Clinical trial results:
A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obeticholic Acid in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis.

Summary

EudraCT number	2017-000474-11
Trial protocol	DE ES GB HU PL
Global end of trial date	08 September 2022

Results information

Result version number	v1 (current)
This version publication date	23 September 2023
First version publication date	23 September 2023

Trial information

Trial identification

Sponsor protocol code	747-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03439254
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intercept Pharmaceuticals, Inc.
Sponsor organisation address	305 Madison Avenue, Morristown, New Jersey, United States, 07960
Public contact	Medical Information, Intercept Pharmaceuticals, Inc., +1 844 782–4278, medinfo@interceptpharma.com
Scientific contact	Medical Information, Intercept Pharmaceuticals, Inc., +1 844 782–4278, medinfo@interceptpharma.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	08 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of OCA treatment compared with placebo on improvement in fibrosis by at least 1 stage with no worsening of Nonalcoholic Steatohepatitis (NASH), using the NASH Clinical Research Network (CRN) scoring system.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the Sponsor’s policies.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2017
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	Canada: 34
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United States: 697
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	France: 48
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Hungary: 8
Worldwide total number of subjects	919
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)	623
From 65 to 84 years	296
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a total of around 286 centers.

Pre-assignment

Screening details:

This was a Phase 3, double-Blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of Obeticholic Acid (OCA) in participants with compensated cirrhosis due to Nonalcoholic Steatohepatitis (NASH). The study comprised of a double-blind (DB) phase (18 months) followed by Open-label extension (OLE) phase(12 months)

Period 1

Period 1 title	Double-blind Phase (18 Months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	DB: Placebo

Arm description:

Participants were randomized to receive placebo once daily orally with water, in conjunction with local standard of care.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo once daily orally with water was administered.

Arm title	DB: OCA 10 Milligrams (mg)

Arm description:

Participants were randomized to receive OCA 10 mg once daily dosing orally with water, in conjunction with local standard of care.

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

Dosage and administration details:

OCA 10 mg once daily dosing orally with water was administered

Arm title	DB: OCA 10 mg Titrated to OCA 25 mg

Arm description:

Participants were randomized to receive OCA 10 mg for the first 3 months prior to uptitrating to OCA 25 mg at Month 3, once daily dosing orally with water, in conjunction with local standard of care. Uptitration was determined based on the laboratory criteria and safety and tolerability assessments completed up to and including Month 3. If uptitration at Month 3 was not feasible, the window for uptitration was extended by up to one calendar month, after consultation and agreement with the Medical Monitor.

Arm type	Experimental
Investigational medicinal product name	OCA 10 mg Titrated to OCA 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA 10 mg for the first 3 months prior to uptitrating to OCA 25 mg at Month 3, once daily dosing orally with water, was administered.

Number of subjects in period 1	DB: Placebo	DB: OCA 10 Milligrams (mg)	DB: OCA 10 mg Titrated to OCA 25 mg
Started	313	296	310
Completed	284	274	275
Not completed	29	22	35
Physician decision	-	-	1
Participant moved to Kansas	1	-	-
Stopped IP due to an AE in Australia	-	1	-
Site closure	-	-	1
Consent withdrawn by subject	12	6	9
Site cover, subject not willing to be transferred	1	-	-
Covid-19 Non-Adverse Event Related Issues	1	-	-
Spouse had surgery, participant unable to take IP	-	-	1
Non- Compliance With Study Drug	1	-	-
Adverse event, non-fatal	11	12	15
Death	1	2	2
Progressive Disease	1	-	-
Lost to follow-up	-	1	5
Drug Holiday	-	-	1

Period 2

Period 2 title	Open Label Extension Phase (12 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	OLE: OCA 10 mg (DB Placebo)

Arm description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to placebo in the DB phase were re-randomized to either receive OCA 10 mg or titrated dose of
OCA 25 mg. Uptitration was determined based on the same criteria and assessments as employed in the DB phase

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

Dosage and administration details:

OCA 10 mg once daily dosing orally with water was administered

Arm title	OLE: OCA 10 mg (DB OCA 10 mg)

Arm description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to OCA 10 mg during the DB phase continued the same dosing regimen they received at the
end of the DB Phase; however, they underwent dummy titration to maintain study blind until all participants completed the DB phase

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

Dosage and administration details:

OCA 10 mg once daily dosing orally with water was administered

Arm title	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)

Arm description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to OCA 10 mg to 25 mg titration during the DB phase continued the same dosing regimen they
received at the end of the DB Phase; however, they underwent dummy titration to maintain study blind until all participants completed the DB phase.

Arm type	Experimental
Investigational medicinal product name	OCA 10 mg Titrated to OCA 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA 10 mg for the first 3 months prior to uptitrating to OCA 25 mg at Month 3, once daily dosing orally with water, was administered.

Number of subjects in period 2[1]	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)
Started	231	221	207
Completed	215	208	192
Not completed	16	13	15
Physician decision	1	-	-
Consent withdrawn by subject	5	3	5
Adverse event, non-fatal	8	5	7
Progressive Disease	1	2	-
Covid-19 Non-AE Related Issues	-	-	1
Lost to follow-up	-	2	-
Increase CR from Baseline	-	1	-
Bariatric Surgery	1	-	1
Medical reasons by Sponsor	-	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase.

