

**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             | v3 (current)  |
| This version publication date     | 25 April 2021   |
| First version publication date    | 21 May 2016   |
| Version creation reason           | • Correction of full data set<br>correcting the errors in the section of non-serious AE |
| Summary attachment (see zip file) | Intercept Study 747-201 Results<br>(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          |
| <b>Arm title</b>             | 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, 6 $\alpha$ -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.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | 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, 6 $\alpha$ -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.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | 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:<br>OCA 10 mg for 3 months during the DB phase.        |                |
| Reporting group title  | DB OCA 50 mg   |
| Reporting group description:<br>OCA 50 mg for 3 months during the DB phase.        |                |
| Reporting group title  | DB OCA Placebo |
| Reporting group description:<br>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:<br>OCA 10 mg for 3 months during the DB phase.  |                |
| Reporting group title  | DB OCA 50 mg   |
| Reporting group description:<br>OCA 50 mg for 3 months during the DB phase.  |                |
| Reporting group title  | DB OCA Placebo |
| Reporting group description:<br>Matching placebo for 3 months during the DB phase.   |                |
| Reporting group title  | LTSE OCA Total |
| Reporting group description:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup>      |  |  |  |
| 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 <sup>[3]</sup> |  |  |  |
| 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)   |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | 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)   |  |

|                                       |                        |  |  |  |
|---------------------------------------|------------------------|--|--|--|
| <b>End point values</b>               | 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.<br>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)

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | 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)

|                                       |                       |  |  |  |
|---------------------------------------|-----------------------|--|--|--|
| <b>End point values</b>               | 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) |           |

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | LTSE OCA Total      |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 28                  |  |  |  |
| Units: Percent change                |                     |  |  |  |
| arithmetic mean (standard deviation) | 57.8 ( $\pm$ 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)

|                                       |                     |  |  |  |
|---------------------------------------|---------------------|--|--|--|
| <b>End point values</b>               | 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) |           |

|                                      |                   |  |  |  |
|--------------------------------------|-------------------|--|--|--|
| <b>End point values</b>              | LTSE OCA Total    |  |  |  |
| Subject group type                   | Reporting group   |  |  |  |
| Number of subjects analysed          | 28                |  |  |  |
| Units: Percent Change                |                   |  |  |  |
| arithmetic mean (standard deviation) | 2.2 ( $\pm$ 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. LTSE: 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 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.

|                       |              |
|-----------------------|--------------|
| Reporting group title | DB OCA 50 mg |
|-----------------------|--------------|

Reporting group description:

OCA 50 mg for 3 months during the DB phase.

| Serious adverse events  | DB OCA 10 mg   | DB OCA Placebo | LTSE OCA Total  |
|---|----------------|----------------|-----------------|
| Total subjects affected by serious adverse events                   |                |                |                 |
| subjects affected / exposed   | 0 / 20 (0.00%) | 1 / 23 (4.35%) | 9 / 28 (32.14%) |
| 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 / 23 (0.00%) | 1 / 28 (3.57%)  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0           |
| Vascular disorders  |                |                |                 |
| Peripheral ischaemia  |                |                |                 |
| subjects affected / exposed   | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%)  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0           |
| Reproductive system and breast                                      |                |                |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| disorders                                       |                |                |                |
| Uterine prolapse                                |                |                |                |
| subjects affected / exposed <sup>[1]</sup>      | 0 / 14 (0.00%) | 0 / 20 (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          |
| Cystocele                                       |                |                |                |
| subjects affected / exposed <sup>[2]</sup>      | 0 / 14 (0.00%) | 0 / 20 (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          |
| Injury, poisoning and procedural complications  |                |                |                |
| Pelvic fracture                                 |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hip fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| 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 disorders                               |                |                |                |
| Bradycardia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| 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 flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tricuspid valve incompetence                    |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericarditis                                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| 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                        |                |                |                |
| Transient ischaemic attack                      |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Haemorrhagic anaemia                            |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 4          |
| 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 / 23 (0.00%) | 1 / 28 (3.57%) |
| 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                      |                |                |                |
| Small intestinal obstruction                    |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| 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 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| 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 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric varices haemorrhage                     |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Bile duct stone                                 |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Jaundice  |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| 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%) | 1 / 23 (4.35%) | 0 / 28 (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                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Polyarthrititis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Pneumonia                                       |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |  |  |
|---|----------------|--|--|
| <b>Serious adverse events</b>                                       | DB OCA 50 mg   |  |  |
| Total subjects affected by serious adverse events                   |                |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%) |  |  |
| 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   | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Vascular disorders  |                |  |  |
| Peripheral ischaemia  |                |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Reproductive system and breast disorders                            |                |  |  |
| Uterine prolapse  |                |  |  |
| subjects affected / exposed <sup>[1]</sup>                          | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Cystocele   |                |  |  |
| subjects affected / exposed <sup>[2]</sup>                          | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Injury, poisoning and procedural complications                      |                |  |  |
| Pelvic fracture   |                |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Hip fracture  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Bradycardia                                     |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atrial flutter                                  |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tricuspid valve incompetence                    |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pericarditis                                    |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Transient ischaemic attack                      |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Haemorrhagic anaemia                            |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ear and labyrinth disorders                     |                |  |  |
| Vertigo   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Gastrointestinal disorders</b>               |                |  |  |
| Small intestinal obstruction                    |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastric varices haemorrhage                     |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Hepatobiliary disorders</b>                  |                |  |  |
| Bile duct stone                                 |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Jaundice  |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Skin and subcutaneous tissue disorders</b>   |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| Rash  |                |  |  |
| subjects affected / exposed                     | 0 / 16 (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                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Polyarthritis                                   |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| 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: 4.99 %

