
RASH VESICULAR			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SKIN EXFOLIATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SKIN FISSURES			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
SKIN LESION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
CHROMATURIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
PROTEINURIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
HYPOGONADISM MALE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 5 (0.00%)	5 / 135 (3.70%)	0 / 19 (0.00%)
occurrences (all)	0	5	0
ARTHRITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
BACK PAIN			
subjects affected / exposed	0 / 5 (0.00%)	6 / 135 (4.44%)	3 / 19 (15.79%)
occurrences (all)	0	6	3
COSTOCHONDRITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
FLANK PAIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
JOINT STIFFNESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
JOINT SWELLING			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
MUSCLE FATIGUE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
MUSCLE SPASMS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
MUSCLE TIGHTNESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
MYALGIA			

subjects affected / exposed	0 / 5 (0.00%)	4 / 135 (2.96%)	0 / 19 (0.00%)
occurrences (all)	0	5	0
NECK PAIN			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
PERIARTHRITIS			
subjects affected / exposed	1 / 5 (20.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
TENDONITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
ACUTE SINUSITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
BRONCHITIS			
subjects affected / exposed	0 / 5 (0.00%)	6 / 135 (4.44%)	0 / 19 (0.00%)
occurrences (all)	0	6	0
CELLULITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
CHLAMYDIAL INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
EAR INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
ERYSIPELAS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

GASTROENTERITIS			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 5 (20.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
GINGIVITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
HERPES ZOSTER			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
HERPES ZOSTER DISSEMINATED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
HERPES ZOSTER OTICUS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
INFLUENZA			
subjects affected / exposed	0 / 5 (0.00%)	5 / 135 (3.70%)	0 / 19 (0.00%)
occurrences (all)	0	5	0
NASOPHARYNGITIS			
subjects affected / exposed	0 / 5 (0.00%)	12 / 135 (8.89%)	4 / 19 (21.05%)
occurrences (all)	0	17	7
ORAL HERPES			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	5	0
PARONYCHIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
PERTUSSIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
PYELONEPHRITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0

PYURIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
RHINITIS			
subjects affected / exposed	1 / 5 (20.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	1	2	0
SECONDARY SYPHILIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
SINUSITIS			
subjects affected / exposed	0 / 5 (0.00%)	2 / 135 (1.48%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
TINEA VERSICOLOUR			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
TONSILLITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
TOOTH ABSCESS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	12 / 135 (8.89%)	1 / 19 (5.26%)
occurrences (all)	0	12	1
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 5 (20.00%)	6 / 135 (4.44%)	2 / 19 (10.53%)
occurrences (all)	1	6	2
VIRAL UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 5 (0.00%)	1 / 135 (0.74%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 5 (20.00%)	3 / 135 (2.22%)	1 / 19 (5.26%)
occurrences (all)	1	3	1
GOUT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
HYPOKALAEMIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 135 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2: Arm K		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 28 (85.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANOGENITAL WARTS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SKIN PAPILLOMA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Vascular disorders			
DIASTOLIC HYPOTENSION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HAEMATOMA			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
HOT FLUSH			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HYPERTENSION			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
THROMBOPHLEBITIS SUPERFICIAL			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
CHEST DISCOMFORT			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
CHEST PAIN			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
CHILLS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
EARLY SATIETY			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
FATIGUE			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
FEELING ABNORMAL			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
FEELING JITTERY			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
INFLUENZA LIKE ILLNESS			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
PAIN			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
PYREXIA			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
TEMPERATURE INTOLERANCE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
TENDERNESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
VESSEL PUNCTURE SITE BRUISE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Social circumstances			
MENOPAUSE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
BREAST MASS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
ERECTILE DYSFUNCTION			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
GENITAL RASH			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
COUGH			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
DYSPNOEA			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
EPISTAXIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
NASAL CONGESTION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
NASAL DRYNESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
RESPIRATORY TRACT CONGESTION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
RHINORRHOEA			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
ABNORMAL DREAMS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
AFFECT LABILITY			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
AGITATION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
ANXIETY			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
CONFUSIONAL STATE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DEPRESSED MOOD			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DEPRESSION			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
INSOMNIA			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
IRRITABILITY			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
LIBIDO INCREASED			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		

MIDDLE INSOMNIA			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
NERVOUSNESS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
NIGHTMARE			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
RESTLESSNESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SLEEP DISORDER			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
STRESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
WITHDRAWAL SYNDROME			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
BLOOD POTASSIUM INCREASED			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
CREATININE RENAL CLEARANCE DECREASED			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HAEMOGLOBIN DECREASED			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
WEIGHT DECREASED			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
WEIGHT INCREASED			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
ANIMAL BITE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
ANKLE FRACTURE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
ARTHROPOD BITE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
CONTUSION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
EXCORIATION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
FALL			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
LIGAMENT SPRAIN			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
MENISCUS INJURY			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
MUSCLE STRAIN			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SKIN ABRASION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
DISTURBANCE IN ATTENTION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DIZZINESS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
DIZZINESS EXERTIONAL			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DYSGEUSIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HEADACHE			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
HYPOAESTHESIA			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
LETHARGY			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
MEMORY IMPAIRMENT			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
NEURALGIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
PARAESTHESIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
PRESYNCOPE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SCIATICA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SINUS HEADACHE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SOMNOLENCE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
SYNCOPE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		

LYMPHADENOPATHY			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Eye disorders			
BLEPHAROSPASM			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DRY EYE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
EYE DISCHARGE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
EYE PRURITUS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
EYELID HAEMATOMA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
EYELID PTOSIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
MYDRIASIS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
OCULAR DISCOMFORT			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
OCULAR HYPERAEMIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
OCULAR ICTERUS			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
ABDOMINAL PAIN			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
APHTHOUS ULCER			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
BARRETT'S OESOPHAGUS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
CONSTIPATION			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
DIARRHOEA			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	3		
DIVERTICULUM			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DRY MOUTH			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
DYSPEPSIA			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		

DYSPHAGIA				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
FAECES PALE				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
FAECES SOFT				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
FLATULENCE				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
GASTRITIS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
GASTROINTESTINAL SOUNDS ABNORMAL				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
GASTROOESOPHAGEAL REFLUX DISEASE				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
GINGIVAL BLEEDING				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
HAEMORRHOIDAL HAEMORRHAGE				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
MOUTH ULCERATION				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
NAUSEA				
subjects affected / exposed	5 / 28 (17.86%)			
occurrences (all)	5			
ORAL PAIN				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
STOMATITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
TOOTHACHE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
VOMITING			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Hepatobiliary disorders			
GALLBLADDER POLYP			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HYPERBILIRUBINAEMIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
JAUNDICE			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
COLD SWEAT			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
DERMATITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DRUG ERUPTION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
DRY SKIN			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
ECZEMA			

subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
ERYTHEMA				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
HYPERHIDROSIS				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
PRURITUS				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
PRURITUS GENERALISED				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
RASH				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
RASH MACULAR				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
RASH PAPULAR				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
RASH PRURITIC				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
RASH VESICULAR				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
SKIN EXFOLIATION				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
SKIN FISSURES				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
SKIN LESION				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
CHROMATURIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
NEPHROLITHIASIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
PROTEINURIA			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Endocrine disorders			
HYPOGONADISM MALE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
ARTHRITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
BACK PAIN			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
COSTOCHONDRITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
FLANK PAIN			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
JOINT STIFFNESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
JOINT SWELLING			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
MUSCLE FATIGUE			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
MUSCLE SPASMS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
MUSCLE TIGHTNESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
MYALGIA			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
NECK PAIN			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
PERIARTHRITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
TENDONITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Infections and infestations			
ACUTE SINUSITIS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
BRONCHITIS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

CELLULITIS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
CHLAMYDIAL INFECTION				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
EAR INFECTION				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
ERYSIPELAS				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
GASTROENTERITIS				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
GASTROENTERITIS VIRAL				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
GINGIVITIS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
HERPES ZOSTER				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
HERPES ZOSTER DISSEMINATED				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
HERPES ZOSTER OTICUS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
INFLUENZA				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
NASOPHARYNGITIS				
subjects affected / exposed	4 / 28 (14.29%)			
occurrences (all)	4			

ORAL HERPES				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
PARONYCHIA				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
PERTUSSIS				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
PYELONEPHRITIS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
PYURIA				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
RHINITIS				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
SECONDARY SYPHILIS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
SINUSITIS				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
STAPHYLOCOCCAL INFECTION				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
TINEA VERSICOLOUR				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
TONSILLITIS				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			

TOOTH ABSCESS			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
GOUT			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HYPOKALAEMIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2014	- Added dolutegravir (DTG) as a qualifying HIV-1 antiretroviral (ARV) for HCV/HIV-1 coinfected subjects and included updates related to the addition of this HIV-1 protease inhibitor throughout the protocol. - Updated the list of exclusionary laboratory parameters that were not eligible to be rescreened and updated the list of eligibility criteria that did not need to be repeated upon rescreening. - Updated the inclusion/exclusion criteria including eligible screening laboratory results. - Specified that female subjects of childbearing potential should have used contraception to prevent pregnancy starting with Study Day 1 and for 7 months after stopping study drugs or as directed by local RBV label per inclusion criterion (No. 3). - Updated the definition of pegylated interferon/ribavirin (pegIFN/RBV)-experienced subjects in the inclusion criteria (No. 5) and throughout the protocol. - Removed inclusion criterion requiring confirmation of a past positive result for anti-HIV antibody (HIV Ab) of HIV-1 infection. - Removed inclusion criterion for subjects who had confirmation of a plasma HIV-1 RNA > LLOQ at least twice prior to screening and inclusion criterion for confirmation of their CD4+ count or CD4+% prior to screening. - Clarified process for confirming the presence or absence of cirrhosis. - Allowed the use of hormonal contraceptives during study drug administration based on results of drug-drug interaction (DDI) studies. - Updated "Failure to Maintain HIV Virologic Suppression" section. - Updated Treatments Administered and Selection and Timing of Dose for Each Subject for atazanavir. - Updated Toxicity Management for consistency with other AbbVie HCV Phase 3 studies. - Added Collection of data regarding known HIV opportunistic infections.
17 July 2014	- Clarified the minimum and maximum number of subjects with no HIV-1 protease inhibitor (PI) exposure other than DRV allowed to enroll in Part 1b to ensure a balanced enrollment of previously PI-naïve and PI-experienced subjects. - Updated language related to hormonal contraceptives for female subjects of childbearing potential, including the use of progestin-only hormonal contraceptive methods. - Updated Inclusion Criterion 13 for subjects to have had confirmation of plasma HIV-1 RNA below LLOQ at least twice during the 24 weeks prior to screening.

05 March 2015	- Revised the treatment arms in Part 2 of the study for 3-direct-acting antiviral agent (DAA) with and without RBV for 12 and 24 weeks, based on data from AbbVie's Phase 3 program in HCV GT1 monoinfected subjects. - Allowed for the inclusion of HCV GT4 subjects into Part 2. - Revised Selection of Study Population to include updated Inclusion and Exclusion criteria specific to subjects screening for Part 2 of the study, moved Inclusion and Exclusion criteria for subjects screening for Part 1b within protocol appendix, and updated subsections related to prior, concomitant, and prohibited medications. - Added DTG and abacavir (ABC) as qualifying HIV-1 ARVs for HCV GT1 or GT4/HIV-1 coinfected subjects and DRV QD as a qualifying HIV-1 antiretroviral for HCV GT4/HIV-1 coinfected subjects in Part 2, based on data from AbbVie's DDI studies. - Shortened the post-treatment follow-up period from 48 weeks to 24 weeks for Part 1b and Part 2 of the study based on data from AbbVie's Phase 3 program. - Expanded the definition for HCV treatment-experienced subjects. - Expanded and updated the study objectives to accommodate the addition of GT4 population and GT1 population with other HCV treatment experience and/or additional HIV ARV medications. - Updated statistical methods based on the updated study primary and the first of the secondary efficacy endpoints to compare the percentage of GT1 subjects in Part 2 achieving SVR12 to the historical SVR12 rate for sofosbuvir plus ribavirin in order to test for non-inferiority. - Updated determination of sample size based on the updated study design.
05 March 2015	(continued) - Moved the longitudinal analysis of CD4+ T cell counts to the safety analysis section. - Updated add-on PegIFN/RBV therapy for subjects participating in Part 1a. - Updated criteria for initiation of Part 2 to remove the inclusion of HCV GT1 subjects on a DRV based HIV-1 ART regimen into Part 2. - Updated Discontinuation of Individual Subjects section to allow for a pregnant subject to continue DAAs administration at the discretion of the investigator. - Updated Treatments Administered and Selection and Timing of Dose for Each Subject sections to clarify the 3-DAA and 2-DAA dosing requirements and RBV dosing for subjects with a screening creatinine clearance (CrCl) < 50 mL/min.
12 June 2015	- Updated Inclusion Criteria (Part 2) Criterion 7 to clarify that subjects must have been positive for anti-HCV Ab and have had an HCV RNA > 1,000 IU/mL at Screening. - Added the inclusion and exclusion criteria specific to Part 1a of the study as appendix, updated the inclusion and exclusion criteria for Part 1b appendix, and made updates throughout the protocol relating to the additional appendix.
15 April 2016	- Removed the specification for a minimum number of 15 subjects in each of Arms F and G due to shortage of subjects available for screening. - Redefined all analyses to be evaluated for the combined group of subjects from Arms E, F, H, I and J in Part 2. Deleted analyses of the combined group of subjects from Arms E, G, H, I, and J in Part 2. Deleted the fixed-sequence testing procedure for the primary and first secondary efficacy endpoints.to align with dosing recommendations in current labeling where the recommended regimen for GT1b-infected patients with cirrhosis was ABT-450/r/ABT-267 and ABT-333 without RBV for 12 weeks. - Deleted analyses comparing Arms F and G (ABT-450/r/ABT-267 + ABT-333 without and with RBV, respectively, for 12 weeks) due to the small sample sizes. - Added the Sanger sequencing assay of the NS5B region as a reflex test methodology due to the Sanger assay's increased sensitivity and use of direct sequencing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported