Clinical trial results:
A Study of INT-747 (6-ECDCA) Monotherapy in Patients with Primary Biliary Cirrhosis

Summary

EudraCT number	2007-001424-12
Trial protocol	GB FR ES AT DE
Global end of trial date	25 September 2017
Results information	
Result version number	v2
This version publication date	31 January 2021
First version publication date	21 May 2016
Version creation reason	• Changes to summary attachments Global End of Trial reached as Long Term Safety Extension ended with Last Patient Last Visit Sep 25 2017. The pdf summary of this study has been updated with EoT date
Summary attachment (see zip file)	Intercept Study 747-201 Results (EudraCT_201DB_v6_Final.pdf)

Trial information

Trial identification	
Sponsor protocol code	747-201
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00570765
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Intercept Pharmaceuticals, Inc.
Sponsor organisation address	9520 Towne Centre Drive, Suite 200, San Diego, CA, United States, 92121
Public contact	Medical Information, Intercept Pharmaceuticals, Inc., +1 844-782-4278, medinfo@interceptpharma.com
Scientific contact	Medical Information, Intercept Pharmaceuticals, Inc., +1 844-782-4278, medinfo@interceptpharma.com

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2010
Global end of trial reached?	Yes
Global end of trial date	25 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of obeticholic acid (OCA) in participants with primary biliary cirrhosis (PBC) on alkaline phosphatase (AP) levels and safety.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	60
EEA total number of subjects	34

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)	50
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started 12/2007 and completed in 6/2010. Due to positive Phase 2 data in another study (2007-001425-10), power calculations were revised and recruitment ended early. Eligible participants who received treatment in the double-blind (DB) phase could continue receiving obeticholic acid (OCA) in the long-term safety extension (LTSE) phase.

Pre-assignment

Screening details:

Screening interim allowed for pre-randomization eligibility assessment of 1 to 4 weeks. Other than a 3-month (pre-Screening) washout for ursodeoxycholic acid (UDCA) and other medications, no washout or run-in period was defined between Screening and randomization. During LTSE, OCA dosing (milligrams [mg]) remained oral once daily.

Period 1

Period 1 title	Double-Blind
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

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

Arm description:

OCA 10 mg for 3 months during the DB phase.

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

Dosage and administration details:

OCA 10 mg was administered orally once daily.

Arm title	DB OCA 50 mg

Arm description:

OCA 50 mg for 3 months during the DB phase.

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

Dosage and administration details:

OCA 50 mg was administered orally once daily.

Arm title	DB OCA Placebo

Arm description:

Matching placebo for 3 months during the DB phase.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule was administered orally once daily.

Number of subjects in period 1	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo
Started	20	16	24
Received at Least 1 Dose of Study Drug	20	16	23
Safety Population	20	16	23
Completed	16	9	23
Not completed	4	7	1
Consent withdrawn by subject	1	-	-
Did Not Receive Study Drug	-	-	1
Adverse event, non-fatal	3	6	-
Protocol deviation	-	1	-

Period 2

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

Arms

Arm title	LTSE OCA Total

Arm description:

After completion of the 3-month DB phase, all eligible participants were offered the opportunity to enter an open-label LTSE for up to 96 months beginning at 10 mg OCA. Doses up to 50 mg daily were evaluated.

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

Dosage and administration details:

OCA was administered orally once daily and provided either in capsule or tablet forms. Capsules for the LTSE phase were provided at OCA dose strengths of 10, 25, and 50 mg while tablets were provided at OCA dose strengths of 10 and 25 mg.

Number of subjects in period 2[1]	LTSE OCA Total
Started	28
Safety Population	28
Completed	16
Not completed	12
Consent withdrawn by subject	1
Physician decision	4
Adverse event, non-fatal	7

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: Eligible participants who completed the DB phase could choose to enroll in the LTSE phase.

Baseline characteristics

Reporting groups	
Reporting group title	DB OCA 10 mg
Reporting group description: OCA 10 mg for 3 months during the DB phase.	
Reporting group title	DB OCA 50 mg
Reporting group description: OCA 50 mg for 3 months during the DB phase.	
Reporting group title	DB OCA Placebo
Reporting group description: Matching placebo for 3 months during the DB phase.	

Reporting group values	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo
Number of subjects	20	16	24
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	16	15	19
>=65 years	4	1	5
Age continuous Units: years			
arithmetic mean	54.8	54.1	55.3
standard deviation	± 10.9	± 7.3	± 10.0
Gender categorical Units: Subjects			
Female	14	16	21
Male	6	0	3
Region of Enrollment Units: Subjects			
France	2	1	1
United States	4	5	8
Canada	3	2	4
Spain	0	1	1
Germany	4	1	3
United Kingdom	7	6	7

Reporting group values	Total		
Number of subjects	60		
Age categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	50		
>=65 years	10		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	51		
Male	9		
Region of Enrollment Units: Subjects			
France	4		
United States	17		
Canada	9		
Spain	2		
Germany	8		
United Kingdom	20		

End points

End points reporting groups

Reporting group title	DB OCA 10 mg
Reporting group description:	
OCA 10 mg for 3 months during the DB phase.	
Reporting group title	DB OCA 50 mg
Reporting group description:	
OCA 50 mg for 3 months during the DB phase.	
Reporting group title	DB OCA Placebo
Reporting group description:	
Matching placebo for 3 months during the DB phase.	
Reporting group title	LTSE OCA Total
Reporting group description:	
After completion of the 3-month DB phase, all eligible participants were offered the opportunity to enter an open-label LTSE for up to 96 months beginning at 10 mg OCA. Doses up to 50 mg daily were evaluated.	

Primary: DB Phase: Mean Percent Change In Serum Alkaline Phosphatase (ALP) From Baseline To Day 85

End point title	DB Phase: Mean Percent Change In Serum Alkaline Phosphatase (ALP) From Baseline To Day 85
End point description:	
The percent change in serum ALP from baseline to Day 85 is reported. The baseline value used was the mean of the pretreatment Screening and Day 0 evaluations.	
End point type	Primary
End point timeframe:	
Baseline, Day 85	

End point values	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	16	23	
Units: Percent change				
arithmetic mean (standard deviation)	-44.5 (± 24.4)	-37.6 (± 21.0)	0.4 (± 15.3)	

Statistical analyses

Statistical analysis title	Percent Change From Baseline to Day 85: Serum ALP
Comparison groups	DB OCA 10 mg v DB OCA 50 mg v DB OCA Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Hierarchical testing strategy was proposed to account for multiple comparisons. Statistical significance was evaluated as follows: if statistical significance at alpha=0.05 is shown for the 10 mg OCA versus placebo, then the statistical significance at alpha=0.05 for the 50 mg OCA versus placebo was evaluated. If no statistical significance was shown at alpha=0.05 at the first step, then the subsequent comparison was not considered statistically significant.

Secondary: DB Phase: Mean Percent Change In Gamma-glutamyl Transferase (GGT) From Baseline To Day 85

End point title	DB Phase: Mean Percent Change In Gamma-glutamyl Transferase (GGT) From Baseline To Day 85

End point description:

As a marker of hepatocellular injury and liver function, the percent change in GGT from baseline to Day 85 is reported.

End point type	Secondary

End point timeframe:

Baseline, Day 85

End point values	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	15	22	
Units: Percent change				
arithmetic mean (standard deviation)	-73 (± 18)	-65 (± 25)	-3 (± 22)	

Statistical analyses

Statistical analysis title	Percent Change in GGT From Baseline to Day 85
Comparison groups	DB OCA 10 mg v DB OCA 50 mg v DB OCA Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: DB Phase: Mean Percent Change In Alanine Transaminase (ALT) From Baseline To Day 85

End point title	DB Phase: Mean Percent Change In Alanine Transaminase (ALT) From Baseline To Day 85

End point description:

As a marker of hepatocellular injury and liver function, the percent change in ALT from baseline to Day 85 is reported.

End point type	Secondary
End point timeframe: Baseline, Day 85	

End point values	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	15	22	
Units: Percent change				
arithmetic mean (standard deviation)	-37 (± 35)	-35 (± 25)	-4 (± 40)	

Statistical analyses

Statistical analysis title	Percent Change in ALT From Baseline to Day 85
Comparison groups	DB OCA 10 mg v DB OCA 50 mg v DB OCA Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)

Secondary: DB Phase: Mean Percent Change In Conjugated Bilirubin From Baseline To Day 85

End point title	DB Phase: Mean Percent Change In Conjugated Bilirubin From Baseline To Day 85
End point description: As a marker of hepatocellular injury and liver function, the percent change in conjugated bilirubin from baseline to Day 85 is reported.	
End point type	Secondary
End point timeframe: Baseline, Day 85	

End point values	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	15	22	
Units: Percent change				
arithmetic mean (standard deviation)	0.7 (± 67.3)	-1.7 (± 39.9)	30.3 (± 69.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Median Percent Change In Serum ALP From Baseline To Month 24, Month 48, Month 72, And Last Available Visit

End point title	LTSE Phase: Median Percent Change In Serum ALP From Baseline To Month 24, Month 48, Month 72, And Last Available Visit

End point description:

The percent change in serum ALP from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Month 24, Month 48, Month 72, Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28[2]			
Units: Percent change				
median (inter-quartile range (Q1-Q3))				
Month 24	-43.1 (-61.3 to -20.2)			
Month 48	-44.4 (-65.5 to -18.6)			
Month 72	-33.4 (-64.5 to -17.9)			
Last Available Visit	-31.8 (-57.5 to -14.0)			

Notes:

[2] - Month 24 (N=23); Month 48 (N=19); Month 72 (N=17); Last Available Visit (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE Phase: Mean Percent Change In Serum ALP From Baseline To Month 24, Month 48, Month 72, And Last Available Visit

End point title	LTSE Phase: Mean Percent Change In Serum ALP From Baseline To Month 24, Month 48, Month 72, And Last Available Visit

End point description:

The percent change in serum ALP from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Month 24, Month 48, Month 72, Last Available Visit (up to 96 months).

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28[3]			
Units: Percent change				
arithmetic mean (standard deviation)				
Month 24	-38.8 (± 29.7)			
Month 48	-39.3 (± 36.6)			
Month 72	-31.7 (± 57.3)			
Last Available Visit	-30.4 (± 36.6)			

Notes:

[3] - Month 24 (N=23); Month 48 (N=19); Month 72 (N=17); Last Available Visit (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Median Percent Change In GGT From Baseline To Last Available Visit

End point title	LTSE: Median Percent Change In GGT From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in GGT from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
median (inter-quartile range (Q1-Q3))	-71.1 (-84.3 to -33.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Mean Percent Change In GGT From Baseline To Last Available Visit

End point title	LTSE: Mean Percent Change In GGT From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in GGT from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
arithmetic mean (standard deviation)	-55.6 (± 41.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Median Percent Change In ALT From Baseline To Last Available Visit

End point title	LTSE: Median Percent Change In ALT From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in ALT from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
median (inter-quartile range (Q1-Q3))	-52.2 (-68.4 to -11.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Mean Percent Change In ALT From Baseline To Last Available Visit

End point title	LTSE: Mean Percent Change In ALT From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in ALT from baseline to the last available visit is reported. The DB baseline value was used as the baseline.
Baseline (DB), Last Available Visit (up to 96 months)

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
arithmetic mean (standard deviation)	-39.6 (± 42.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Median Percent Change In Conjugated Bilirubin From Baseline To Last Available Visit

End point title	LTSE: Median Percent Change In Conjugated Bilirubin From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in conjugated bilirubin from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
median (inter-quartile range (Q1-Q3))	33.3 (-11.1 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Mean Percent Change In Conjugated Bilirubin From Baseline To Last Available Visit

End point title	LTSE: Mean Percent Change In Conjugated Bilirubin From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in conjugated bilirubin from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
arithmetic mean (standard deviation)	57.8 (± 103.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Median Percent Change In Total Bilirubin From Baseline To Last Available Visit

End point title	LTSE: Median Percent Change In Total Bilirubin From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in total bilirubin from baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent change				
median (inter-quartile range (Q1-Q3))	5.2 (-21.4 to 25.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: LTSE: Mean Percent Change In Total Bilirubin From Baseline To Last Available Visit

End point title	LTSE: Mean Percent Change In Total Bilirubin From Baseline To Last Available Visit

End point description:

As a marker of hepatocellular injury and liver function, the percent change in total bilirubin from

baseline to the last available visit is reported. The DB baseline value was used as the baseline.

End point type	Secondary

End point timeframe:

Baseline (DB), Last Available Visit (up to 96 months)

End point values	LTSE OCA Total			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percent Change				
arithmetic mean (standard deviation)	2.2 (± 35.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB: Adverse events were collected starting when the participant took the first dose of study medication (following Day 0) and during study participation, through the follow-up visit at Month 3. LSTE: Baseline (DB Month 3) up to 96 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	DB OCA 10 mg

Reporting group description:

OCA 10 mg for 3 months during the DB phase.

Reporting group title	DB OCA 50 mg

Reporting group description:

OCA 50 mg for 3 months during the DB phase.

Reporting group title	DB OCA Placebo

Reporting group description:

Matching placebo for 3 months during the DB phase.

Reporting group title	LTSE OCA Total

Reporting group description:

After completion of the 3-month DB phase, all participants were offered the opportunity to enter an open-label LTSE for up to 96 months beginning at 10 mg OCA. Doses up to 50 mg daily were evaluated.

Serious adverse events	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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			
Peripheral ischaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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
Reproductive system and breast			

disorders			
Uterine prolapse			
subjects affected / exposed[1]	0 / 14 (0.00%)	0 / 16 (0.00%)	0 / 20 (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
Cystocele			
subjects affected / exposed[2]	0 / 14 (0.00%)	0 / 16 (0.00%)	0 / 20 (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			
Pelvic fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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
Hip fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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 flutter			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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
Tricuspid valve incompetence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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			
Transient ischaemic attack			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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			
Small intestinal obstruction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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
Gastric varices haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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			
Rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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
Polyarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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			
Pneumonia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (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 Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 28 (32.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed[1]	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystocele			
subjects affected / exposed[2]	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric varices haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyarthritis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

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

Non-serious adverse events	DB OCA 10 mg	DB OCA 50 mg	DB OCA Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)	16 / 16 (100.00%)	19 / 23 (82.61%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lipoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lung neoplasm			

subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Thyroid neoplasm			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Varicose vein			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	3 / 23 (13.04%)
occurrences (all)	0	1	3
Feeling cold			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			

subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	2 / 23 (8.70%)
occurrences (all)	0	1	2
Oedema peripheral			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Sarcoidosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Breast tenderness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Gynaecomastia			
subjects affected / exposed[3]	1 / 14 (7.14%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Menorrhagia			
subjects affected / exposed[4]	1 / 14 (7.14%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ovarian cyst			
subjects affected / exposed[5]	0 / 14 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 20 (5.00%)	1 / 16 (6.25%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 16 (12.50%)	1 / 23 (4.35%)
occurrences (all)	2	2	1
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
White blood cells urine			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Patella fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dizziness			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	5
Facial neuralgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 20 (20.00%)	2 / 16 (12.50%)	5 / 23 (21.74%)
occurrences (all)	5	3	6
Irregular sleep phase			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Coagulopathy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Lymphoid tissue hyperplasia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Eye disorders			
Cataract			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Iritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	2 / 16 (12.50%)	1 / 23 (4.35%)
occurrences (all)	1	2	1
Abdominal pain lower			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Abdominal tenderness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Coeliac disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Colonic polyp			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Constipation			

subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Diverticulum			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Faecal incontinence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Faeces pale			
subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Flatulence			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Glossodynia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Hiatus hernia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	4 / 16 (25.00%)	4 / 23 (17.39%)
occurrences (all)	0	4	5
Oesophagitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Parotid gland enlargement			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Salivary gland enlargement			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	1 / 16 (6.25%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hepatic pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Dry skin			

subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
Eczema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lichen planus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	14 / 20 (70.00%)	15 / 16 (93.75%)	7 / 23 (30.43%)
occurrences (all)	24	22	11
Rash			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Rash macular			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Rash papular			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Skin lesion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Spider naevus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
Fibromyalgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Muscle spasm			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Osteoporosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Influenza			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	3 / 20 (15.00%)	1 / 16 (6.25%)	2 / 23 (8.70%)
occurrences (all)	3	1	2
Otitis media			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Urinary tract infection			
subjects affected / exposed	3 / 20 (15.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Fluid overload			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	LTSE OCA Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Lipoma			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Lung neoplasm			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Thyroid neoplasm			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypertension			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Varicose vein			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	14 / 28 (50.00%)		
occurrences (all)	16		
Feeling cold			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Sarcoidosis			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Breast tenderness			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Gynaecomastia			
subjects affected / exposed[3]	0 / 23 (0.00%)		
occurrences (all)	0		
Menorrhagia			
subjects affected / exposed[4]	1 / 23 (4.35%)		
occurrences (all)	2		
Ovarian cyst			
subjects affected / exposed[5]	2 / 23 (8.70%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Dyspnoea exertional			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Sinus congestion			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Cardiac murmur			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
White blood cells urine			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
Fall			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	7		
Patella fracture			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Post-traumatic pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Palpitations			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Nervous system disorders			
Aphonia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Facial neuralgia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	12		
Irregular sleep phase			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Memory impairment			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	6		
Paraesthesia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Coagulopathy			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Lymphadenopathy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Lymphoid tissue hyperplasia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Dry eye			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Iritis			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Abdominal distension			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	8		
Abdominal pain			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	10		
Abdominal pain lower			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	10		
Abdominal tenderness			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Coeliac disease			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Colonic polyp			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	12		
Diverticulum			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		

Dry mouth				
subjects affected / exposed	4 / 28 (14.29%)			
occurrences (all)	5			
Dyspepsia				
subjects affected / exposed	4 / 28 (14.29%)			
occurrences (all)	5			
Faecal incontinence				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Faeces pale				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Flatulence				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Gastritis				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Gastrooesophageal reflux disease				
subjects affected / exposed	5 / 28 (17.86%)			
occurrences (all)	7			
Glossodynia				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences (all)	0			
Haemorrhoids				
subjects affected / exposed	5 / 28 (17.86%)			
occurrences (all)	5			
Hiatus hernia				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Nausea				
subjects affected / exposed	11 / 28 (39.29%)			
occurrences (all)	19			
Oesophagitis				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	3			

Parotid gland enlargement subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Salivary gland enlargement subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Toothache subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 3		
Vomiting subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 8		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Hepatic pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Alopecia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Dry skin subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Eczema subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4		
Erythema subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Lichen planus			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	25 / 28 (89.29%)		
occurrences (all)	107		
Rash			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Rash macular			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Spider naevus			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Vitiligo			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Nephrolithiasis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Renal cyst			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 28 (46.43%)		
occurrences (all)	33		
Back pain			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	8		
Fibromyalgia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Muscle spasm			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	7		
Musculoskeletal pain			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Myalgia			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	12		
Osteoarthritis			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Osteoporosis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	8		
Rheumatoid arthritis			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Rotator cuff syndrome			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Tendonitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Cystitis			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
Ear infection			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Eye infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Laryngitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 5		
Otitis media subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Pneumonia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Rhinitis subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Sinusitis subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 11		
Tinea pedis subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Tooth infection subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 28 (32.14%) 11		
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 9		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Fluid overload			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Vitamin D deficiency			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	6		

Notes:

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2007	Added additional Day 8 visit of the DB phase.
13 November 2008	Added an LTSE, open-label phase.
17 February 2009	Added additional study assessments and mandated study discontinuation criteria.
16 June 2009	Added specified LTSE duration and a 2-week visit for Placebo arm in the DB phase.
12 February 2010	Correction to Schedule of Procedures.
16 December 2010	Requested an extension to previously requested 18-month LTSE phase duration.
12 February 2011	Requested an extension of duration of open-label treatment from 18 months to 36 months.
26 April 2012	Added tablet information and also included a request for an extension in duration to the LTSE phase to 54 months.
04 March 2014	Requested to further extend the study duration for an additional 18 months (to 72 months).
30 September 2015	Increased the study duration for a further 18 months (to 90 months).
14 February 2017	Revised and consolidated 2 prior amendments by removing language regarding OCA doses above 50 mg and for the United Kingdom only, extending the study duration to 108 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Limitations of the study include the use of ursodeoxycholic acid that disallowed meeting key inclusion/exclusion criteria, a short double-blind phase, and the reason participants were not receiving ursodeoxycholic acid at baseline was not captured.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29023915