| Non-serious adverse events  | DB OCA 10 mg     | DB OCA Placebo   | LTSE OCA Total    |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events               |                  |                  |                   |
| subjects affected / exposed   | 18 / 20 (90.00%) | 19 / 23 (82.61%) | 28 / 28 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                   |
| Haemangioma   |                  |                  |                   |
| subjects affected / exposed   | 0 / 20 (0.00%)   | 0 / 23 (0.00%)   | 2 / 28 (7.14%)    |
| occurrences (all)   | 0                | 0                | 2                 |
| Lipoma  |                  |                  |                   |
| subjects affected / exposed   | 0 / 20 (0.00%)   | 0 / 23 (0.00%)   | 2 / 28 (7.14%)    |
| occurrences (all)   | 0                | 0                | 2                 |
| Lung neoplasm   |                  |                  |                   |

|  |                |                 |                  |
|--|----------------|-----------------|------------------|
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 0 / 28 (0.00%)   |
| occurrences (all)                                    | 0              | 0               | 0                |
| Thyroid neoplasm                                     |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                                    | 0              | 0               | 2                |
| Vascular disorders                                   |                |                 |                  |
| Hot flush  |                |                 |                  |
| subjects affected / exposed                          | 1 / 20 (5.00%) | 0 / 23 (0.00%)  | 1 / 28 (3.57%)   |
| occurrences (all)                                    | 1              | 0               | 1                |
| Hypertension   |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                                    | 0              | 0               | 2                |
| Hypotension  |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                                    | 0              | 0               | 2                |
| Varicose vein  |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 3 / 28 (10.71%)  |
| occurrences (all)                                    | 0              | 0               | 3                |
| General disorders and administration site conditions |                |                 |                  |
| Asthenia   |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 1 / 28 (3.57%)   |
| occurrences (all)                                    | 0              | 0               | 1                |
| Chest discomfort                                     |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                                    | 0              | 0               | 2                |
| Chills   |                |                 |                  |
| subjects affected / exposed                          | 1 / 20 (5.00%) | 1 / 23 (4.35%)  | 2 / 28 (7.14%)   |
| occurrences (all)                                    | 1              | 1               | 2                |
| Fatigue  |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 3 / 23 (13.04%) | 14 / 28 (50.00%) |
| occurrences (all)                                    | 0              | 3               | 16               |
| Feeling cold   |                |                 |                  |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 0 / 28 (0.00%)   |
| occurrences (all)                                    | 0              | 0               | 0                |
| Influenza like illness                               |                |                 |                  |

|   |                     |                     |                       |
|---|---------------------|---------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0 | 2 / 23 (8.70%)<br>2 | 3 / 28 (10.71%)<br>7  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 7 / 28 (25.00%)<br>11 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0 | 2 / 23 (8.70%)<br>2 | 3 / 28 (10.71%)<br>3  |
| Immune system disorders<br>Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)        | 0 / 20 (0.00%)<br>0 | 1 / 23 (4.35%)<br>1 | 2 / 28 (7.14%)<br>3   |
| Sarcoidosis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1 | 0 / 23 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0   |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2   |
| Reproductive system and breast disorders<br>Breast mass<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2   |
| Breast tenderness<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 20 (5.00%)<br>1 | 0 / 23 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0   |
| Gynaecomastia<br>subjects affected / exposed <sup>[3]</sup><br>occurrences (all)                            | 1 / 14 (7.14%)<br>1 | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0   |
| Menorrhagia<br>subjects affected / exposed <sup>[4]</sup><br>occurrences (all)                              | 1 / 14 (7.14%)<br>1 | 0 / 20 (0.00%)<br>0 | 1 / 23 (4.35%)<br>2   |
| Ovarian cyst<br>subjects affected / exposed <sup>[5]</sup><br>occurrences (all)                             | 0 / 14 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 2 / 23 (8.70%)<br>2   |
| Respiratory, thoracic and mediastinal disorders   |                     |                     |                       |

|                                      |                |                |                 |
|--------------------------------------|----------------|----------------|-----------------|
| Asthma                               |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0              | 0              | 5               |
| Cough                                |                |                |                 |
| subjects affected / exposed          | 1 / 20 (5.00%) | 1 / 23 (4.35%) | 5 / 28 (17.86%) |
| occurrences (all)                    | 1              | 1              | 5               |
| Dyspnoea                             |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)                    | 0              | 0              | 3               |
| Dyspnoea exertional                  |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0              | 0              | 2               |
| Nasal congestion                     |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 4 / 28 (14.29%) |
| occurrences (all)                    | 0              | 0              | 4               |
| Oropharyngeal pain                   |                |                |                 |
| subjects affected / exposed          | 1 / 20 (5.00%) | 1 / 23 (4.35%) | 2 / 28 (7.14%)  |
| occurrences (all)                    | 1              | 1              | 4               |
| Rhinorrhoea                          |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0              | 0              | 2               |
| Sinus congestion                     |                |                |                 |
| subjects affected / exposed          | 1 / 20 (5.00%) | 1 / 23 (4.35%) | 3 / 28 (10.71%) |
| occurrences (all)                    | 1              | 1              | 4               |
| Psychiatric disorders                |                |                |                 |
| Anxiety                              |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)                    | 0              | 0              | 3               |
| Insomnia                             |                |                |                 |
| subjects affected / exposed          | 1 / 20 (5.00%) | 1 / 23 (4.35%) | 5 / 28 (17.86%) |
| occurrences (all)                    | 2              | 1              | 6               |
| Investigations                       |                |                |                 |
| Blood alkaline phosphatase increased |                |                |                 |
| subjects affected / exposed          | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0              | 0              | 2               |
| Cardiac murmur                       |                |                |                 |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                            | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 3 / 28 (10.71%)<br>3 |
| White blood cells urine<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                              |                     |                     |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)               | 1 / 20 (5.00%)<br>1 | 0 / 23 (0.00%)<br>0 | 4 / 28 (14.29%)<br>6 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 5 / 28 (17.86%)<br>7 |
| Patella fracture<br>subjects affected / exposed<br>occurrences (all)        | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2  |
| Post-traumatic pain<br>subjects affected / exposed<br>occurrences (all)     | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)         | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 4 / 28 (14.29%)<br>4 |
| Cardiac disorders   |                     |                     |                      |
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)         | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 3 / 28 (10.71%)<br>3 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)            | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 3 / 28 (10.71%)<br>4 |
| Nervous system disorders  |                     |                     |                      |
| Aphonia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2  |
| Dizziness   |                     |                     |                      |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 20 (0.00%)  | 4 / 23 (17.39%) | 5 / 28 (17.86%) |
| occurrences (all)                    | 0               | 5               | 5               |
| Facial neuralgia                     |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                    | 0               | 0               | 0               |
| Headache                             |                 |                 |                 |
| subjects affected / exposed          | 4 / 20 (20.00%) | 5 / 23 (21.74%) | 8 / 28 (28.57%) |
| occurrences (all)                    | 5               | 6               | 12              |
| Irregular sleep phase                |                 |                 |                 |
| subjects affected / exposed          | 1 / 20 (5.00%)  | 0 / 23 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Memory impairment                    |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 3 / 28 (10.71%) |
| occurrences (all)                    | 0               | 0               | 3               |
| Migraine                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 3 / 28 (10.71%) |
| occurrences (all)                    | 0               | 0               | 6               |
| Paraesthesia                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0               | 0               | 2               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 3 / 28 (10.71%) |
| occurrences (all)                    | 0               | 0               | 4               |
| Coagulopathy                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0               | 0               | 2               |
| Lymphadenopathy                      |                 |                 |                 |
| subjects affected / exposed          | 1 / 20 (5.00%)  | 0 / 23 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Lymphoid tissue hyperplasia          |                 |                 |                 |
| subjects affected / exposed          | 1 / 20 (5.00%)  | 0 / 23 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Thrombocytopenia                     |                 |                 |                 |
| subjects affected / exposed          | 0 / 20 (0.00%)  | 0 / 23 (0.00%)  | 2 / 28 (7.14%)  |
| occurrences (all)                    | 0               | 0               | 2               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Eye disorders               |                |                |                 |
| Cataract                    |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Dry eye                     |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 23 (4.35%) | 3 / 28 (10.71%) |
| occurrences (all)           | 0              | 1              | 3               |
| Iritis                      |                |                |                 |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Gastrointestinal disorders  |                |                |                 |
| Abdominal discomfort        |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 4 / 28 (14.29%) |
| occurrences (all)           | 0              | 0              | 5               |
| Abdominal distension        |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 6 / 28 (21.43%) |
| occurrences (all)           | 0              | 0              | 8               |
| Abdominal pain              |                |                |                 |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 23 (4.35%) | 6 / 28 (21.43%) |
| occurrences (all)           | 1              | 1              | 10              |
| Abdominal pain lower        |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)           | 0              | 0              | 4               |
| Abdominal pain upper        |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 23 (8.70%) | 7 / 28 (25.00%) |
| occurrences (all)           | 0              | 2              | 10              |
| Abdominal tenderness        |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)           | 0              | 0              | 3               |
| Coeliac disease             |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Colonic polyp               |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)           | 0              | 0              | 3               |
| Constipation                |                |                |                 |

|                                  |                |                |                 |
|----------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 9 / 28 (32.14%) |
| occurrences (all)                | 0              | 0              | 11              |
| Diarrhoea                        |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 1 / 23 (4.35%) | 8 / 28 (28.57%) |
| occurrences (all)                | 0              | 1              | 12              |
| Diverticulum                     |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 4 / 28 (14.29%) |
| occurrences (all)                | 0              | 0              | 4               |
| Dry mouth                        |                |                |                 |
| subjects affected / exposed      | 1 / 20 (5.00%) | 1 / 23 (4.35%) | 4 / 28 (14.29%) |
| occurrences (all)                | 1              | 1              | 5               |
| Dyspepsia                        |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 1 / 23 (4.35%) | 4 / 28 (14.29%) |
| occurrences (all)                | 0              | 1              | 5               |
| Faecal incontinence              |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%)  |
| occurrences (all)                | 0              | 0              | 1               |
| Faeces pale                      |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)                | 0              | 0              | 0               |
| Flatulence                       |                |                |                 |
| subjects affected / exposed      | 1 / 20 (5.00%) | 0 / 23 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)                | 1              | 0              | 0               |
| Gastritis                        |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                | 0              | 0              | 2               |
| Gastrooesophageal reflux disease |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 5 / 28 (17.86%) |
| occurrences (all)                | 0              | 0              | 7               |
| Glossodynia                      |                |                |                 |
| subjects affected / exposed      | 1 / 20 (5.00%) | 0 / 23 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)                | 1              | 0              | 0               |
| Haemorrhoids                     |                |                |                 |
| subjects affected / exposed      | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 5 / 28 (17.86%) |
| occurrences (all)                | 0              | 0              | 5               |
| Hiatus hernia                    |                |                |                 |



|  |                |                 |                  |
|--|----------------|-----------------|------------------|
| subjects affected / exposed            | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                      | 0              | 0               | 2                |
| Nausea                                 |                |                 |                  |
| subjects affected / exposed            | 0 / 20 (0.00%) | 4 / 23 (17.39%) | 11 / 28 (39.29%) |
| occurrences (all)                      | 0              | 5               | 19               |
| Oesophagitis                           |                |                 |                  |
| subjects affected / exposed            | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 3 / 28 (10.71%)  |
| occurrences (all)                      | 0              | 0               | 3                |
| Parotid gland enlargement              |                |                 |                  |
| subjects affected / exposed            | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 0 / 28 (0.00%)   |
| occurrences (all)                      | 0              | 0               | 0                |
| Salivary gland enlargement             |                |                 |                  |
| subjects affected / exposed            | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 0 / 28 (0.00%)   |
| occurrences (all)                      | 0              | 0               | 0                |
| Toothache                              |                |                 |                  |
| subjects affected / exposed            | 0 / 20 (0.00%) | 1 / 23 (4.35%)  | 1 / 28 (3.57%)   |
| occurrences (all)                      | 0              | 1               | 3                |
| Vomiting                               |                |                 |                  |
| subjects affected / exposed            | 1 / 20 (5.00%) | 1 / 23 (4.35%)  | 4 / 28 (14.29%)  |
| occurrences (all)                      | 1              | 1               | 8                |
| Hepatobiliary disorders                |                |                 |                  |
| Cholelithiasis                         |                |                 |                  |
| subjects affected / exposed            | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 3 / 28 (10.71%)  |
| occurrences (all)                      | 0              | 0               | 3                |
| Hepatic pain                           |                |                 |                  |
| subjects affected / exposed            | 1 / 20 (5.00%) | 0 / 23 (0.00%)  | 1 / 28 (3.57%)   |
| occurrences (all)                      | 1              | 0               | 1                |
| Skin and subcutaneous tissue disorders |                |                 |                  |
| Acne                                   |                |                 |                  |
| subjects affected / exposed            | 1 / 20 (5.00%) | 0 / 23 (0.00%)  | 0 / 28 (0.00%)   |
| occurrences (all)                      | 1              | 0               | 0                |
| Alopecia                               |                |                 |                  |
| subjects affected / exposed            | 1 / 20 (5.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                      | 1              | 0               | 2                |
| Dry skin                               |                |                 |                  |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                 | 0 / 20 (0.00%)   | 1 / 23 (4.35%)  | 1 / 28 (3.57%)   |
| occurrences (all)                           | 0                | 2               | 1                |
| Eczema                                      |                  |                 |                  |
| subjects affected / exposed                 | 0 / 20 (0.00%)   | 0 / 23 (0.00%)  | 4 / 28 (14.29%)  |
| occurrences (all)                           | 0                | 0               | 4                |
| Erythema                                    |                  |                 |                  |
| subjects affected / exposed                 | 0 / 20 (0.00%)   | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                           | 0                | 0               | 2                |
| Lichen planus                               |                  |                 |                  |
| subjects affected / exposed                 | 0 / 20 (0.00%)   | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                           | 0                | 0               | 2                |
| Palmar-plantar erythrodysaesthesia syndrome |                  |                 |                  |
| subjects affected / exposed                 | 1 / 20 (5.00%)   | 0 / 23 (0.00%)  | 0 / 28 (0.00%)   |
| occurrences (all)                           | 1                | 0               | 0                |
| Pruritus                                    |                  |                 |                  |
| subjects affected / exposed                 | 14 / 20 (70.00%) | 7 / 23 (30.43%) | 25 / 28 (89.29%) |
| occurrences (all)                           | 24               | 11              | 107              |
| Rash  |                  |                 |                  |
| subjects affected / exposed                 | 0 / 20 (0.00%)   | 1 / 23 (4.35%)  | 3 / 28 (10.71%)  |
| occurrences (all)                           | 0                | 1               | 3                |
| Rash macular                                |                  |                 |                  |
| subjects affected / exposed                 | 1 / 20 (5.00%)   | 0 / 23 (0.00%)  | 1 / 28 (3.57%)   |
| occurrences (all)                           | 2                | 0               | 1                |
| Rash papular                                |                  |                 |                  |
| subjects affected / exposed                 | 1 / 20 (5.00%)   | 0 / 23 (0.00%)  | 1 / 28 (3.57%)   |
| occurrences (all)                           | 2                | 0               | 1                |
| Skin lesion                                 |                  |                 |                  |
| subjects affected / exposed                 | 1 / 20 (5.00%)   | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                           | 1                | 0               | 2                |
| Spider naevus                               |                  |                 |                  |
| subjects affected / exposed                 | 0 / 20 (0.00%)   | 0 / 23 (0.00%)  | 3 / 28 (10.71%)  |
| occurrences (all)                           | 0                | 0               | 3                |
| Vitiligo                                    |                  |                 |                  |
| subjects affected / exposed                 | 1 / 20 (5.00%)   | 0 / 23 (0.00%)  | 1 / 28 (3.57%)   |
| occurrences (all)                           | 1                | 0               | 1                |

|   |                |                 |                  |
|---|----------------|-----------------|------------------|
| Renal and urinary disorders                     |                |                 |                  |
| Haematuria                                      |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                               | 0              | 0               | 3                |
| Nephrolithiasis                                 |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                               | 0              | 0               | 3                |
| Renal cyst                                      |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                               | 0              | 0               | 2                |
| Endocrine disorders                             |                |                 |                  |
| Hypothyroidism                                  |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                               | 0              | 0               | 2                |
| Musculoskeletal and connective tissue disorders |                |                 |                  |
| Arthralgia                                      |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 2 / 23 (8.70%)  | 13 / 28 (46.43%) |
| occurrences (all)                               | 0              | 2               | 33               |
| Back pain                                       |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 4 / 23 (17.39%) | 7 / 28 (25.00%)  |
| occurrences (all)                               | 0              | 4               | 8                |
| Fibromyalgia                                    |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 2 / 28 (7.14%)   |
| occurrences (all)                               | 0              | 0               | 2                |
| Muscle spasm                                    |                |                 |                  |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 1 / 23 (4.35%)  | 5 / 28 (17.86%)  |
| occurrences (all)                               | 1              | 1               | 7                |
| Musculoskeletal pain                            |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 23 (4.35%)  | 5 / 28 (17.86%)  |
| occurrences (all)                               | 0              | 1               | 6                |
| Myalgia   |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 6 / 28 (21.43%)  |
| occurrences (all)                               | 0              | 0               | 12               |
| Osteoarthritis                                  |                |                 |                  |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 0 / 23 (0.00%)  | 4 / 28 (14.29%)  |
| occurrences (all)                               | 0              | 0               | 4                |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Osteoporosis                |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 6 / 28 (21.43%) |
| occurrences (all)           | 0              | 0              | 8               |
| Rheumatoid arthritis        |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Rotator cuff syndrome       |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 3               |
| Tendonitis                  |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Infections and infestations |                |                |                 |
| Bronchitis                  |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 4               |
| Cystitis                    |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 4 / 28 (14.29%) |
| occurrences (all)           | 0              | 0              | 6               |
| Ear infection               |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 3               |
| Eye infection               |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Gastroenteritis             |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Herpes zoster               |                |                |                 |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Influenza                   |                |                |                 |

|                                    |                 |                |                 |
|------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 4               |
| Laryngitis                         |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 2               |
| Lower respiratory tract infection  |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 2               |
| Nasopharyngitis                    |                 |                |                 |
| subjects affected / exposed        | 3 / 20 (15.00%) | 2 / 23 (8.70%) | 3 / 28 (10.71%) |
| occurrences (all)                  | 3               | 2              | 5               |
| Otitis media                       |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 2               |
| Pneumonia                          |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 2               |
| Rhinitis                           |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 2               |
| Sinusitis                          |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 6 / 28 (21.43%) |
| occurrences (all)                  | 0               | 0              | 11              |
| Tinea pedis                        |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)                  | 0               | 0              | 2               |
| Tooth infection                    |                 |                |                 |
| subjects affected / exposed        | 0 / 20 (0.00%)  | 0 / 23 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)                  | 0               | 0              | 3               |
| Upper respiratory tract infection  |                 |                |                 |
| subjects affected / exposed        | 2 / 20 (10.00%) | 0 / 23 (0.00%) | 9 / 28 (32.14%) |
| occurrences (all)                  | 3               | 0              | 11              |
| Urinary tract infection            |                 |                |                 |
| subjects affected / exposed        | 3 / 20 (15.00%) | 0 / 23 (0.00%) | 5 / 28 (17.86%) |
| occurrences (all)                  | 3               | 0              | 9               |
| Metabolism and nutrition disorders |                 |                |                 |

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2  |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)    | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0  |
| Fluid overload<br>subjects affected / exposed<br>occurrences (all)       | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 20 (0.00%)<br>0 | 1 / 23 (4.35%)<br>1 | 2 / 28 (7.14%)<br>3  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0 | 0 / 23 (0.00%)<br>0 | 6 / 28 (21.43%)<br>6 |

|  |                     |  |  |
|--|---------------------|--|--|
| <b>Non-serious adverse events</b>  | DB OCA 50 mg        |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 16 / 16 (100.00%)   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Haemangioma<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 |  |  |
| Lipoma<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 |  |  |
| Lung neoplasm<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1 |  |  |
| Thyroid neoplasm<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 |  |  |
| Vascular disorders<br>Hot flush<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Hypertension   |                     |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| Hypotension  |                |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| Varicose vein  |                |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| General disorders and administration site conditions |                |  |  |
| Asthenia   |                |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%) |  |  |
| occurrences (all)                                    | 1              |  |  |
| Chest discomfort                                     |                |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| Chills   |                |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| Fatigue  |                |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%) |  |  |
| occurrences (all)                                    | 1              |  |  |
| Feeling cold   |                |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%) |  |  |
| occurrences (all)                                    | 1              |  |  |
| Influenza like illness                               |                |  |  |
| subjects affected / exposed                          | 1 / 16 (6.25%) |  |  |
| occurrences (all)                                    | 1              |  |  |
| Oedema peripheral                                    |                |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| Pyrexia  |                |  |  |
| subjects affected / exposed                          | 0 / 16 (0.00%) |  |  |
| occurrences (all)                                    | 0              |  |  |
| Immune system disorders                              |                |  |  |

|   |   |  |  |
|---|---|--|--|
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0   |  |  |
| Sarcoidosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0   |  |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0   |  |  |
| Reproductive system and breast disorders<br>Breast mass<br>subjects affected / exposed<br>occurrences (all)<br><br>Breast tenderness<br>subjects affected / exposed<br>occurrences (all)<br><br>Gynaecomastia<br>subjects affected / exposed <sup>[3]</sup><br>occurrences (all)<br><br>Menorrhagia<br>subjects affected / exposed <sup>[4]</sup><br>occurrences (all)<br><br>Ovarian cyst<br>subjects affected / exposed <sup>[5]</sup><br>occurrences (all) | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea exertional   | 0 / 16 (0.00%)<br>0<br><br>1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0   |  |  |



|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Nasal congestion                               |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Oropharyngeal pain                             |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Rhinorrhoea                                    |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Sinus congestion                               |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Psychiatric disorders                          |                 |  |  |
| Anxiety  |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Insomnia                                       |                 |  |  |
| subjects affected / exposed                    | 2 / 16 (12.50%) |  |  |
| occurrences (all)                              | 2               |  |  |
| Investigations                                 |                 |  |  |
| Blood alkaline phosphatase increased           |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Cardiac murmur                                 |                 |  |  |
| subjects affected / exposed                    | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Weight decreased                               |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| White blood cells urine                        |                 |  |  |
| subjects affected / exposed                    | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Injury, poisoning and procedural complications |                 |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Contusion<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 16 (0.00%)<br>0  |  |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 16 (0.00%)<br>0  |  |  |
| Patella fracture<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 16 (0.00%)<br>0  |  |  |
| Post-traumatic pain<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 16 (0.00%)<br>0  |  |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 16 (0.00%)<br>0  |  |  |
| Cardiac disorders<br>Angina pectoris<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  |  |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 16 (0.00%)<br>0  |  |  |
| Nervous system disorders<br>Aphonia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 16 (0.00%)<br>0  |  |  |
| Facial neuralgia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 16 (6.25%)<br>1  |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 16 (12.50%)<br>3 |  |  |
| Irregular sleep phase  |                      |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>  |  |  |  |
| <p>Memory impairment</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>   |  |  |  |
| <p>Migraine</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p>  |  |  |  |
| <p>Paraesthesia</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>  |  |  |  |
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Coagulopathy</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Lymphadenopathy</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Lymphoid tissue hyperplasia</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> |  |  |  |
| <p>Eye disorders</p> <p>Cataract</p> <p>subjects affected / exposed</p> <p>0 / 16 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>1 / 16 (6.25%)</p> <p>occurrences (all)</p> <p>1</p> <p>Iritis</p>   |  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Gastrointestinal disorders  |                 |  |  |
| Abdominal discomfort        |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Abdominal distension        |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 2               |  |  |
| Abdominal pain              |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 2               |  |  |
| Abdominal pain lower        |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Abdominal pain upper        |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Abdominal tenderness        |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Coeliac disease             |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Colonic polyp               |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Constipation                |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 2               |  |  |
| Diarrhoea                   |                 |  |  |
| subjects affected / exposed | 2 / 16 (12.50%) |  |  |
| occurrences (all)           | 2               |  |  |
| Diverticulum                |                 |  |  |
| subjects affected / exposed | 0 / 16 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| Dry mouth                        |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Dyspepsia                        |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Faecal incontinence              |                 |  |  |
| subjects affected / exposed      | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Faeces pale                      |                 |  |  |
| subjects affected / exposed      | 2 / 16 (12.50%) |  |  |
| occurrences (all)                | 2               |  |  |
| Flatulence                       |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Gastritis                        |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Gastrooesophageal reflux disease |                 |  |  |
| subjects affected / exposed      | 1 / 16 (6.25%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Glossodynia                      |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Haemorrhoids                     |                 |  |  |
| subjects affected / exposed      | 2 / 16 (12.50%) |  |  |
| occurrences (all)                | 2               |  |  |
| Hiatus hernia                    |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Nausea                           |                 |  |  |
| subjects affected / exposed      | 4 / 16 (25.00%) |  |  |
| occurrences (all)                | 4               |  |  |
| Oesophagitis                     |                 |  |  |
| subjects affected / exposed      | 0 / 16 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Parotid gland enlargement<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 16 (6.25%)<br>1 |  |  |
| Salivary gland enlargement<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 16 (6.25%)<br>1 |  |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 16 (6.25%)<br>1 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 16 (6.25%)<br>1 |  |  |
| Hepatobiliary disorders<br>Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 16 (0.00%)<br>0 |  |  |
| Hepatic pain<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 16 (0.00%)<br>0 |  |  |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 |  |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 16 (0.00%)<br>0 |  |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 16 (6.25%)<br>1 |  |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 |  |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 16 (0.00%)<br>0 |  |  |
| Lichen planus  |                     |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Palmar-plantar erythrodysaesthesia syndrome |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Pruritus                                    |                  |  |  |
| subjects affected / exposed                 | 15 / 16 (93.75%) |  |  |
| occurrences (all)                           | 22               |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                 | 1 / 16 (6.25%)   |  |  |
| occurrences (all)                           | 1                |  |  |
| Rash macular                                |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Rash papular                                |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Skin lesion                                 |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Spider naevus                               |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Vitiligo                                    |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Renal and urinary disorders                 |                  |  |  |
| Haematuria                                  |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Nephrolithiasis                             |                  |  |  |
| subjects affected / exposed                 | 0 / 16 (0.00%)   |  |  |
| occurrences (all)                           | 0                |  |  |
| Renal cyst                                  |                  |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 16 (0.00%)<br>0 |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 |  |  |
| Fibromyalgia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Muscle spasm<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 16 (0.00%)<br>0 |  |  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Osteoporosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1 |  |  |
| Rheumatoid arthritis  |                     |  |  |



|                                   |                |  |  |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Rotator cuff syndrome             |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Tendonitis                        |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Infections and infestations       |                |  |  |
| Bronchitis                        |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Cystitis                          |                |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Ear infection                     |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Eye infection                     |                |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Gastroenteritis                   |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Herpes zoster                     |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Influenza                         |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Laryngitis                        |                |  |  |
| subjects affected / exposed       | 0 / 16 (0.00%) |  |  |
| occurrences (all)                 | 0              |  |  |
| Lower respiratory tract infection |                |  |  |
| subjects affected / exposed       | 1 / 16 (6.25%) |  |  |
| occurrences (all)                 | 1              |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| Nasopharyngitis                    |                |  |  |
| subjects affected / exposed        | 1 / 16 (6.25%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Otitis media                       |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Pneumonia                          |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Rhinitis                           |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Sinusitis                          |                |  |  |
| subjects affected / exposed        | 1 / 16 (6.25%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Tinea pedis                        |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Tooth infection                    |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Upper respiratory tract infection  |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Urinary tract infection            |                |  |  |
| subjects affected / exposed        | 1 / 16 (6.25%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Decreased appetite                 |                |  |  |
| subjects affected / exposed        | 0 / 16 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Diabetes mellitus                  |                |  |  |
| subjects affected / exposed        | 1 / 16 (6.25%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Fluid overload                     |                |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 16 (0.00%) |  |  |
| occurrences (all)           | 0              |  |  |
| Hypokalaemia                |                |  |  |
| subjects affected / exposed | 0 / 16 (0.00%) |  |  |
| occurrences (all)           | 0              |  |  |
| Vitamin D deficiency        |                |  |  |
| subjects affected / exposed | 0 / 16 (0.00%) |  |  |
| occurrences (all)           | 0              |  |  |

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>

