Clinical trial results:
A Phase 3, Double-Blind, Placebo-Controlled Trial and Long-Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis

Summary

EudraCT number	2011-004728-36
Trial protocol	BE NL DE SE AT ES GB IT PL
Global end of trial date	17 December 2018

Results information

Result version number	v1
This version publication date	30 September 2020
First version publication date	30 September 2020

Trial information

Trial identification

Sponsor protocol code	747-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01473524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intercept Pharmaceuticals, Inc.
Sponsor organisation address	4760 Eastgate Mall, San Diego/CA, United States, 92121
Public contact	Medical Information, Intercept Pharmaceuticals, Inc., medinfo@interceptpharma.com
Scientific contact	Medical Information, Intercept Pharmaceuticals, Inc., 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	28 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study were to assess the effects of obeticholic acid (OCA) on serum alkaline phosphatase (ALP) and total bilirubin, together as a composite endpoint and on safety in participants with primary biliary cirrhosis (PBC).

Protection of trial subjects:

The trial was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All the local regulatory requirements pertinent to safety of trial subjects have also been followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2012
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: 8
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 32
Worldwide total number of subjects	217
EEA total number of subjects	146

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)	177
From 65 to 84 years	39
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment into hospitals and physicians' clinics started January 2012 and completed December 2012.

Pre-assignment

Screening details:

Screening interim allowed for pre-randomization eligibility assessment of 1 to 8 weeks. A total of 217 participants were randomized into the double-blind phase of the study, however, 216 received treatment with study drug. One randomized participant discontinued prior to receiving any study drug.

Period 1

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

Blinding implementation details:

Participants were randomized to receive OCA or matching placebo during the 12-month DB phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	DB OCA 5-10 mg

Arm description:

OCA 5 mg for 6 months and then titrating up to 10 mg based on tolerability and response for the remaining 6 months of the DB phase.

After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Arm type	Experimental
Investigational medicinal product name	obeticholic acid
Investigational medicinal product code	INT-747
Other name	6α-ethyl chenodeoxycholic acid (6-ECDCA)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA was administered orally once daily and provided in tablet form in 2 strengths: 5 mg and 10 mg.

Arm title	DB OCA 10 mg

Arm description:

OCA 10 mg 12 months during the DB phase. After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Arm type	Experimental
Investigational medicinal product name	obeticholic acid
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Other name	6α-ethyl chenodeoxycholic acid (6-ECDCA)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA was administered orally once daily and provided in tablet form in 2 strengths: 5 mg and 10 mg.

Arm title	DB Placebo

Arm description:

Matching placebo for 12 months during the DB phase. After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

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:

Matching placebo tablets were administered orally once daily.

Number of subjects in period 1	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo
Started	71	73	73
Received at least 1 dose of study drug	70	73	73
Completed	64	64	70
Not completed	7	9	3
Consent withdrawn by subject	2	1	1
Adverse event, non-fatal	4	8	2
Death	1	-	-

Period 2

Period 2 title	Long-Term Safety Extension (LTSE) Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LTSE OCA (DB OCA 5-10 mg)

Arm description:

Participants previously receiving OCA 5 to 10 mg in the DB phase received OCA in the open-label long-term safety extension (LTSE) phase for up to 5 years beginning at 5 mg, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Arm type	Experimental
Investigational medicinal product name	obeticholic acid
Investigational medicinal product code	INT-747
Other name	6α-ethyl chenodeoxycholic acid (6-ECDCA)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA was administered orally once daily and provided in tablet form in 2 strengths: 5 mg and 10 mg.

Arm title	LTSE OCA (DB OCA 10 mg)

Arm description:

Participants previously receiving OCA 10 mg in the DB phase received OCA in the open-label LTSE phase for up to 5 years beginning at 5 mg, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Arm type	Experimental
Investigational medicinal product name	obeticholic acid
Investigational medicinal product code	INT-747
Other name	6α-ethyl chenodeoxycholic acid (6-ECDCA)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA was administered orally once daily and provided in tablet form in 2 strengths: 5 mg and 10 mg.

Arm title	LTSE OCA (DB Placebo)

Arm description:

Participants previously receiving placebo in the DB phase received OCA in the open-label LTSE phase for up to 5 years beginning at 5 mg, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Arm type	Experimental
Investigational medicinal product name	obeticholic acid
Investigational medicinal product code	INT-747
Other name	6α-ethyl chenodeoxycholic acid (6-ECDCA)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OCA was administered orally once daily and provided in tablet form in 2 strengths: 5 mg and 10 mg.

Number of subjects in period 2[1]	LTSE OCA (DB OCA 5-10 mg)	LTSE OCA (DB OCA 10 mg)	LTSE OCA (DB Placebo)
Started	63	64	66
Received at least 1 dose of OCA in LTSE	63	64	66
Completed	54	47	45
Not completed	9	17	21
Liver Transplantation	-	-	1
Consent withdrawn by subject	3	3	6
Principal Investigator Decision	1	1	3
Other Clinical/ Laboratory Adverse Event	2	4	6
Death	-	1	-
Adverse Event of Pruritus	1	5	2
Pregnancy	1	-	-

Protocol Violation	-	-	1
Lost to follow-up	1	3	2

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: One participant in the double-blind OCA 5-10 mg group did not enroll in the LTSE phase. Four participants in the double-blind placebo group did not enroll in the LTSE phase.

Baseline characteristics

Reporting groups

Reporting group title	DB OCA 5-10 mg

Reporting group description:

OCA 5 mg for 6 months and then titrating up to 10 mg based on tolerability and response for the remaining 6 months of the DB phase.

After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	DB OCA 10 mg

Reporting group description:

OCA 10 mg 12 months during the DB phase. After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	DB Placebo

Reporting group description:

Matching placebo for 12 months during the DB phase. After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo
Number of subjects	71	73	73
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)	61	56	60
From 65-84 years	10	16	13
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	55.7	56.2	55.5
standard deviation	± 10.46	± 11.00	± 10.03
Gender categorical Units: Subjects			
Female	66	63	68
Male	5	10	5
Race/Ethnicity Units: Subjects			
Asian	1	1	1
Black or African American	1	1	1

Other	1	1	5
White	68	70	66
Region of Enrollment Units: Subjects			
United States	18	19	17
United Kingdom	8	5	9
Spain	4	2	3
Canada	2	2	4
Austria	2	0	1
Netherlands	3	7	6
Sweden	3	1	0
Belgium	2	9	5
Poland	4	6	4
Italy	11	10	11
Australia	5	1	3
France	0	0	1
Germany	9	11	9
ALP Units: U/L			
arithmetic mean	324.78	316.34	327.49
standard deviation	± 115.766	± 103.881	± 115.014
Total Bilirubin Units: umol/L			
arithmetic mean	10.172	11.278	11.757
standard deviation	± 5.512	± 6.634	± 7.227
Direct Bilirubin Units: umol/L			
arithmetic mean	4.399	4.868	5.469
standard deviation	± 4.495	± 4.473	± 6.214
ALT Units: U/L			
arithmetic mean	61.66	56.31	55.99
standard deviation	± 38.766	± 39.741	± 30.312
AST Units: U/L			
arithmetic mean	52.32	50.49	48.79
standard deviation	± 25.114	± 31.100	± 22.449
Gamma-Glutamyltransferase Units: U/L			
arithmetic mean	251.11	261.07	309.58
standard deviation	± 166.469	± 207.396	± 449.356

Reporting group values	Total		
Number of subjects	217		
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)	177		
From 65-84 years	39		
85 years and over	1		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	197		
Male	20		
Race/Ethnicity			
Units: Subjects			
Asian	3		
Black or African American	3		
Other	7		
White	204		
Region of Enrollment			
Units: Subjects			
United States	54		
United Kingdom	22		
Spain	9		
Canada	8		
Austria	3		
Netherlands	16		
Sweden	4		
Belgium	16		
Poland	14		
Italy	32		
Australia	9		
France	1		
Germany	29		
ALP			
Units: U/L			
arithmetic mean			
standard deviation	-		
Total Bilirubin			
Units: umol/L			
arithmetic mean			
standard deviation	-		
Direct Bilirubin			
Units: umol/L			
arithmetic mean			
standard deviation	-		
ALT			
Units: U/L			
arithmetic mean			
standard deviation	-		
AST			

Units: U/L arithmetic mean standard deviation	- 		
Gamma-Glutamyltransferase Units: U/L arithmetic mean standard deviation	- 		

Subject analysis sets	
Subject analysis set title	DB OCA 5-10 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to-treat Population: All participants who were randomized and received at least 1 dose of study drug.	
Subject analysis set title	DB OCA 10 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to-treat Population: All participants who were randomized and received at least 1 dose of study drug.	
Subject analysis set title	DB Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent-to-treat Population: All participants who were randomized and received at least 1 dose of study drug.	
Subject analysis set title	Overall LTSE OCA
Subject analysis set type	Safety analysis
Subject analysis set description: After completion of the 12-month DB phase all participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.	

Reporting group values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo
Number of subjects	70	73	73
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)	60	56	60
From 65-84 years	10	16	13
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	55.8	56.2	55.5
standard deviation	± 10.53	± 11.00	± 10.03

Gender categorical Units: Subjects			
Female	65	63	68
Male	5	10	5
Race/Ethnicity Units: Subjects			
Asian	1	1	1
Black or African American	1	1	1
Other	1	1	5
White	67	70	66
Region of Enrollment Units: Subjects			
United States	18	19	17
United Kingdom	8	5	9
Spain	4	2	3
Canada	2	2	4
Austria	2	0	1
Netherlands	3	7	6
Sweden	3	1	0
Belgium	2	9	5
Poland	4	6	4
Italy	11	10	11
Australia	5	1	3
France	0	0	1
Germany	8	11	9
ALP Units: U/L			
arithmetic mean	325.87	316.34	327.49
standard deviation	± 116.238	± 103.881	± 115.014
Total Bilirubin Units: umol/L			
arithmetic mean	10.192	11.278	11.757
standard deviation	± 5.549	± 6.634	± 7.227
Direct Bilirubin Units: umol/L			
arithmetic mean	4.398	4.868	5.469
standard deviation	± 4.528	± 4.473	± 6.214
ALT Units: U/L			
arithmetic mean	61.56	56.31	55.99
standard deviation	± 39.037	± 39.741	± 30.312
AST Units: U/L			
arithmetic mean	52.25	50.49	48.79
standard deviation	± 25.289	± 31.100	± 22.449
Gamma-Glutamyltransferase Units: U/L			
arithmetic mean	252.83	261.07	309.58
standard deviation	± 167.038	± 207.396	± 449.356

Reporting group values	Overall LTSE OCA		

Number of subjects	193		
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)	157		
From 65-84 years	36		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	55.4		
standard deviation	±		
Gender categorical Units: Subjects			
Female	177		
Male	16		
Race/Ethnicity Units: Subjects			
Asian	2		
Black or African American	3		
Other	7		
White	181		
Region of Enrollment Units: Subjects			
United States	48		
United Kingdom	18		
Spain	9		
Canada	8		
Austria	3		
Netherlands	15		
Sweden	2		
Belgium	15		
Poland	13		
Italy	29		
Australia	8		
France	1		
Germany	24		
ALP Units: U/L			
arithmetic mean	317.11		
standard deviation	± 120.153		
Total Bilirubin Units: umol/L			
arithmetic mean	11.483		
standard deviation	± 6.99		
Direct Bilirubin			

Units: umol/L			
arithmetic mean	5.259		
standard deviation	± 5.589		
ALT			
Units: U/L			
arithmetic mean	56.70		
standard deviation	± 37.030		
AST			
Units: U/L			
arithmetic mean	51.24		
standard deviation	± 33.485		
Gamma-Glutamyltransferase			
Units: U/L			
arithmetic mean	275.21		
standard deviation	± 306.020		

End points

End points reporting groups

Reporting group title	DB OCA 5-10 mg

Reporting group description:

OCA 5 mg for 6 months and then titrating up to 10 mg based on tolerability and response for the remaining 6 months of the DB phase.

After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	DB OCA 10 mg

Reporting group description:

OCA 10 mg 12 months during the DB phase. After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	DB Placebo

Reporting group description:

Matching placebo for 12 months during the DB phase. After completion of the 12-month DB phase participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	LTSE OCA (DB OCA 5-10 mg)

Reporting group description:

Participants previously receiving OCA 5 to 10 mg in the DB phase received OCA in the open-label long-term safety extension (LTSE) phase for up to 5 years beginning at 5 mg, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	LTSE OCA (DB OCA 10 mg)

Reporting group description:

Participants previously receiving OCA 10 mg in the DB phase received OCA in the open-label LTSE phase for up to 5 years beginning at 5 mg, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	LTSE OCA (DB Placebo)

Reporting group description:

Participants previously receiving placebo in the DB phase received OCA in the open-label LTSE phase for up to 5 years beginning at 5 mg, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Subject analysis set title	DB OCA 5-10 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-treat Population: All participants who were randomized and received at least 1 dose of study drug.

Subject analysis set title	DB OCA 10 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-treat Population: All participants who were randomized and received at least 1 dose of study drug.

Subject analysis set title	DB Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-treat Population: All participants who were randomized and received at least 1 dose of study drug.

Subject analysis set title	Overall LTSE OCA

Subject analysis set type	Safety analysis

Subject analysis set description:

After completion of the 12-month DB phase all participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Primary: DB Phase: Composite Endpoint Alkaline Phosphatase (ALP) And Total Bilirubin, 10 mg OCA Versus Placebo

End point title	DB Phase: Composite Endpoint Alkaline Phosphatase (ALP) And Total Bilirubin, 10 mg OCA Versus Placebo

End point description:

Percentage of participants at Month 12 with ALP < 1.67 x upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP decrease of ≥ 15% from baseline.

End point type	Primary

End point timeframe:

DB Month 12

End point values	DB OCA 10 mg	DB Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	73		
Units: percentage of participants				
number (not applicable)	47	10		

Statistical analyses

Statistical analysis title	ALP and Total Bilirubin: OCA 10 mg at Month 12

Statistical analysis description:

Statistical analysis of composite endpoint ALP and total bilirubin.

Comparison groups	DB OCA 10 mg v DB Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - H0: The response rates are equal between placebo and 10 mg OCA. H1: The response rates are different between placebo and 10 mg OCA.
[2] - Cochran–Mantel–Haenszel General Association test stratified by randomization strata factor.

Primary: LTSE Phase: Composite Endpoint ALP And Total Bilirubin

End point title	LTSE Phase: Composite Endpoint ALP And Total Bilirubin[3]

End point description:

Percentage of participants at Months 24, 36, 48, and 60 with ALP < 1.67x ULN and total bilirubin ≤ ULN and ALP decrease of ≥ 15% from baseline. DB Month 12 is the baseline for the LTSE phase.

End point type	Primary

End point timeframe:

Baseline (DB Month 12), LTSE Months 24, 36, 48, and 60

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: Quantitative statistical analyses were not performed for this end point.

End point values	LTSE OCA (DB OCA 5-10 mg)	LTSE OCA (DB OCA 10 mg)	LTSE OCA (DB Placebo)	Overall LTSE OCA
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	63[4]	64[5]	66[6]	193[7]
Units: percentage of participants				
number (not applicable)				
Baseline (Double-blind Month 12)	51	56	9	38
LTSE Month 12	55	58	41	51
LTSE Month 24	60	61	54	58
LTSE Month 36	48	51	49	49
LTSE Month 48	52	55	60	56
LTSE Month 60	48	52	50	50

Notes:

[4] - Baseline (63); Month 12 (60); Month 24 (57); Month 36 (56); Month 48 (50); Month 60 (31)

[5] - Baseline (63); Month 12 (59); Month 24 (57); Month 36 (55); Month 48 (53); Month 60 (21)

[6] - Baseline (66); Month 12 (59); Month 24 (52); Month 36 (49); Month 48 (48); Month 60 (24)

[7] - Baseline (192); Month 12 (178); Month 24 (166); Month 36 (160); Month 48 (151); Month 60 (76)

Statistical analyses

No statistical analyses for this end point

Secondary: DB Phase: Composite Endpoint ALP And Total Bilirubin, 10 mg Versus Placebo

End point title	DB Phase: Composite Endpoint ALP And Total Bilirubin, 10 mg Versus Placebo

End point description:

Percentage of participants at Month 6 with ALP < 1.67x ULN and total bilirubin ≤ ULN and ALP decrease of ≥ 15% from baseline.

End point type	Secondary

End point timeframe:

DB Month 6

End point values	DB OCA 10 mg	DB Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	73		
Units: percentage of participants				
number (not applicable)	51	7		

Statistical analyses

Statistical analysis title	ALP and Total Bilirubin: OCA 10 mg at Month 6
Statistical analysis description:	
Statistical analysis of composite endpoint ALP and total bilirubin.	
Comparison groups	DB OCA 10 mg v DB Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - H0: The response rates are equal between placebo and 10 mg OCA. H1: The response rates are different between placebo and 10 mg OCA.
[9] - Cochran–Mantel–Haenszel General Association test stratified by randomization strata factor.

Secondary: DB Phase: Composite Endpoint ALP And Total Bilirubin, 5-10 mg Versus Placebo

End point title	DB Phase: Composite Endpoint ALP And Total Bilirubin, 5-10 mg Versus Placebo
End point description:	
Percentage of participants at Month 12 with ALP < 1.67x ULN and total bilirubin ≤ ULN and ALP decrease of ≥ 15% from baseline.	
End point type	Secondary
End point timeframe:	
DB Month 12	

End point values	DB OCA 5-10 mg	DB Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (not applicable)	46	10		

Statistical analyses

Statistical analysis title	ALP and Total Bilirubin: OCA 5-10 mg at Month 12
Statistical analysis description:	
Statistical analysis of composite endpoint ALP and total bilirubin.	
Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - H0: The response rates are equal between placebo and 5-10 mg OCA. H1: The response rates are different between placebo and 5-10 mg OCA.
[11] - Cochran–Mantel–Haenszel General Association test stratified by randomization strata factor.

Secondary: DB Phase: Composite Endpoint ALP and Total Bilirubin, 5-10 mg Versus Placebo

End point title	DB Phase: Composite Endpoint ALP and Total Bilirubin, 5-10 mg Versus Placebo

End point description:

Percentage of participants at Month 6 with ALP < 1.67x ULN and total bilirubin ≤ ULN and ALP decrease of ≥ 15% from baseline.

End point type	Secondary

End point timeframe:

DB Month 6

End point values	DB OCA 5-10 mg	DB Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (not applicable)	34	7		

Statistical analyses

Statistical analysis title	ALP and Total Bilirubin: OCA 5-10 mg at Month 6

Statistical analysis description:

Statistical analysis of composite endpoint ALP and total bilirubin.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel

Notes:

[12] - H0: The response rates are equal between placebo and 5-10 mg OCA. H1: The response rates are different between placebo and 5-10 mg OCA.
[13] - Cochran–Mantel–Haenszel General Association test stratified by randomization strata factor.

Secondary: DB Phase: ALP Absolute Change From Baseline To Month 12

End point title	DB Phase: ALP Absolute Change From Baseline To Month 12

End point description:

Blood samples were evaluated for ALP levels. ALP Absolute Change From Baseline (ALP at Month 12 - ALP at Baseline) is presented.

End point type	Secondary

End point timeframe:

Baseline, DB Month 12

End point values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64[14]	62[15]	70[16]	
Units: U/L				
least squares mean (standard error)	-112.51 (± 14.36)	-129.90 (± 14.60)	-14.42 (± 14.74)	

Notes:

[14] - Participants who had analyzable data at the specified timepoint.

[15] - Participants who had analyzable data at the specified timepoint.

[16] - Participants who had analyzable data at the specified timepoint.

Statistical analyses

Statistical analysis title	ALP Change From Baseline To Month 12

Statistical analysis description:

Statistical analysis of the ALP change from baseline to Month 12.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	ANCOVA

Notes:

[17] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Statistical analysis title	ALP Change From Baseline To Month 12

Statistical analysis description:

Statistical analysis of the ALP change from baseline to Month 12.

Comparison groups	DB Placebo v DB OCA 10 mg
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	ANCOVA

Notes:

[18] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Secondary: DB Phase: Total Bilirubin Absolute Change From Baseline To Month 12

End point title	DB Phase: Total Bilirubin Absolute Change From Baseline To Month 12

End point description:

Blood samples were evaluated for bilirubin levels. Total bilirubin absolute change from baseline (total bilirubin at Month 12 - total bilirubin at Baseline) is presented.

End point type	Secondary

End point timeframe:

Baseline, DB Month 12

End point values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64[19]	62[20]	70[21]	
Units: umol/L				
least squares mean (standard error)	-0.33 (± 0.68)	-0.90 (± 0.71)	1.98 (± 0.70)	

Notes:

[19] - Had analyzable data at the specified timepoint.

[20] - Had analyzable data at the specified timepoint.

[21] - Had analyzable data at the specified timepoint.

Statistical analyses

Statistical analysis title	Total Bilirubin Change From Baseline to Month 12

Statistical analysis description:

Statistical analysis of the total bilirubin change from baseline to Month 12.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [22]
Method	ANCOVA

Notes:

[22] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Statistical analysis title	Total Bilirubin Change From Baseline to Month 12

Statistical analysis description:

Statistical analysis of the total bilirubin change from baseline to Month 12.

Comparison groups	DB Placebo v DB OCA 10 mg
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	ANCOVA

Notes:

[23] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Secondary: DB Phase: Direct Bilirubin Absolute Change From Baseline To Month 12

End point title	DB Phase: Direct Bilirubin Absolute Change From Baseline To Month 12

End point description:

Blood samples were evaluated for bilirubin levels. Direct bilirubin absolute change from baseline (direct bilirubin at Month 12 - direct bilirubin at Baseline) is presented.

End point type	Secondary

End point timeframe:

Baseline, DB Month 12

End point values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64[24]	62[25]	70[26]	
Units: umol/L				
least squares mean (standard error)	-0.13 (± 0.52)	-0.49 (± 0.54)	1.89 (± 0.53)	

Notes:

[24] - Had analyzable data at specified timepoint.

[25] - Had analyzable data at specified timepoint.

[26] - Had analyzable data at specified timepoint.

Statistical analyses

Statistical analysis title	Direct Bilirubin Change from Baseline to Month 12

Statistical analysis description:

Statistical analysis of direct bilirubin change from baseline.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	ANCOVA

Notes:

[27] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Statistical analysis title	Direct Bilirubin Change from Baseline to Month 12

Statistical analysis description:

Statistical analysis of direct bilirubin change from baseline.

Comparison groups	DB OCA 10 mg v DB Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	ANCOVA

Notes:

[28] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Secondary: DB Phase: ALT Absolute Change From Baseline To Month 12

End point title	DB Phase: ALT Absolute Change From Baseline To Month 12

End point description:

Blood samples were evaluated for ALT levels. ALT absolute change from baseline (ALT at Month 12 - ALT at Baseline) is presented.

End point type	Secondary

End point timeframe:

Baseline, DB Month 12

End point values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64[29]	62[30]	70[31]	
Units: U/L				
least squares mean (standard error)	-21.26 (± 3.27)	-25.31 (± 3.35)	-4.95 (± 3.32)	

Notes:

[29] - Had analyzable data at specified timepoints.

[30] - Had analyzable data at specified timepoints.

[31] - Had analyzable data at specified timepoints.

Statistical analyses

Statistical analysis title	ALT Change From Baseline to Month 12

Statistical analysis description:

Statistical analysis of ALT change from baseline.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	ANCOVA

Notes:

[32] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Statistical analysis title	ALT Change From Baseline to Month 12

Statistical analysis description:

Statistical analysis of ALT change from baseline.

Comparison groups	DB Placebo v DB OCA 10 mg
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	ANCOVA

Notes:

[33] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Secondary: DB Phase: AST Absolute Change From Baseline To Month 12

End point title	DB Phase: AST Absolute Change From Baseline To Month 12

End point description:

Blood samples were evaluated for AST levels. AST absolute change from baseline (AST at Month 12 - AST at Baseline) is presented.

End point type	Secondary

End point timeframe:

Baseline, DB Month 12

End point values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64[34]	62[35]	70[36]	
Units: U/L				
least squares mean (standard error)	-13.03 (± 4.17)	-15.00 (± 4.28)	1.04 (± 4.22)	

Notes:

[34] - Had analyzable data at specified timepoint.

[35] - Had analyzable data at specified timepoint.

[36] - Had analyzable data at specified timepoint.

Statistical analyses

Statistical analysis title	AST Change From Baseline to Month 12

Statistical analysis description:

Statistical Analysis for AST change from baseline.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [37]
Method	ANCOVA

Notes:

[37] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Statistical analysis title	AST Change From Baseline to Month 12

Statistical analysis description:

Statistical Analysis for AST change from baseline.

Comparison groups	DB Placebo v DB OCA 10 mg
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [38]
Method	ANCOVA

Notes:

[38] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Secondary: DB Phase: Gamma-glutamyltransferase (GGT) Absolute Change From Baseline To Month 12

End point title	DB Phase: Gamma-glutamyltransferase (GGT) Absolute Change From Baseline To Month 12

End point description:

Blood samples were evaluated for GGT levels. GGT absolute change from baseline (GGT at Month 12 - GGT at Baseline) is presented.

End point type	Secondary

End point timeframe:

Baseline, DB Month 12

End point values	DB OCA 5-10 mg	DB OCA 10 mg	DB Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64[39]	62[40]	70[41]	
Units: U/L				
least squares mean (standard error)	-140.83 (± 24.70)	-176.66 (± 25.58)	6.70 (± 25.56)	

Notes:

[39] - Had analyzable data at specified timepoint.

[40] - Had analyzable data at specified timepoint.

[41] - Had analyzable data at specified timepoint.

Statistical analyses

Statistical analysis title	GGT Change From Baseline to Month 12

Statistical analysis description:

Statistical Analysis for GGT change from baseline.

Comparison groups	DB OCA 5-10 mg v DB Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [42]
Method	ANCOVA

Notes:

[42] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Statistical analysis title	GGT Change From Baseline to Month 12

Statistical analysis description:

Statistical Analysis for GGT change from baseline.

Comparison groups	DB Placebo v DB OCA 10 mg
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [43]
Method	ANCOVA

Notes:

[43] - ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Secondary: LTSE Phase: ALP Levels

End point title	LTSE Phase: ALP Levels

End point description:

Blood samples were evaluated for ALP levels.

End point type	Secondary

End point timeframe:

LTSE Day 0 and LTSE Months 12, 24, 36, 48, and 60

End point values	LTSE OCA (DB OCA 5-10 mg)	LTSE OCA (DB OCA 10 mg)	LTSE OCA (DB Placebo)	Overall LTSE OCA
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	63[44]	64[45]	66[46]	193[47]
Units: U/L				
arithmetic mean (standard deviation)				
LTSE Day 0	218.69 (± 100.328)	191.24 (± 61.381)	317.79 (± 139.666)	243.75 (± 118.910)
LTSE Month 12	209.49 (± 93.157)	198.68 (± 75.799)	226.28 (± 105.404)	211.47 (± 92.439)
LTSE Month 24	195.14 (± 80.361)	194.57 (± 66.593)	215.99 (± 83.469)	201.47 (± 77.117)
LTSE Month 36	204.52 (± 68.019)	214.66 (± 158.831)	205.37 (± 65.206)	208.27 (± 107.114)
LTSE Month 48	189.75 (± 55.929)	192.00 (± 59.761)	198.70 (± 65.551)	193.38 (± 60.170)
LTSE Month 60	200.90 (± 97.475)	191.37 (± 62.404)	209.38 (± 82.240)	200.94 (± 83.436)

Notes:

[44] - Day 0 (63); Month 12 (60); Month 24 (57); Month 36 (56); Month 48 (50); Month 60 (31)

[45] - Day 0 (63); Month 12 (59); Month 24 (57); Month 36 (55); Month 48 (53); Month 60 (21)

[46] - Day 0 (66); Month 12 (59); Month 24 (52); Month 36 (49); Month 48 (48); Month 60 (24)

[47] - Day 0 (192); Month 12 (178); Month 24 (166); Month 36 (160); Month 48 (151); Month 60 (76)

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: ALP Change From DB Baseline

End point title	LTSE Phase: ALP Change From DB Baseline

End point description:

Blood samples were evaluated for ALP levels. ALP Change From Baseline (ALP at LTSE Months 12, 24, 36, 48, and 60 - ALP at Baseline) is presented. DB baseline is the mean of all available evaluations prior to DB treatment.

End point type	Secondary

End point timeframe:

DB Baseline, LTSE Months 12, 24, 36, 48, and 60

End point values	LTSE OCA (DB OCA 5-10 mg)	LTSE OCA (DB OCA 10 mg)	LTSE OCA (DB Placebo)	Overall LTSE OCA
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	63[48]	64[49]	66[50]	193[51]
Units: U/L				
arithmetic mean (standard deviation)				
Month 12	-106.63 (± 98.448)	-104.39 (± 82.496)	-104.36 (± 83.074)	-105.13 (± 87.882)
Month 24	-120.86 (± 96.614)	-102.52 (± 79.413)	-100.99 (± 87.181)	-108.34 (± 87.980)
Month 36	-100.98 (± 109.952)	-84.65 (± 137.293)	-112.73 (± 89.661)	-98.96 (± 114.635)
Month 48	-118.23 (± 101.527)	-101.50 (± 91.335)	-115.51 (± 106.774)	-111.49 (± 99.433)
Month 60	-118.99 (± 147.126)	-117.49 (± 95.587)	-119.52 (± 108.949)	-118.74 (± 121.391)

Notes:
[48] - Month 12 (60); Month 24 (57); Month 36 (56); Month 48 (50); Month 60 (31)
[49] - Month 12 (59); Month 24 (57); Month 36 (55); Month 48 (53); Month 60 (21)
[50] - Month 12 (59); Month 24 (52); Month 36 (49); Month 48 (48); Month 60 (24)
[51] - Month 12 (178); Month 24 (166); Month 36 (160); Month 48 (151); Month 60 (60)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Phase: Baseline up to 12 months (1 year). LSTE phase: Baseline (DB Month 12) up to 60 months (5 years).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	DB 5-10 mg

Reporting group description:

OCA 5 mg for 6 months and then titrating up to 10 mg based on tolerability and response for remaining 6 months of the DB phase.

Reporting group title	DB OCA 10 mg

Reporting group description:

OCA 10 mg for 12 months during the DB phase.

Reporting group title	DB Placebo

Reporting group description:

Matching placebo for 12 months during the DB phase.

Reporting group title	LTSE OCA (DB OCA 5-10 mg)

Reporting group description:

Participants previously receiving OCA 5 to 10 mg in the DB phase received OCA beginning at 5 mg in the open-label LTSE for up to 5 years, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	LTSE OCA (DB 10 mg)

Reporting group description:

Participants previously receiving OCA 10 mg in the DB phase received OCA beginning at 5 mg in the open-label LTSE for up to 5 years, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	LTSE OCA (DB Placebo)

Reporting group description:

Participants previously receiving placebo in the DB phase received OCA beginning at 5 mg in the open-label LTSE for up to 5 years, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Reporting group title	Overall LTSE OCA

Reporting group description:

After completion of the 12-month DB phase, all participants were offered the opportunity to enter an open-label LTSE for up to 5 years beginning at 5 mg OCA, and then the dose could be titrated up. Initially, participants were allowed to titrate to doses up to 25 mg, however, the maximum dose was then limited to 10 mg.

Serious adverse events	DB 5-10 mg	DB OCA 10 mg	DB Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 70 (15.71%)	8 / 73 (10.96%)	3 / 73 (4.11%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 myeloid leukaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 neoplasm malignant			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 neoplast malignant recurrent			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Lip neoplastm malignant stage unspecified			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 oncocytoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Hypertension			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Intra-abdominal haematoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Temporal arteritis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Varicose vein			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Non-cardiac chest pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyserositis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Dyspnoea			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Major depression			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Medical observation			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Anastomotic ulcer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Clavicle fracture			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Lower limb fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Meniscus lesion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 haemorrhage			

subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Radius fracture			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 compression fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Tibia fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Atrial fibrillation			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Cardiomyopathy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Myocardial infarction			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Sick sinus syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 encephalopathy			

subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Loss of consciousness			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Syncope			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Cataract			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 pain lower			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 wall haematoma			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Haematemesis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Oedematous pancreatitis			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Splenic artery aneurysm			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Cholecystitis acute			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Cholelithiasis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Hyperplastic cholecystopathy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Jaundice			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Neurodermatitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Nephropathy toxic			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 atrophy			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 failure			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 failure acute			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Haemarthrosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 sclerosis			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Bacterial sepsis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Erysipelas			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 chronic			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Sepsis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Vaginal infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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			
Hypoglycaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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
Hyponatraemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (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	LTSE OCA (DB OCA	LTSE OCA (DB 10	LTSE OCA (DB

	5-10 mg)	mg)	Placebo)
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 63 (47.62%)	19 / 64 (29.69%)	20 / 66 (30.30%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm malignant			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplast malignant recurrent			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lip neoplastm malignant stage unspecified			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal oncocytoma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	2 / 63 (3.17%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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
Oedema			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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
Polyserositis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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
Interstitial lung disease			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Medical observation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus lesion			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Post procedural haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	2 / 63 (3.17%)	2 / 64 (3.13%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 63 (0.00%)	2 / 64 (3.13%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			

subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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
Ischaemic stroke			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 63 (1.59%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	1 / 63 (1.59%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedematous pancreatitis			

subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	2 / 63 (3.17%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic artery aneurysm			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperplastic cholecystopathy			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (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			
Neurodermatitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal atrophy			

subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 63 (3.17%)	5 / 64 (7.81%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic sclerosis			

subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	0 / 66 (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
Parotitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 63 (4.76%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	0 / 66 (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	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Overall LTSE OCA		

Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 193 (35.75%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic neoplasm malignant			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic neoplast malignant recurrent			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lip neoplastm malignant stage			

unspecified				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal oncocytoma				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal haematoma				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Temporal arteritis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicose vein				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Non-cardiac chest pain				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polyserositis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Medical observation				

subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meniscus lesion			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			

subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Aortic valve stenosis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				

subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sick sinus syndrome				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carpal tunnel syndrome				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Splenic infarction			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall haematoma				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedematous pancreatitis				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal prolapse				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Splenic artery aneurysm				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperplastic cholecystopathy				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Neurodermatitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephropathy toxic				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal atrophy				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Haemarthrosis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	7 / 193 (3.63%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic sclerosis				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parotitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis chronic				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vaginal infection				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypoglycaemia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	DB 5-10 mg	DB OCA 10 mg	DB Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 70 (91.43%)	64 / 73 (87.67%)	62 / 73 (84.93%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	1 / 73 (1.37%)
occurrences (all)	0	2	1
Hypotension			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 70 (2.86%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	2	1	1
Fatigue			
subjects affected / exposed	11 / 70 (15.71%)	17 / 73 (23.29%)	10 / 73 (13.70%)
occurrences (all)	13	25	12
Influenza like illness			
subjects affected / exposed	1 / 70 (1.43%)	3 / 73 (4.11%)	1 / 73 (1.37%)
occurrences (all)	1	4	1
Oedema peripheral			
subjects affected / exposed	2 / 70 (2.86%)	5 / 73 (6.85%)	2 / 73 (2.74%)
occurrences (all)	2	7	3
Pyrexia			
subjects affected / exposed	0 / 70 (0.00%)	5 / 73 (6.85%)	1 / 73 (1.37%)
occurrences (all)	0	6	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 70 (2.86%)	1 / 73 (1.37%)	2 / 73 (2.74%)
occurrences (all)	2	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 70 (5.71%)	6 / 73 (8.22%)	5 / 73 (6.85%)
occurrences (all)	5	6	9

Dyspnoea			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	3 / 73 (4.11%)
occurrences (all)	1	1	3
Epistaxis			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	3 / 73 (4.11%)
occurrences (all)	3	0	4
Nasal congestion			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	5 / 70 (7.14%)	6 / 73 (8.22%)	1 / 73 (1.37%)
occurrences (all)	5	8	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	3	0	3
Depressed mood			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	2 / 70 (2.86%)	3 / 73 (4.11%)	7 / 73 (9.59%)
occurrences (all)	2	3	8
Sleep disorder			
subjects affected / exposed	3 / 70 (4.29%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	7	0	0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			

subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	3 / 70 (4.29%)	2 / 73 (2.74%)	2 / 73 (2.74%)
occurrences (all)	3	3	2
Excoriation			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Ligament rupture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Meniscus lesion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	4 / 70 (5.71%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	4	1	3
Rib fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Scratch			
subjects affected / exposed	1 / 70 (1.43%)	3 / 73 (4.11%)	0 / 73 (0.00%)
occurrences (all)	1	4	0
Tendon rupture			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	2 / 70 (2.86%)	5 / 73 (6.85%)	1 / 73 (1.37%)
occurrences (all)	3	5	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 70 (4.29%)	2 / 73 (2.74%)	2 / 73 (2.74%)
occurrences (all)	5	2	2
Headache			
subjects affected / exposed	12 / 70 (17.14%)	6 / 73 (8.22%)	13 / 73 (17.81%)
occurrences (all)	26	7	16
Hypoaesthesia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Sciatica			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 70 (2.86%)	3 / 73 (4.11%)	4 / 73 (5.48%)
occurrences (all)	2	3	5
Iron deficiency anaemia			

subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Splenomegaly			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Vertigo			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 70 (1.43%)	2 / 73 (2.74%)	2 / 73 (2.74%)
occurrences (all)	1	2	2
Dry eye			
subjects affected / exposed	2 / 70 (2.86%)	4 / 73 (5.48%)	4 / 73 (5.48%)
occurrences (all)	3	4	4
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 70 (7.14%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences (all)	5	0	5
Abdominal distension			
subjects affected / exposed	3 / 70 (4.29%)	3 / 73 (4.11%)	7 / 73 (9.59%)
occurrences (all)	3	3	7
Abdominal pain			
subjects affected / exposed	3 / 70 (4.29%)	1 / 73 (1.37%)	6 / 73 (8.22%)
occurrences (all)	3	1	6
Abdominal pain lower			

subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	5 / 70 (7.14%)	4 / 73 (5.48%)	5 / 73 (6.85%)
occurrences (all)	5	5	8
Ascites			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	5 / 70 (7.14%)	5 / 73 (6.85%)	4 / 73 (5.48%)
occurrences (all)	5	5	7
Dental caries			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	2 / 70 (2.86%)	8 / 73 (10.96%)	8 / 73 (10.96%)
occurrences (all)	3	10	13
Dry mouth			
subjects affected / exposed	2 / 70 (2.86%)	3 / 73 (4.11%)	2 / 73 (2.74%)
occurrences (all)	2	3	2
Dyspepsia			
subjects affected / exposed	4 / 70 (5.71%)	0 / 73 (0.00%)	8 / 73 (10.96%)
occurrences (all)	4	0	11
Gastric polyps			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Gastritis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 70 (2.86%)	4 / 73 (5.48%)	4 / 73 (5.48%)
occurrences (all)	2	5	6
Haemorrhoids			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Hiatus hernia			

subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	4 / 70 (5.71%)	8 / 73 (10.96%)	9 / 73 (12.33%)
occurrences (all)	5	10	18
Portal hypertensive gastropathy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Toothache			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Varices oesophageal			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	3 / 70 (4.29%)	3 / 73 (4.11%)	5 / 73 (6.85%)
occurrences (all)	3	3	8
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Hepatic cirrhosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Hepatomegaly			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Dry skin			

subjects affected / exposed	1 / 70 (1.43%)	2 / 73 (2.74%)	1 / 73 (1.37%)
occurrences (all)	1	2	1
Eczema			
subjects affected / exposed	4 / 70 (5.71%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	4	2	0
Erythema			
subjects affected / exposed	1 / 70 (1.43%)	3 / 73 (4.11%)	0 / 73 (0.00%)
occurrences (all)	1	3	0
Hyperhidrosis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	1	0	2
Night sweats			
subjects affected / exposed	3 / 70 (4.29%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	39 / 70 (55.71%)	50 / 73 (68.49%)	28 / 73 (38.36%)
occurrences (all)	93	99	49
Rash			
subjects affected / exposed	3 / 70 (4.29%)	4 / 73 (5.48%)	3 / 73 (4.11%)
occurrences (all)	3	4	3
Rash pruritic			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Skin lesion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	3 / 73 (4.11%)
occurrences (all)	0	1	3
Urticaria			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	4 / 70 (5.71%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	4	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 70 (5.71%)	7 / 73 (9.59%)	3 / 73 (4.11%)
occurrences (all)	5	7	3
Back pain			
subjects affected / exposed	4 / 70 (5.71%)	4 / 73 (5.48%)	8 / 73 (10.96%)
occurrences (all)	4	5	8
Bone pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	2 / 70 (2.86%)	2 / 73 (2.74%)	4 / 73 (5.48%)
occurrences (all)	2	2	5
Musculoskeletal pain			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Myalgia			
subjects affected / exposed	1 / 70 (1.43%)	3 / 73 (4.11%)	0 / 73 (0.00%)
occurrences (all)	1	3	0
Neck pain			
subjects affected / exposed	1 / 70 (1.43%)	2 / 73 (2.74%)	1 / 73 (1.37%)
occurrences (all)	1	2	2
Osteoarthritis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Osteopenia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Osteoporosis			

subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Pain in extremity			
subjects affected / exposed	3 / 70 (4.29%)	1 / 73 (1.37%)	3 / 73 (4.11%)
occurrences (all)	3	1	3
Plantar fasciitis			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 70 (5.71%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	4	1	0
Cystitis			
subjects affected / exposed	1 / 70 (1.43%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	2	2	0
Diverticulum			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	3 / 70 (4.29%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	3	1	0
Herpes zoster			
subjects affected / exposed	0 / 70 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	5 / 70 (7.14%)	4 / 73 (5.48%)	4 / 73 (5.48%)
occurrences (all)	5	4	5
Lower respiratory tract infection			
subjects affected / exposed	2 / 70 (2.86%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	17 / 70 (24.29%)	13 / 73 (17.81%)	13 / 73 (17.81%)
occurrences (all)	27	15	19

Oral herpes			
subjects affected / exposed	1 / 70 (1.43%)	1 / 73 (1.37%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Pharyngitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	3 / 73 (4.11%)
occurrences (all)	0	0	3
Sinusitis			
subjects affected / exposed	1 / 70 (1.43%)	4 / 73 (5.48%)	0 / 73 (0.00%)
occurrences (all)	1	5	0
Tooth infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 70 (5.71%)	4 / 73 (5.48%)	8 / 73 (10.96%)
occurrences (all)	4	4	8
Urinary tract infection			
subjects affected / exposed	4 / 70 (5.71%)	4 / 73 (5.48%)	8 / 73 (10.96%)
occurrences (all)	6	6	15
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Vitamin D deficiency			
subjects affected / exposed	0 / 70 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1

Non-serious adverse events	LTSE OCA (DB OCA 5-10 mg)	LTSE OCA (DB 10 mg)	LTSE OCA (DB Placebo)

Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 63 (96.83%)	62 / 64 (96.88%)	64 / 66 (96.97%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 63 (7.94%)	6 / 64 (9.38%)	8 / 66 (12.12%)
occurrences (all)	6	7	8
Hypotension			
subjects affected / exposed	2 / 63 (3.17%)	2 / 64 (3.13%)	4 / 66 (6.06%)
occurrences (all)	2	3	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	6 / 66 (9.09%)
occurrences (all)	2	7	6
Fatigue			
subjects affected / exposed	24 / 63 (38.10%)	24 / 64 (37.50%)	15 / 66 (22.73%)
occurrences (all)	46	43	20
Influenza like illness			
subjects affected / exposed	4 / 63 (6.35%)	6 / 64 (9.38%)	1 / 66 (1.52%)
occurrences (all)	4	9	1
Oedema peripheral			
subjects affected / exposed	10 / 63 (15.87%)	8 / 64 (12.50%)	8 / 66 (12.12%)
occurrences (all)	15	12	10
Pyrexia			
subjects affected / exposed	5 / 63 (7.94%)	6 / 64 (9.38%)	5 / 66 (7.58%)
occurrences (all)	6	8	5
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 63 (6.35%)	2 / 64 (3.13%)	1 / 66 (1.52%)
occurrences (all)	4	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 63 (19.05%)	11 / 64 (17.19%)	12 / 66 (18.18%)
occurrences (all)	23	16	16
Dyspnoea			
subjects affected / exposed	1 / 63 (1.59%)	4 / 64 (6.25%)	2 / 66 (3.03%)
occurrences (all)	1	6	2

Epistaxis			
subjects affected / exposed	3 / 63 (4.76%)	2 / 64 (3.13%)	3 / 66 (4.55%)
occurrences (all)	4	3	5
Nasal congestion			
subjects affected / exposed	3 / 63 (4.76%)	2 / 64 (3.13%)	0 / 66 (0.00%)
occurrences (all)	3	2	0
Oropharyngeal pain			
subjects affected / exposed	6 / 63 (9.52%)	8 / 64 (12.50%)	4 / 66 (6.06%)
occurrences (all)	6	11	6
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 63 (4.76%)	1 / 64 (1.56%)	3 / 66 (4.55%)
occurrences (all)	5	1	3
Depressed mood			
subjects affected / exposed	0 / 63 (0.00%)	4 / 64 (6.25%)	1 / 66 (1.52%)
occurrences (all)	0	5	2
Depression			
subjects affected / exposed	5 / 63 (7.94%)	5 / 64 (7.81%)	3 / 66 (4.55%)
occurrences (all)	6	6	4
Insomnia			
subjects affected / exposed	6 / 63 (9.52%)	7 / 64 (10.94%)	7 / 66 (10.61%)
occurrences (all)	6	7	11
Sleep disorder			
subjects affected / exposed	3 / 63 (4.76%)	1 / 64 (1.56%)	2 / 66 (3.03%)
occurrences (all)	8	1	2
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	3 / 66 (4.55%)
occurrences (all)	0	0	3
Hepatic enzyme increased			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	1	5	1
Low density lipoprotein increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 64 (1.56%)	3 / 66 (4.55%)
occurrences (all)	0	1	4
Weight decreased			

subjects affected / exposed	3 / 63 (4.76%)	2 / 64 (3.13%)	1 / 66 (1.52%)
occurrences (all)	3	2	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	4 / 66 (6.06%)
occurrences (all)	0	0	4
Contusion			
subjects affected / exposed	2 / 63 (3.17%)	5 / 64 (7.81%)	3 / 66 (4.55%)
occurrences (all)	2	5	3
Excoriation			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	0 / 66 (0.00%)
occurrences (all)	1	3	0
Fall			
subjects affected / exposed	4 / 63 (6.35%)	0 / 64 (0.00%)	4 / 66 (6.06%)
occurrences (all)	4	0	4
Ligament rupture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 64 (0.00%)	3 / 66 (4.55%)
occurrences (all)	0	0	3
Meniscus lesion			
subjects affected / exposed	1 / 63 (1.59%)	5 / 64 (7.81%)	1 / 66 (1.52%)
occurrences (all)	2	5	1
Procedural pain			
subjects affected / exposed	8 / 63 (12.70%)	4 / 64 (6.25%)	4 / 66 (6.06%)
occurrences (all)	9	5	7
Rib fracture			
subjects affected / exposed	3 / 63 (4.76%)	2 / 64 (3.13%)	0 / 66 (0.00%)
occurrences (all)	3	2	0
Scratch			
subjects affected / exposed	1 / 63 (1.59%)	6 / 64 (9.38%)	2 / 66 (3.03%)
occurrences (all)	1	7	3
Tendon rupture			
subjects affected / exposed	0 / 63 (0.00%)	3 / 64 (4.69%)	0 / 66 (0.00%)
occurrences (all)	0	3	0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	2 / 66 (3.03%)
occurrences (all)	1	7	2
Bradycardia			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences (all)	3	0	1
Cardiac murmur			
subjects affected / exposed	3 / 63 (4.76%)	2 / 64 (3.13%)	2 / 66 (3.03%)
occurrences (all)	3	2	2
Palpitations			
subjects affected / exposed	4 / 63 (6.35%)	5 / 64 (7.81%)	2 / 66 (3.03%)
occurrences (all)	6	5	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 63 (7.94%)	7 / 64 (10.94%)	2 / 66 (3.03%)
occurrences (all)	9	7	2
Headache			
subjects affected / exposed	20 / 63 (31.75%)	15 / 64 (23.44%)	9 / 66 (13.64%)
occurrences (all)	43	22	10
Hypoaesthesia			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences (all)	5	0	0
Paraesthesia			
subjects affected / exposed	2 / 63 (3.17%)	2 / 64 (3.13%)	3 / 66 (4.55%)
occurrences (all)	3	2	3
Sciatica			
subjects affected / exposed	3 / 63 (4.76%)	3 / 64 (4.69%)	3 / 66 (4.55%)
occurrences (all)	3	4	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 63 (12.70%)	7 / 64 (10.94%)	4 / 66 (6.06%)
occurrences (all)	12	8	5
Iron deficiency anaemia			
subjects affected / exposed	1 / 63 (1.59%)	1 / 64 (1.56%)	3 / 66 (4.55%)
occurrences (all)	4	1	4
Splenomegaly			

subjects affected / exposed	4 / 63 (6.35%)	2 / 64 (3.13%)	1 / 66 (1.52%)
occurrences (all)	5	2	1
Thrombocytopenia			
subjects affected / exposed	0 / 63 (0.00%)	3 / 64 (4.69%)	2 / 66 (3.03%)
occurrences (all)	0	3	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	3	3	1
Vertigo			
subjects affected / exposed	4 / 63 (6.35%)	2 / 64 (3.13%)	2 / 66 (3.03%)
occurrences (all)	7	2	2
Eye disorders			
Cataract			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	2	4	1
Conjunctivitis			
subjects affected / exposed	2 / 63 (3.17%)	5 / 64 (7.81%)	1 / 66 (1.52%)
occurrences (all)	4	6	1
Dry eye			
subjects affected / exposed	3 / 63 (4.76%)	10 / 64 (15.63%)	2 / 66 (3.03%)
occurrences (all)	4	11	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 63 (7.94%)	0 / 64 (0.00%)	2 / 66 (3.03%)
occurrences (all)	5	0	2
Abdominal distension			
subjects affected / exposed	5 / 63 (7.94%)	7 / 64 (10.94%)	5 / 66 (7.58%)
occurrences (all)	7	7	5
Abdominal pain			
subjects affected / exposed	11 / 63 (17.46%)	7 / 64 (10.94%)	8 / 66 (12.12%)
occurrences (all)	15	9	8
Abdominal pain lower			
subjects affected / exposed	3 / 63 (4.76%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences (all)	4	1	1
Abdominal pain upper			

subjects affected / exposed	9 / 63 (14.29%)	10 / 64 (15.63%)	12 / 66 (18.18%)
occurrences (all)	12	11	13
Ascites			
subjects affected / exposed	6 / 63 (9.52%)	1 / 64 (1.56%)	3 / 66 (4.55%)
occurrences (all)	9	1	4
Constipation			
subjects affected / exposed	12 / 63 (19.05%)	9 / 64 (14.06%)	7 / 66 (10.61%)
occurrences (all)	12	9	8
Dental caries			
subjects affected / exposed	4 / 63 (6.35%)	1 / 64 (1.56%)	4 / 66 (6.06%)
occurrences (all)	5	1	6
Diarrhoea			
subjects affected / exposed	8 / 63 (12.70%)	11 / 64 (17.19%)	14 / 66 (21.21%)
occurrences (all)	15	17	26
Dry mouth			
subjects affected / exposed	3 / 63 (4.76%)	5 / 64 (7.81%)	3 / 66 (4.55%)
occurrences (all)	4	5	3
Dyspepsia			
subjects affected / exposed	7 / 63 (11.11%)	8 / 64 (12.50%)	5 / 66 (7.58%)
occurrences (all)	12	8	5
Gastric polyps			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	0 / 66 (0.00%)
occurrences (all)	1	4	0
Gastritis			
subjects affected / exposed	2 / 63 (3.17%)	6 / 64 (9.38%)	3 / 66 (4.55%)
occurrences (all)	2	7	3
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 63 (11.11%)	9 / 64 (14.06%)	4 / 66 (6.06%)
occurrences (all)	7	12	4
Haemorrhoids			
subjects affected / exposed	5 / 63 (7.94%)	1 / 64 (1.56%)	5 / 66 (7.58%)
occurrences (all)	6	1	5
Hiatus hernia			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	1	3	1
Nausea			

subjects affected / exposed	14 / 63 (22.22%)	13 / 64 (20.31%)	10 / 66 (15.15%)
occurrences (all)	20	19	15
Portal hypertensive gastropathy			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	2 / 66 (3.03%)
occurrences (all)	3	0	2
Rectal haemorrhage			
subjects affected / exposed	1 / 63 (1.59%)	2 / 64 (3.13%)	4 / 66 (6.06%)
occurrences (all)	1	2	4
Toothache			
subjects affected / exposed	2 / 63 (3.17%)	5 / 64 (7.81%)	3 / 66 (4.55%)
occurrences (all)	2	6	3
Varices oesophageal			
subjects affected / exposed	8 / 63 (12.70%)	2 / 64 (3.13%)	1 / 66 (1.52%)
occurrences (all)	8	3	1
Vomiting			
subjects affected / exposed	5 / 63 (7.94%)	7 / 64 (10.94%)	2 / 66 (3.03%)
occurrences (all)	7	9	2
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	5 / 63 (7.94%)	4 / 64 (6.25%)	1 / 66 (1.52%)
occurrences (all)	6	4	1
Hepatic cirrhosis			
subjects affected / exposed	1 / 63 (1.59%)	2 / 64 (3.13%)	4 / 66 (6.06%)
occurrences (all)	1	2	4
Hepatomegaly			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences (all)	3	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	2 / 66 (3.03%)
occurrences (all)	5	0	7
Dry skin			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	5 / 66 (7.58%)
occurrences (all)	1	3	5
Eczema			

subjects affected / exposed	5 / 63 (7.94%)	4 / 64 (6.25%)	5 / 66 (7.58%)
occurrences (all)	5	4	7
Erythema			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	3 / 66 (4.55%)
occurrences (all)	4	4	4
Hyperhidrosis			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	0 / 66 (0.00%)
occurrences (all)	3	0	0
Night sweats			
subjects affected / exposed	3 / 63 (4.76%)	0 / 64 (0.00%)	1 / 66 (1.52%)
occurrences (all)	3	0	1
Pruritus			
subjects affected / exposed	49 / 63 (77.78%)	51 / 64 (79.69%)	50 / 66 (75.76%)
occurrences (all)	249	198	180
Rash			
subjects affected / exposed	7 / 63 (11.11%)	5 / 64 (7.81%)	2 / 66 (3.03%)
occurrences (all)	9	5	2
Rash pruritic			
subjects affected / exposed	0 / 63 (0.00%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	0	3	1
Skin lesion			
subjects affected / exposed	3 / 63 (4.76%)	5 / 64 (7.81%)	6 / 66 (9.09%)
occurrences (all)	5	7	8
Urticaria			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	1	4	4
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	2	3	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 63 (6.35%)	3 / 64 (4.69%)	3 / 66 (4.55%)
occurrences (all)	4	3	3
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	14 / 63 (22.22%)	17 / 64 (26.56%)	15 / 66 (22.73%)
occurrences (all)	17	23	18
Back pain			
subjects affected / exposed	10 / 63 (15.87%)	11 / 64 (17.19%)	10 / 66 (15.15%)
occurrences (all)	13	15	10
Bone pain			
subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	1	3	1
Joint swelling			
subjects affected / exposed	3 / 63 (4.76%)	1 / 64 (1.56%)	4 / 66 (6.06%)
occurrences (all)	3	1	4
Muscle spasms			
subjects affected / exposed	4 / 63 (6.35%)	4 / 64 (6.25%)	3 / 66 (4.55%)
occurrences (all)	4	7	3
Musculoskeletal pain			
subjects affected / exposed	4 / 63 (6.35%)	5 / 64 (7.81%)	3 / 66 (4.55%)
occurrences (all)	5	6	3
Myalgia			
subjects affected / exposed	4 / 63 (6.35%)	7 / 64 (10.94%)	2 / 66 (3.03%)
occurrences (all)	5	9	2
Neck pain			
subjects affected / exposed	3 / 63 (4.76%)	4 / 64 (6.25%)	5 / 66 (7.58%)
occurrences (all)	3	4	5
Osteoarthritis			
subjects affected / exposed	4 / 63 (6.35%)	6 / 64 (9.38%)	5 / 66 (7.58%)
occurrences (all)	5	8	7
Osteopenia			
subjects affected / exposed	9 / 63 (14.29%)	6 / 64 (9.38%)	6 / 66 (9.09%)
occurrences (all)	9	6	7
Osteoporosis			
subjects affected / exposed	2 / 63 (3.17%)	4 / 64 (6.25%)	5 / 66 (7.58%)
occurrences (all)	2	5	6
Pain in extremity			
subjects affected / exposed	7 / 63 (11.11%)	5 / 64 (7.81%)	8 / 66 (12.12%)
occurrences (all)	11	5	9

Plantar fasciitis			
subjects affected / exposed	0 / 63 (0.00%)	3 / 64 (4.69%)	1 / 66 (1.52%)
occurrences (all)	0	4	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 63 (11.11%)	7 / 64 (10.94%)	6 / 66 (9.09%)
occurrences (all)	7	7	10
Cystitis			
subjects affected / exposed	5 / 63 (7.94%)	5 / 64 (7.81%)	2 / 66 (3.03%)
occurrences (all)	12	15	3
Diverticulum			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	0 / 66 (0.00%)
occurrences (all)	2	3	0
Ear infection			
subjects affected / exposed	1 / 63 (1.59%)	1 / 64 (1.56%)	3 / 66 (4.55%)
occurrences (all)	1	2	3
Gastroenteritis			
subjects affected / exposed	4 / 63 (6.35%)	1 / 64 (1.56%)	5 / 66 (7.58%)
occurrences (all)	4	1	6
Herpes zoster			
subjects affected / exposed	1 / 63 (1.59%)	7 / 64 (10.94%)	4 / 66 (6.06%)
occurrences (all)	1	8	4
Influenza			
subjects affected / exposed	12 / 63 (19.05%)	12 / 64 (18.75%)	10 / 66 (15.15%)
occurrences (all)	17	17	17
Lower respiratory tract infection			
subjects affected / exposed	4 / 63 (6.35%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences (all)	8	2	5
Nasopharyngitis			
subjects affected / exposed	23 / 63 (36.51%)	23 / 64 (35.94%)	11 / 66 (16.67%)
occurrences (all)	66	39	22
Oral herpes			
subjects affected / exposed	3 / 63 (4.76%)	1 / 64 (1.56%)	1 / 66 (1.52%)
occurrences (all)	4	1	1
Pharyngitis			

subjects affected / exposed	1 / 63 (1.59%)	3 / 64 (4.69%)	2 / 66 (3.03%)
occurrences (all)	1	6	2
Pneumonia			
subjects affected / exposed	2 / 63 (3.17%)	5 / 64 (7.81%)	5 / 66 (7.58%)
occurrences (all)	2	8	6
Respiratory tract infection			
subjects affected / exposed	5 / 63 (7.94%)	4 / 64 (6.25%)	4 / 66 (6.06%)
occurrences (all)	6	5	5
Sinusitis			
subjects affected / exposed	7 / 63 (11.11%)	9 / 64 (14.06%)	8 / 66 (12.12%)
occurrences (all)	7	11	11
Tooth infection			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	2 / 66 (3.03%)
occurrences (all)	3	3	2
Upper respiratory tract infection			
subjects affected / exposed	12 / 63 (19.05%)	11 / 64 (17.19%)	11 / 66 (16.67%)
occurrences (all)	21	17	16
Urinary tract infection			
subjects affected / exposed	17 / 63 (26.98%)	19 / 64 (29.69%)	15 / 66 (22.73%)
occurrences (all)	31	27	23
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 63 (0.00%)	3 / 64 (4.69%)	3 / 66 (4.55%)
occurrences (all)	0	3	5
Hypercholesterolaemia			
subjects affected / exposed	3 / 63 (4.76%)	2 / 64 (3.13%)	3 / 66 (4.55%)
occurrences (all)	4	2	3
Vitamin D deficiency			
subjects affected / exposed	2 / 63 (3.17%)	3 / 64 (4.69%)	3 / 66 (4.55%)
occurrences (all)	2	3	3

Non-serious adverse events	Overall LTSE OCA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	187 / 193 (96.89%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	19 / 193 (9.84%)		
occurrences (all)	21		
Hypotension			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	15		
Fatigue			
subjects affected / exposed	63 / 193 (32.64%)		
occurrences (all)	109		
Influenza like illness			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	26 / 193 (13.47%)		
occurrences (all)	37		
Pyrexia			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	19		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	7 / 193 (3.63%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 193 (18.13%)		
occurrences (all)	55		
Dyspnoea			
subjects affected / exposed	7 / 193 (3.63%)		
occurrences (all)	9		
Epistaxis			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	12		

Nasal congestion subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 5		
Oropharyngeal pain subjects affected / exposed occurrences (all)	18 / 193 (9.33%) 23		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 9		
Depressed mood subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 7		
Depression subjects affected / exposed occurrences (all)	13 / 193 (6.74%) 16		
Insomnia subjects affected / exposed occurrences (all)	20 / 193 (10.36%) 24		
Sleep disorder subjects affected / exposed occurrences (all)	6 / 193 (3.11%) 11		
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 3		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 7		
Low density lipoprotein increased subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 5		
Weight decreased subjects affected / exposed occurrences (all)	6 / 193 (3.11%) 6		
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Contusion			
subjects affected / exposed	10 / 193 (5.18%)		
occurrences (all)	10		
Excoriation			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Fall			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	8		
Ligament rupture			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Meniscus lesion			
subjects affected / exposed	7 / 193 (3.63%)		
occurrences (all)	8		
Procedural pain			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	21		
Rib fracture			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	5		
Scratch			
subjects affected / exposed	9 / 193 (4.66%)		
occurrences (all)	11		
Tendon rupture			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	10		
Bradycardia			

subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 4		
Cardiac murmur subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 7		
Palpitations subjects affected / exposed occurrences (all)	11 / 193 (5.70%) 13		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	14 / 193 (7.25%) 18		
Headache subjects affected / exposed occurrences (all)	44 / 193 (22.80%) 75		
Hypoaesthesia subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 5		
Paraesthesia subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 8		
Sciatica subjects affected / exposed occurrences (all)	9 / 193 (4.66%) 11		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	19 / 193 (9.84%) 25		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 9		
Splenomegaly subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 8		
Thrombocytopenia			

subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	7		
Vertigo			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	11		
Eye disorders			
Cataract			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	7		
Conjunctivitis			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	11		
Dry eye			
subjects affected / exposed	15 / 193 (7.77%)		
occurrences (all)	17		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	7 / 193 (3.63%)		
occurrences (all)	7		
Abdominal distension			
subjects affected / exposed	17 / 193 (8.81%)		
occurrences (all)	19		
Abdominal pain			
subjects affected / exposed	26 / 193 (13.47%)		
occurrences (all)	32		
Abdominal pain lower			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	31 / 193 (16.06%)		
occurrences (all)	36		
Ascites			

subjects affected / exposed	10 / 193 (5.18%)			
occurrences (all)	14			
Constipation				
subjects affected / exposed	28 / 193 (14.51%)			
occurrences (all)	29			
Dental caries				
subjects affected / exposed	9 / 193 (4.66%)			
occurrences (all)	12			
Diarrhoea				
subjects affected / exposed	33 / 193 (17.10%)			
occurrences (all)	58			
Dry mouth				
subjects affected / exposed	11 / 193 (5.70%)			
occurrences (all)	12			
Dyspepsia				
subjects affected / exposed	20 / 193 (10.36%)			
occurrences (all)	25			
Gastric polyps				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences (all)	5			
Gastritis				
subjects affected / exposed	11 / 193 (5.70%)			
occurrences (all)	12			
Gastrooesophageal reflux disease				
subjects affected / exposed	20 / 193 (10.36%)			
occurrences (all)	23			
Haemorrhoids				
subjects affected / exposed	11 / 193 (5.70%)			
occurrences (all)	12			
Hiatus hernia				
subjects affected / exposed	5 / 193 (2.59%)			
occurrences (all)	5			
Nausea				
subjects affected / exposed	37 / 193 (19.17%)			
occurrences (all)	54			
Portal hypertensive gastropathy				

subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 5		
Rectal haemorrhage subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 7		
Toothache subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 11		
Varices oesophageal subjects affected / exposed occurrences (all)	11 / 193 (5.70%) 12		
Vomiting subjects affected / exposed occurrences (all)	14 / 193 (7.25%) 18		
Hepatobiliary disorders			
Cholelithiasis subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 11		
Hepatic cirrhosis subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 7		
Hepatomegaly subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 4		
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 12		
Dry skin subjects affected / exposed occurrences (all)	9 / 193 (4.66%) 9		
Eczema subjects affected / exposed occurrences (all)	14 / 193 (7.25%) 16		
Erythema			

subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	12		
Hyperhidrosis			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Night sweats			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	150 / 193 (77.72%)		
occurrences (all)	627		
Rash			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	16		
Rash pruritic			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Skin lesion			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	20		
Urticaria			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	9		
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	6		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	10 / 193 (5.18%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	46 / 193 (23.83%)		
occurrences (all)	58		
Back pain			

subjects affected / exposed	31 / 193 (16.06%)		
occurrences (all)	38		
Bone pain			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	5		
Joint swelling			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	14		
Musculoskeletal pain			
subjects affected / exposed	12 / 193 (6.22%)		
occurrences (all)	14		
Myalgia			
subjects affected / exposed	13 / 193 (6.74%)		
occurrences (all)	16		
Neck pain			
subjects affected / exposed	12 / 193 (6.22%)		
occurrences (all)	12		
Osteoarthritis			
subjects affected / exposed	15 / 193 (7.77%)		
occurrences (all)	20		
Osteopenia			
subjects affected / exposed	21 / 193 (10.88%)		
occurrences (all)	22		
Osteoporosis			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	13		
Pain in extremity			
subjects affected / exposed	20 / 193 (10.36%)		
occurrences (all)	25		
Plantar fasciitis			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	5		
Infections and infestations			

Bronchitis				
subjects affected / exposed	20 / 193 (10.36%)			
occurrences (all)	24			
Cystitis				
subjects affected / exposed	12 / 193 (6.22%)			
occurrences (all)	30			
Diverticulum				
subjects affected / exposed	5 / 193 (2.59%)			
occurrences (all)	5			
Ear infection				
subjects affected / exposed	5 / 193 (2.59%)			
occurrences (all)	6			
Gastroenteritis				
subjects affected / exposed	10 / 193 (5.18%)			
occurrences (all)	11			
Herpes zoster				
subjects affected / exposed	12 / 193 (6.22%)			
occurrences (all)	13			
Influenza				
subjects affected / exposed	34 / 193 (17.62%)			
occurrences (all)	51			
Lower respiratory tract infection				
subjects affected / exposed	6 / 193 (3.11%)			
occurrences (all)	15			
Nasopharyngitis				
subjects affected / exposed	57 / 193 (29.53%)			
occurrences (all)	127			
Oral herpes				
subjects affected / exposed	5 / 193 (2.59%)			
occurrences (all)	6			
Pharyngitis				
subjects affected / exposed	6 / 193 (3.11%)			
occurrences (all)	9			
Pneumonia				
subjects affected / exposed	12 / 193 (6.22%)			
occurrences (all)	16			

Respiratory tract infection subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Tooth infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 13 / 193 (6.74%) 16 24 / 193 (12.44%) 29 7 / 193 (3.63%) 8 34 / 193 (17.62%) 54 51 / 193 (26.42%) 81		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all) Hypercholesterolaemia subjects affected / exposed occurrences (all) Vitamin D deficiency subjects affected / exposed occurrences (all)	 6 / 193 (3.11%) 8 8 / 193 (4.15%) 9 8 / 193 (4.15%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2012	• The schedule of transient elastography assessments was altered. • Changes to entry criteria were made to better reflect the intent of the protocol. • Liver biopsy schedule was adjusted.
24 September 2012	• The requirement for use of contraception was extended to 30 days after the end of treatment visit. • The titration procedure was edited to include 10 mg increments. • Baseline dual-emission x-ray absorptiometry scan was removed as a requirement for participants who had a scan within 6 months prior to enrollment.
25 August 2014	• Protocol was modified to allow participants who were tolerating 5 mg OCA daily to be titrated to a maximum of 10 mg daily. Participants who were titrated above 10 mg prior to Version 4 were allowed to remain on their current dose or be decreased as clinically indicated. • Requirement for LTSE Follow-up visit was removed.
21 March 2018	• Introduction was revised to highlight the need for close monitoring specifically in participants with clinical evidence of hepatic decompensation and other complications due to advanced cirrhosis. • Effective with Protocol Version 5: All participants under Protocol Version 3 and prior who were receiving > 10 mg OCA daily had their doses down-titrated to ≤ 10 mg OCA daily. After implementation of Protocol Version 5, no participant was titrated beyond 10 mg OCA at any time during the LTSE. Additionally, dosing regimens were updated for participants with moderate and severe hepatic impairment (Child-Pugh B and Child-Pugh C), not to exceed 10 mg OCA twice weekly, to align with label dosing guidelines. •Updated with discontinuation criteria for decompensation events and biochemical thresholds. A plan for monitoring and a drug-induced liver injury algorithm was included to ensure careful monitoring and drug interruption/discontinuation. Additionally, "Close Observation" per "Food and Drug Administration Guidance for Industry on Drug Induced Liver Injury" was clearly defined in the protocol to ensure that participants who experienced a potential drug-induced liver injury underwent a full evaluation. • Guidance added that participants should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation. • Guidance added that the investigator should contact the study Medical Monitor upon awareness when any signs and symptoms of hepatic decompensation are observed in any participant. • Guidance added for monitoring amylase and lipase levels in participants experiencing acute pancreatitis or cholecystitis. • List of analytes amended and samples for biomarkers of hepatic fibrosis and/or inflammation, bile acids, PBC autoantibodies, and other cytokines and interleukins were no longer to be collected or analyzed in the LTSE phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19554543

http://www.ncbi.nlm.nih.gov/pubmed/27532829

http://www.ncbi.nlm.nih.gov/pubmed/30922873