Baseline characteristics

Reporting groups	
Reporting group title	DB: Placebo
Reporting group description:	
Participants were randomized to receive placebo once daily orally with water, in conjunction with local standard of care.	
Reporting group title	DB: OCA 10 Milligrams (mg)
Reporting group description:	
Participants were randomized to receive OCA 10 mg once daily dosing orally with water, in conjunction with local standard of care.	
Reporting group title	DB: OCA 10 mg Titrated to OCA 25 mg
Reporting group description:	
Participants were randomized to receive OCA 10 mg for the first 3 months prior to uptitrating to OCA 25 mg at Month 3, once daily dosing orally with water, in conjunction with local standard of care. Uptitration was determined based on the laboratory criteria and safety and tolerability assessments completed up to and including Month 3. If uptitration at Month 3 was not feasible, the window for uptitration was extended by up to one calendar month, after consultation and agreement with the Medical Monitor.	

Reporting group values	DB: Placebo	DB: OCA 10 Milligrams (mg)	DB: OCA 10 mg Titrated to OCA 25 mg
Number of subjects	313	296	310
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	217	194	212
From 65-84 years	96	102	98
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.5	60.1	60.1
standard deviation	± 8.99	± 8.70	± 8.67
Gender categorical Units: Subjects			
Female	212	184	209
Male	101	112	101
Ethnicity Units: Subjects			
Hispanic or Latino	44	52	55
Not Hispanic or Latino	246	217	233
Unknown or Not Reported	23	27	22
Race Units: Subjects			

American Indian or Alaska Native	3	3	4
Asian	8	5	5
Native Hawaiian or Other Pacific Islander	0	1	3
Black or African American	4	6	4
White	272	254	272
More than one race	1	2	1
Unknown or Not Reported	25	25	21

Reporting group values	Total		
Number of subjects	919		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	623		
From 65-84 years	296		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	605		
Male	314		
Ethnicity			
Units: Subjects			
Hispanic or Latino	151		
Not Hispanic or Latino	696		
Unknown or Not Reported	72		
Race			
Units: Subjects			
American Indian or Alaska Native	10		
Asian	18		
Native Hawaiian or Other Pacific Islander	4		
Black or African American	14		
White	798		
More than one race	4		
Unknown or Not Reported	71		

End points

End points reporting groups

Reporting group title	DB: Placebo

Reporting group description:

Participants were randomized to receive placebo once daily orally with water, in conjunction with local standard of care.

Reporting group title	DB: OCA 10 Milligrams (mg)

Reporting group description:

Participants were randomized to receive OCA 10 mg once daily dosing orally with water, in conjunction with local standard of care.

Reporting group title	DB: OCA 10 mg Titrated to OCA 25 mg

Reporting group description:

Participants were randomized to receive OCA 10 mg for the first 3 months prior to uptitrating to OCA 25 mg at Month 3, once daily dosing orally with water, in conjunction with local standard of care. Uptitration was determined based on the laboratory criteria and safety and tolerability assessments completed up to and including Month 3. If uptitration at Month 3 was not feasible, the window for uptitration was extended by up to one calendar month, after consultation and agreement with the Medical Monitor.

Reporting group title	OLE: OCA 10 mg (DB Placebo)

Reporting group description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to placebo in the DB phase were re-randomized to either receive OCA 10 mg or titrated dose of
OCA 25 mg. Uptitration was determined based on the same criteria and assessments as employed in the DB phase

Reporting group title	OLE: OCA 10 mg (DB OCA 10 mg)

Reporting group description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to OCA 10 mg during the DB phase continued the same dosing regimen they received at the
end of the DB Phase; however, they underwent dummy titration to maintain study blind until all participants completed the DB phase

Reporting group title	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)

Reporting group description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to OCA 10 mg to 25 mg titration during the DB phase continued the same dosing regimen they
received at the end of the DB Phase; however, they underwent dummy titration to maintain study blind until all participants completed the DB phase.

Primary: DB Phase: Percentage of Responders Showing Improvement in Fibrosis by at Least 1 Stage Without Worsening of Nonalcoholic Steatohepatitis (NASH)

End point title	DB Phase: Percentage of Responders Showing Improvement in Fibrosis by at Least 1 Stage Without Worsening of Nonalcoholic Steatohepatitis (NASH)

End point description:

Fibrosis stage evaluated by NASH Clinical Research Network(CRN)Fibrosis Staging System with stages:0=no fibrosis;1=perisinusoidal/periportal;1A=mild,zone 3,perisinusoidal;1B=moderate,zone 3,perisinusoidal;1C=portal/periportal;2=perisinusoidal and portal/periportal;3=bridging fibrosis;4=cirrhosis.No worsening of steatohepatitis defined as no worsening of lobular inflammation or hepatocellular ballooning grade per scoring in relevant nonalcoholic fatty liver disease activity score(NAS)categories.NAS is semiquantitative scoring system based on unweighted sum of:steatosis

to 3=>66%),lobular inflammation(0=no foci to 3=>4 foci/200x),hepatocellular ballooning(0=none to 2=many cells/prominent ballooning)scores.Total scale range:0-12;0:no features of fatty liver disease and 12:highest degree of fatty liver disease.Higher scores:worse symptoms.Responders:did not discontinue treatment due to Adverse event(AE) or did not die and had evaluable post-Baseline biopsy assessment.

End point type	Primary

End point timeframe:

Up to 18 months

End point values	DB: Placebo	DB: OCA 10 Milligrams (mg)	DB: OCA 10 mg Titrated to OCA 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	313	296	310	
Units: Percentage of responders				
number (not applicable)	9.9	11.1	11.9	

Statistical analyses

Statistical analysis title	DB: Placebo, DB: OCA 10 Milligrams (mg)
Comparison groups	DB: Placebo v DB: OCA 10 Milligrams (mg)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.6172
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response ratio(Mantel-Haenszel estimate)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.79

Notes:

[1] - Treatment / Placebo Response Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by Baseline diabetes status (yes/no).

Statistical analysis title	DB: Placebo, DB: OCA 10 mg Titrated to OCA 25 mg
Comparison groups	DB: Placebo v DB: OCA 10 mg Titrated to OCA 25 mg
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.4184
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response ratio(Mantel-Haenszel estimate)
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.89

Notes:

[2] - Treatment / Placebo Response Ratio = Percentage of Responders in Active Treatment Arm / Percentage of Responders in Placebo, stratified by Baseline diabetes status (yes/no).

Primary: OLE Phase: Number of Participants With Non-serious Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	OLE Phase: Number of Participants With Non-serious Adverse Events (AEs) and Serious Adverse Events (SAEs)[3]

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. An SAE is any untoward medical occurrence that, at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect or any other situation according to medical or scientific judgment. Safety Population: included all randomized participants who received at least 1 dose of investigational product (OCA or placebo).

End point type	Primary

End point timeframe:

Up to 12 months

Notes:

[3] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	207	
Units: Participants				
number (not applicable)				
AEs	199	213	197	
SAEs	26	50	48	

Statistical analyses

No statistical analyses for this end point

Primary: OLE Phase: Number of Participants Reporting All-cause Mortality

End point title	OLE Phase: Number of Participants Reporting All-cause Mortality[4]

End point description:

All-cause mortality is defined as death due to any cause. Number of participants reporting all-cause mortality is presented.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[4] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	207	
Units: Participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: OLE Phase: Number of Participants With Adjudicated Liver Related Clinical Outcomes: Ascites, Hepatocellular Carcinoma (HCC) and Non-liver Related Death

End point title	OLE Phase: Number of Participants With Adjudicated Liver Related Clinical Outcomes: Ascites, Hepatocellular Carcinoma (HCC) and Non-liver Related Death[5]

End point description:

Adjudication was performed under the review of Hepatic Safety Adjudication Committee (HSAC) of all available data for each identified participant to determine liver injury status. Number of participants with adjudicated liver related clinical outcomes for the following is presented: Ascites (secondary to cirrhosis and requiring medical intervention), Hepatocellular carcinoma (HCC) and non-liver related death.

End point type	Primary

End point timeframe:

Up to 12 months

Notes:

[5] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	207	
Units: Participants				
number (not applicable)				
Ascites	1	0	2	
HCC	3	1	1	
Non-liver related death	1	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: OLE Phase: Number of Participants With Adjudicated Liver Related Clinical Outcomes: Worsening of Child-Pugh Score

End point title	OLE Phase: Number of Participants With Adjudicated Liver Related Clinical Outcomes: Worsening of Child-Pugh Score[6]

End point description:

The Child-Pugh classification was a scoring system used for the classification of the severity of cirrhosis. It included three continuous variables (bilirubin, albumin, and international normalized ratio) and two discrete variables (ascites and encephalopathy). Each variable was scored 1-3 with 3 indicating most severe derangement. The determination of Child-Pugh score ranged from 5 to 15. The higher the score, the sicker the participant. Adjudication was performed
under the review of HSAC of all available data for each identified participant to determine liver injury status. Number of participants with adjudicated liver related clinical outcomes for worsening of Child-Pugh score is presented.

End point type	Primary

End point timeframe:

Up to 12 months

Notes:

[6] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	207	
Units: Participants				
number (not applicable)	0	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: OLE Phase: Number of Participants With Adjudicated Liver Related Clinical Outcomes: Model for End-Stage Liver Disease (MELD) Score ≥15

End point title	OLE Phase: Number of Participants With Adjudicated Liver Related Clinical Outcomes: Model for End-Stage Liver Disease (MELD) Score ≥15[7]

End point description:

MELD was a scoring system for assessing the severity of chronic liver disease and to assess prognosis and suitability for liver transplantation. It uses the participant's values for total bilirubin, serum creatinine, and the international normalized ratio for prothrombin time to predict survival. MELD score ranges from 6 (less ill) to 40 (gravely ill) with scores and mortality probability being: Score 40=71.3% mortality; Scores 30-39=52.6% mortality; Scores 20-29=19.6%
mortality; Scores10-19=6.0% mortality; Score 9 or less=1.9% mortality. Higher scores indicated greater disease severity. Adjudication was performed under the review of HSAC of all available data for each identified participant to determine liver injury status. Number of participants with adjudicated liver related clinical outcomes for MELD score ≥15 is presented.

End point type	Primary

End point timeframe:

Up to 12 months

Notes:

[7] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	207	
Units: Participants				
number (not applicable)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 18 months for DB phase and Up to 1 year for OLE phase

Adverse event reporting additional description:

Safety Population: included all randomized participants who received at least 1 dose of investigational product (OCA or placebo).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	DB: Placebo

Reporting group description:

Participants were randomized to receive placebo once daily orally with water, in conjunction with local standard of care.

Reporting group title	DB: OCA 10 Milligrams (mg)

Reporting group description:

Participants were randomized to receive OCA 10 mg once daily dosing orally with water, in conjunction with local standard of care.

Reporting group title	DB: OCA 10 mg Titrated to OCA 25 mg

Reporting group description:

Participants were randomized to receive OCA 10 mg for the first 3 months prior to uptitrating to OCA 25 mg at Month 3, once daily dosing orally with water, in conjunction with local standard of care. Uptitration was determined based on the laboratory criteria and safety and tolerability assessments completed prior to Month 3. If uptitration at Month 3 was not feasible, the window for uptitration was extended by up to one calendar month, after consultation and agreement with the Medical Monitor.

Reporting group title	OLE: OCA 10 mg (DB Placebo)

Reporting group description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to placebo in the DB phase were re-randomized to either receive OCA 10 mg or titrated dose of
OCA 25 mg. Uptitration was determined based on the same criteria and assessments as employed in the DB phase.

Reporting group title	OLE: OCA 10 mg (DB OCA 10 mg)

Reporting group description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to OCA 10 mg during the DB phase continued the same dosing regimen they received at the
end of the DB Phase; however, they underwent dummy titration to maintain study blind until all participants completed the DB phase.

Reporting group title	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)

Reporting group description:

Participants who completed the DB phase (and continued to receive investigational product) were eligible to enroll into the OLE phase. All participants received OCA upon entry into the OLE phase. Participants randomized to OCA 10 mg to 25 mg titration during the DB phase continued the same dosing regimen they
received at the end of the DB Phase; however, they underwent dummy titration to maintain study blind until all participants completed the DB phase.

Serious adverse events	DB: Placebo	DB: OCA 10 Milligrams (mg)	DB: OCA 10 mg Titrated to OCA 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 312 (15.38%)	55 / 295 (18.64%)	54 / 309 (17.48%)
number of deaths (all causes)	5	3	3
number of deaths resulting from adverse events	4	3	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
B precursor type acute leukaemia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bladder cancer			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bladder transitional cell carcinoma			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Breast cancer			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Breast cancer metastatic			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Carcinoid tumour of the small bowel			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Extramammary Paget's disease			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatocellular carcinoma			

subjects affected / exposed	0 / 312 (0.00%)	3 / 295 (1.02%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 312 (0.00%)	2 / 295 (0.68%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cell carcinoma recurrent			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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			
Aortic stenosis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertension			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypovolaemic shock			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Asthenia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Death			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Impaired healing			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Oedema peripheral			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Granuloma			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Pyrexia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	3 / 309 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Dyspnoea exertional			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Pulmonary embolism			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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			
Adjustment disorder			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anxiety			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Major depression			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 312 (0.00%)	2 / 295 (0.68%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Panic attack			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Investigations			

Troponin increased			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Joint injury			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Limb crushing injury			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Post procedural fever			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	3 / 295 (1.02%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0

Procedural pain			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	3 / 309 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 3
Road traffic accident			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	2 / 312 (0.64%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fall			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Femoral neck fracture			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Foot fracture			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Humerus fracture			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Post procedural complication			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Subdural haematoma			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Ulna fracture			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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			
Acute left ventricular failure			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 312 (0.64%)	0 / 295 (0.00%)	2 / 309 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 2
Angina unstable			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 312 (0.96%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Coronary artery occlusion			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Palpitations			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ventricular extrasystoles			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Aortic valve incompetence			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Bradycardia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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 failure			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Nervous system disorders			
Brain stem infarction			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	3 / 309 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Hepatic encephalopathy			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hypoaesthesia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Meningoradiculitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Paraesthesia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			

subjects affected / exposed	0 / 312 (0.00%)	3 / 295 (1.02%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 312 (0.64%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Encephalopathy			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Facial paralysis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Myelopathy			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Presyncope			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Bicytopenia			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vertigo positional			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 312 (0.64%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1

Ascites			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Colitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cryptitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	2 / 295 (0.68%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intra-abdominal haematoma			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oesophageal ulcer			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Rectal prolapse			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Umbilical hernia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vomiting			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abdominal hernia obstructive			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Enteritis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Gastritis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Haematochezia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Ileus			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Large intestine polyp			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Pancreatitis acute			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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 haemorrhage			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cholecystitis			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cholecystitis acute			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cholelithiasis			
subjects affected / exposed	0 / 312 (0.00%)	2 / 295 (0.68%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Hepatic cirrhosis			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic failure			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatitis alcoholic			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Hepatorenal syndrome			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hydrocholecystis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemobilia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Hepatic lesion			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Panniculitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blister			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Rash vesicular			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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			
Acute kidney injury			
subjects affected / exposed	2 / 312 (0.64%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 1
Nephrolithiasis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal impairment			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Hyperthyroidism			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cervical spinal stenosis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Posterior tibial tendon dysfunction			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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

Costochondritis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Lupus-like syndrome			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Osteoarthritis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Osteonecrosis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Spinal stenosis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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			
Abscess limb			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	0 / 312 (0.00%)	2 / 295 (0.68%)	3 / 309 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 3
Campylobacter infection			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cellulitis orbital			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis staphylococcal			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Clostridium difficile colitis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epididymitis			

subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Escherichia sepsis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Influenza			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Localised infection			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peritonitis			

subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia bacterial			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 312 (0.32%)	0 / 295 (0.00%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Suspected COVID-19			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	2 / 309 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Bursitis infective			

subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Cryptococcal fungaemia			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Endocarditis enterococcal			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Orchitis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Urosepsis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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 / 312 (0.00%)	1 / 295 (0.34%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 312 (0.32%)	1 / 295 (0.34%)	4 / 309 (1.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 6
Gout			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperglycaemia			

subjects affected / exposed	0 / 312 (0.00%)	2 / 295 (0.68%)	1 / 309 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Hypoglycaemia			
subjects affected / exposed	0 / 312 (0.00%)	1 / 295 (0.34%)	0 / 309 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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
Metabolic acidosis			
subjects affected / exposed	0 / 312 (0.00%)	0 / 295 (0.00%)	0 / 309 (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	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 231 (12.12%)	54 / 221 (24.43%)	50 / 207 (24.15%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
B precursor type acute leukaemia			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	2 / 221 (0.90%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bladder cancer			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Breast cancer			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	2 / 207 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Breast cancer metastatic			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Carcinoid tumour of the small bowel			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Colorectal cancer			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Extramammary Paget's disease			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Glioblastoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hepatocellular carcinoma			
subjects affected / exposed	3 / 231 (1.30%)	3 / 221 (1.36%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 4	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Lung neoplasm malignant			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Prostate cancer			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Renal cell carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cell carcinoma recurrent			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 231 (0.00%)	2 / 221 (0.90%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 231 (0.43%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Hypertension			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hypertensive emergency			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Asthenia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Death			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Impaired healing			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Non-cardiac chest pain			
subjects affected / exposed	2 / 231 (0.87%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Oedema peripheral			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Granuloma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Anaphylactic reaction			

subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Asthma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	3 / 207 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Dyspnoea exertional			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Haemothorax			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Pneumothorax			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Respiratory failure			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Acute respiratory failure			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pulmonary embolism			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Anxiety			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Major depression			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Mental status changes			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Panic attack			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
Troponin increased			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Ankle fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Joint injury			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Ligament rupture			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Limb crushing injury			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Post procedural fever			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Procedural pain			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	4 / 207 (1.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Road traffic accident			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Fall			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Femoral neck fracture			

subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 231 (0.43%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Angina pectoris			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Angina unstable			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 231 (0.87%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 failure acute			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Coronary artery disease			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Left ventricular failure			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Palpitations			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Sinus bradycardia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ventricular extrasystoles			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aortic valve incompetence			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bradycardia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	2 / 207 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Cardiac failure			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	2 / 207 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Hepatic encephalopathy			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hypoaesthesia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Meningoradiculitis			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Migraine			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Paraesthesia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	1 / 231 (0.43%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Facial paralysis			

subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Bicytopenia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 loss anaemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vertigo positional			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Eye disorders			

Blindness unilateral			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	2 / 207 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Ascites			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Cryptitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Faecaloma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 haemorrhage			

subjects affected / exposed	1 / 231 (0.43%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Melaena			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Oesophageal ulcer			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Pancreatitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 prolapse			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Vomiting			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Abdominal hernia obstructive			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enteritis			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastritis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haematochezia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ileus			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Large intestine polyp			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	2 / 221 (0.90%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cholecystitis			

subjects affected / exposed	0 / 231 (0.00%)	2 / 221 (0.90%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Cholecystitis acute			
subjects affected / exposed	1 / 231 (0.43%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hepatic failure			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hepatitis alcoholic			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hepatorenal syndrome			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hydrocholecystis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Haemobilia			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatic lesion			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Portal vein thrombosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Panniculitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Rash			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Blister			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rash vesicular			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Nephrolithiasis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal colic			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 impairment			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperthyroidism			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Cervical spinal stenosis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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

Musculoskeletal chest pain			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Posterior tibial tendon dysfunction			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Arthritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Costochondritis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lupus-like syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Spinal stenosis			

subjects affected / exposed	1 / 231 (0.43%)	0 / 221 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Appendicitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	3 / 207 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
COVID-19 pneumonia			
subjects affected / exposed	4 / 231 (1.73%)	3 / 221 (1.36%)	7 / 207 (3.38%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 5	0 / 3	0 / 7
Campylobacter infection			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	0 / 231 (0.00%)	2 / 221 (0.90%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cellulitis orbital			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Cellulitis staphylococcal			

subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Clostridium difficile colitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Diverticulitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epididymitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Escherichia sepsis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 infection			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Localised infection			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Peritonitis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Pneumonia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			

subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Suspected COVID-19			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	2 / 207 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Bursitis infective			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cryptococcal fungaemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endocarditis enterococcal			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Orchitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urosepsis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 231 (0.43%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	3 / 207 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 6
Gout			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hyperglycaemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Hypoglycaemia			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	0 / 207 (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
Lactic acidosis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 231 (0.00%)	0 / 221 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

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

Non-serious adverse events	DB: Placebo	DB: OCA 10 Milligrams (mg)	DB: OCA 10 mg Titrated to OCA 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	293 / 312 (93.91%)	279 / 295 (94.58%)	291 / 309 (94.17%)
Investigations			
Blood bilirubin increased			
subjects affected / exposed	12 / 312 (3.85%)	16 / 295 (5.42%)	17 / 309 (5.50%)
occurrences (all)	14	21	22
Blood creatinine increased			
subjects affected / exposed	10 / 312 (3.21%)	15 / 295 (5.08%)	13 / 309 (4.21%)
occurrences (all)	14	17	14
Low density lipoprotein increased			
subjects affected / exposed	7 / 312 (2.24%)	36 / 295 (12.20%)	34 / 309 (11.00%)
occurrences (all)	8	40	38
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 312 (3.53%)	9 / 295 (3.05%)	13 / 309 (4.21%)
occurrences (all)	12	9	14
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 312 (3.21%)	16 / 295 (5.42%)	17 / 309 (5.50%)
occurrences (all)	12	16	19
Headache			
subjects affected / exposed	26 / 312 (8.33%)	16 / 295 (5.42%)	23 / 309 (7.44%)
occurrences (all)	29	18	28
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 312 (11.22%)	28 / 295 (9.49%)	37 / 309 (11.97%)
occurrences (all)	38	33	47
Oedema peripheral			
subjects affected / exposed	13 / 312 (4.17%)	11 / 295 (3.73%)	16 / 309 (5.18%)
occurrences (all)	16	13	16
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	22 / 312 (7.05%)	26 / 295 (8.81%)	26 / 309 (8.41%)
occurrences (all)	24	28	28
Abdominal pain			

subjects affected / exposed	22 / 312 (7.05%)	37 / 295 (12.54%)	25 / 309 (8.09%)
occurrences (all)	27	42	29
Abdominal pain lower			
subjects affected / exposed	9 / 312 (2.88%)	5 / 295 (1.69%)	6 / 309 (1.94%)
occurrences (all)	9	5	6
Constipation			
subjects affected / exposed	21 / 312 (6.73%)	30 / 295 (10.17%)	37 / 309 (11.97%)
occurrences (all)	25	31	39
Diarrhoea			
subjects affected / exposed	40 / 312 (12.82%)	29 / 295 (9.83%)	26 / 309 (8.41%)
occurrences (all)	51	30	33
Dry mouth			
subjects affected / exposed	10 / 312 (3.21%)	10 / 295 (3.39%)	12 / 309 (3.88%)
occurrences (all)	10	10	12
Flatulence			
subjects affected / exposed	6 / 312 (1.92%)	6 / 295 (2.03%)	11 / 309 (3.56%)
occurrences (all)	7	6	12
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 312 (3.53%)	7 / 295 (2.37%)	10 / 309 (3.24%)
occurrences (all)	11	7	10
Nausea			
subjects affected / exposed	45 / 312 (14.42%)	38 / 295 (12.88%)	52 / 309 (16.83%)
occurrences (all)	59	42	66
Varices oesophageal			
subjects affected / exposed	23 / 312 (7.37%)	21 / 295 (7.12%)	22 / 309 (7.12%)
occurrences (all)	23	21	22
Vomiting			
subjects affected / exposed	18 / 312 (5.77%)	24 / 295 (8.14%)	26 / 309 (8.41%)
occurrences (all)	23	27	33
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 312 (4.17%)	15 / 295 (5.08%)	23 / 309 (7.44%)
occurrences (all)	13	17	27
Dyspnoea			

subjects affected / exposed	8 / 312 (2.56%)	6 / 295 (2.03%)	11 / 309 (3.56%)
occurrences (all)	8	6	12
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	101 / 312 (32.37%)	123 / 295 (41.69%)	178 / 309 (57.61%)
occurrences (all)	131	187	296
Rash			
subjects affected / exposed	15 / 312 (4.81%)	12 / 295 (4.07%)	32 / 309 (10.36%)
occurrences (all)	18	16	37
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 312 (4.49%)	17 / 295 (5.76%)	10 / 309 (3.24%)
occurrences (all)	14	18	11
Depression			
subjects affected / exposed	16 / 312 (5.13%)	6 / 295 (2.03%)	9 / 309 (2.91%)
occurrences (all)	16	6	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	41 / 312 (13.14%)	30 / 295 (10.17%)	33 / 309 (10.68%)
occurrences (all)	47	38	42
Back pain			
subjects affected / exposed	20 / 312 (6.41%)	19 / 295 (6.44%)	20 / 309 (6.47%)
occurrences (all)	22	21	21
Muscle spasms			
subjects affected / exposed	13 / 312 (4.17%)	13 / 295 (4.41%)	18 / 309 (5.83%)
occurrences (all)	14	15	24
Myalgia			
subjects affected / exposed	5 / 312 (1.60%)	5 / 295 (1.69%)	14 / 309 (4.53%)
occurrences (all)	5	6	14
Pain in extremity			
subjects affected / exposed	15 / 312 (4.81%)	18 / 295 (6.10%)	11 / 309 (3.56%)
occurrences (all)	16	19	13
Infections and infestations			
Bronchitis			
subjects affected / exposed	23 / 312 (7.37%)	19 / 295 (6.44%)	10 / 309 (3.24%)
occurrences (all)	28	21	11

COVID-19			
subjects affected / exposed	12 / 312 (3.85%)	8 / 295 (2.71%)	11 / 309 (3.56%)
occurrences (all)	14	8	15
Nasopharyngitis			
subjects affected / exposed	23 / 312 (7.37%)	15 / 295 (5.08%)	17 / 309 (5.50%)
occurrences (all)	25	16	21
Sinusitis			
subjects affected / exposed	24 / 312 (7.69%)	24 / 295 (8.14%)	20 / 309 (6.47%)
occurrences (all)	25	30	25
Upper respiratory tract infection			
subjects affected / exposed	26 / 312 (8.33%)	20 / 295 (6.78%)	30 / 309 (9.71%)
occurrences (all)	32	21	38
Urinary tract infection			
subjects affected / exposed	36 / 312 (11.54%)	47 / 295 (15.93%)	32 / 309 (10.36%)
occurrences (all)	47	69	45
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	12 / 312 (3.85%)	20 / 295 (6.78%)	22 / 309 (7.12%)
occurrences (all)	12	21	23
Hyperglycaemia			
subjects affected / exposed	8 / 312 (2.56%)	5 / 295 (1.69%)	10 / 309 (3.24%)
occurrences (all)	9	5	12
Hyperlipidaemia			
subjects affected / exposed	6 / 312 (1.92%)	17 / 295 (5.76%)	22 / 309 (7.12%)
occurrences (all)	6	17	23

Non-serious adverse events	OLE: OCA 10 mg (DB Placebo)	OLE: OCA 10 mg (DB OCA 10 mg)	OLE: Titrated to OCA 25 mg(DB OCA 10 mg Titrated to OCA 25 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 231 (85.28%)	215 / 221 (97.29%)	197 / 207 (95.17%)
Investigations			
Blood bilirubin increased			
subjects affected / exposed	7 / 231 (3.03%)	15 / 221 (6.79%)	12 / 207 (5.80%)
occurrences (all)	7	27	22
Blood creatinine increased			
subjects affected / exposed	8 / 231 (3.46%)	19 / 221 (8.60%)	16 / 207 (7.73%)
occurrences (all)	10	26	23

Low density lipoprotein increased			
subjects affected / exposed	11 / 231 (4.76%)	33 / 221 (14.93%)	25 / 207 (12.08%)
occurrences (all)	11	36	27
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 231 (3.46%)	11 / 221 (4.98%)	16 / 207 (7.73%)
occurrences (all)	8	12	18
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 231 (2.60%)	16 / 221 (7.24%)	14 / 207 (6.76%)
occurrences (all)	7	16	15
Headache			
subjects affected / exposed	15 / 231 (6.49%)	19 / 221 (8.60%)	24 / 207 (11.59%)
occurrences (all)	17	22	29
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 231 (6.49%)	28 / 221 (12.67%)	27 / 207 (13.04%)
occurrences (all)	18	35	36
Oedema peripheral			
subjects affected / exposed	6 / 231 (2.60%)	14 / 221 (6.33%)	16 / 207 (7.73%)
occurrences (all)	6	17	16
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 231 (1.73%)	22 / 221 (9.95%)	23 / 207 (11.11%)
occurrences (all)	4	23	25
Abdominal pain			
subjects affected / exposed	10 / 231 (4.33%)	30 / 221 (13.57%)	22 / 207 (10.63%)
occurrences (all)	11	36	29
Abdominal pain lower			
subjects affected / exposed	3 / 231 (1.30%)	8 / 221 (3.62%)	6 / 207 (2.90%)
occurrences (all)	3	10	6
Constipation			
subjects affected / exposed	13 / 231 (5.63%)	26 / 221 (11.76%)	29 / 207 (14.01%)
occurrences (all)	15	32	33
Diarrhoea			

subjects affected / exposed	12 / 231 (5.19%)	25 / 221 (11.31%)	22 / 207 (10.63%)
occurrences (all)	14	25	29
Dry mouth			
subjects affected / exposed	1 / 231 (0.43%)	10 / 221 (4.52%)	12 / 207 (5.80%)
occurrences (all)	1	10	13
Flatulence			
subjects affected / exposed	2 / 231 (0.87%)	5 / 221 (2.26%)	12 / 207 (5.80%)
occurrences (all)	2	5	13
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 231 (2.16%)	8 / 221 (3.62%)	11 / 207 (5.31%)
occurrences (all)	6	8	11
Nausea			
subjects affected / exposed	19 / 231 (8.23%)	31 / 221 (14.03%)	40 / 207 (19.32%)
occurrences (all)	26	38	53
Varices oesophageal			
subjects affected / exposed	0 / 231 (0.00%)	1 / 221 (0.45%)	1 / 207 (0.48%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	11 / 231 (4.76%)	18 / 221 (8.14%)	22 / 207 (10.63%)
occurrences (all)	12	18	25
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 231 (2.60%)	14 / 221 (6.33%)	19 / 207 (9.18%)
occurrences (all)	7	16	24
Dyspnoea			
subjects affected / exposed	1 / 231 (0.43%)	8 / 221 (3.62%)	11 / 207 (5.31%)
occurrences (all)	1	9	15
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	72 / 231 (31.17%)	100 / 221 (45.25%)	121 / 207 (58.45%)
occurrences (all)	106	157	211
Rash			
subjects affected / exposed	14 / 231 (6.06%)	16 / 221 (7.24%)	27 / 207 (13.04%)
occurrences (all)	16	21	33
Psychiatric disorders			

Insomnia			
subjects affected / exposed	3 / 231 (1.30%)	16 / 221 (7.24%)	11 / 207 (5.31%)
occurrences (all)	3	18	13
Depression			
subjects affected / exposed	1 / 231 (0.43%)	6 / 221 (2.71%)	8 / 207 (3.86%)
occurrences (all)	1	6	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 231 (6.49%)	30 / 221 (13.57%)	30 / 207 (14.49%)
occurrences (all)	16	41	42
Back pain			
subjects affected / exposed	6 / 231 (2.60%)	21 / 221 (9.50%)	22 / 207 (10.63%)
occurrences (all)	6	25	25
Muscle spasms			
subjects affected / exposed	1 / 231 (0.43%)	20 / 221 (9.05%)	16 / 207 (7.73%)
occurrences (all)	1	22	18
Myalgia			
subjects affected / exposed	2 / 231 (0.87%)	7 / 221 (3.17%)	11 / 207 (5.31%)
occurrences (all)	2	8	13
Pain in extremity			
subjects affected / exposed	4 / 231 (1.73%)	19 / 221 (8.60%)	10 / 207 (4.83%)
occurrences (all)	5	22	11
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 231 (2.60%)	17 / 221 (7.69%)	10 / 207 (4.83%)
occurrences (all)	6	21	10
COVID-19			
subjects affected / exposed	8 / 231 (3.46%)	23 / 221 (10.41%)	32 / 207 (15.46%)
occurrences (all)	8	26	38
Nasopharyngitis			
subjects affected / exposed	7 / 231 (3.03%)	22 / 221 (9.95%)	14 / 207 (6.76%)
occurrences (all)	9	25	20
Sinusitis			
subjects affected / exposed	7 / 231 (3.03%)	24 / 221 (10.86%)	21 / 207 (10.14%)
occurrences (all)	8	36	33
Upper respiratory tract infection			

subjects affected / exposed	9 / 231 (3.90%)	23 / 221 (10.41%)	25 / 207 (12.08%)
occurrences (all)	10	28	32
Urinary tract infection			
subjects affected / exposed	14 / 231 (6.06%)	40 / 221 (18.10%)	31 / 207 (14.98%)
occurrences (all)	17	64	60
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	8 / 231 (3.46%)	18 / 221 (8.14%)	21 / 207 (10.14%)
occurrences (all)	8	19	22
Hyperglycaemia			
subjects affected / exposed	4 / 231 (1.73%)	7 / 221 (3.17%)	10 / 207 (4.83%)
occurrences (all)	4	14	16
Hyperlipidaemia			
subjects affected / exposed	7 / 231 (3.03%)	16 / 221 (7.24%)	17 / 207 (8.21%)
occurrences (all)	7	16	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2018	The purpose of Country-Specific Protocol Addendum 2 (13 Dec 2018) is to ensure that uptitration is limited to a subset of subjects who meet additional specific criteria as outlined below. Within the population described above, only those subjects who meet all of the following criteria will be eligible for uptitration at Month 3: • Total bilirubin ≤1.2 milligrams per deciliter (mg/dL), serum albumin ≥3.5 grams per deciliter (g/dL), International normalized ratio (INR) <1.5, and platelet count >100,000/cubic millimeters (mm^3) at baseline, and at all visits prior to Month 3 (including any unscheduled visits). • Medical Monitor approval following a safety and tolerability assessment comprised of a subject level consolidated review of adverse events, safety laboratories including liver biochemistries, physical exam, comorbid conditions, and concomitant medications with a focus on potentially hepatotoxic concomitant medications, and/or any new treatment(s) for comorbid condition(s) using all data available prior to Month 3 visit as described in the protocol. Those subjects who are randomized to the titration arm and do not meet these criteria will not be uptitrated for the remainder of the study. If at any time during the study, a subject who has undergone uptitration has abnormal total bilirubin (>1.2 mg/dL), serum albumin (<3.5 g/dL), INR ≥1.5, or platelet count ≤100,000/mm3, the laboratory assessment(s) should be repeated within 7 days. If upon repeat evaluation, value(s) remain outside the specified criteria, investigational product should be downtitrated to a maximum daily dose of 10 mg and the medical monitor should be notified promptly. All uptitration and downtitration will be implemented in a blinded fashion within Interactive web response system (IWRS) to maintain the integrity of the study blind.
20 April 2020	The purpose of this Country-Specific Protocol Addendum 1 (20 Apr 2020) to Protocol Version 6 (dated 6 Mar 2020) is to clarify that the reference to enroll approximately 900 subjects in the protocol does not pertain to the French sites participating in Study 747-304. Enrollment ceased in France on September 30, 2019, immediately after receiving an unfavorable opinion on review of Protocol Version 5 from the French CEC. The unfavorable opinion letter indicated that the French CEC specifically objected to expanding the number of subjects in the study from approximately 540 to 900 subjects. To account for the French CEC's specific objection to Protocol Version 5, this country-specific protocol addendum will remain in place for all future amendments. Protocol Version 6 maintains the changes implemented as part of Protocol Version 5, and all parameters included in Protocol Version 6, except total patient enrollment numbers, will apply to all randomized subjects in France
01 May 2020	The restrictions that have recently been imposed to contain the global COVID-19 pandemic, such as social distancing measures, stay at home orders, and other limitations have impeded the ability of subjects and site staff to complete protocol-specified procedures. Some study sites are not able to perform protocol-specified procedures and assessments. In addition, some subjects are unable to return to study sites for evaluations and/or to receive continued supply of investigational product (IP). The purpose of this Country-Specific Protocol Addendum is to describe the requirements and processes under which subjects who are unable to return to study sites may complete protocol specified assessments and continue to receive investigational product until in-person site visits can resume. In an effort to minimize the potential adverse impact of restrictions from the COVID-19 pandemic on achieving the objectives of the study, while continuing to ensure the safety of participating subjects, the following approaches will apply to the study protocol, effective immediately.

05 May 2020	The restrictions that have recently been imposed to contain the global COVID-19 pandemic, such as social distancing measures, stay at home orders, and other limitations have impeded the ability of subjects and site staff to complete protocol-specified procedures. Specifically, a subset of sites cannot perform elective procedures such as the Month 18 liver biopsy (for assessment of the primary efficacy endpoint) and endoscopic gastroduodenoscopy (EGD), required to assess eligibility for the open label extension (OLE) phase. The purpose of this Country-Specific Protocol Addendum (dated 05 May 2020) is to describe the requirements and processes under which subjects who have been unable to complete the liver biopsy procedure at the Month 18 visit may receive blinded investigational product beyond the Month 18 visit for a maximum of 3 additional months or until the liver biopsy procedure can be completed, whichever occurs earlier. In an effort to minimize the potential adverse impact of restrictions from the COVID-19 pandemic on achieving the objectives of the study, while continuing to ensure the safety of participating subjects, the following revisions will be made to the study protocol, effective immediately.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported