



## Clinical trial results:

### A Phase 4, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Pharmacokinetics and Safety of Obeticholic Acid in Patients with Primary Biliary Cholangitis and Moderate to Severe Hepatic Impairment

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2017-001762-13       |
| Trial protocol           | ES DE BE HU EE LT IT |
| Global end of trial date | 09 July 2021         |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 24 July 2022 |
| First version publication date | 24 July 2022 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 747-401 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03633227 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Intercept Pharmaceuticals, Inc.  |
| Sponsor organisation address | 305 Madison Avenue, Morristown, NJ, United States, 07960   |
| Public contact               | Medical Information, Intercept Pharmaceuticals, Inc., +1 844-782-4278, medinfo@interceptpharma.com |
| Scientific contact           | Medical Information, Intercept Pharmaceuticals, Inc., +1 844-782-4278, medinfo@interceptpharma.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 20 June 2022 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 09 July 2021 |
| Was the trial ended prematurely? | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) of Obeticholic acid (OCA) and its conjugates, glycine 6 $\alpha$ -ethyl chenodeoxycholic acid (glyco-OCA) and taurine 6 $\alpha$ -ethyl chenodeoxycholic acid (tauro-OCA), and OCA metabolite glucuronide (OCA-glucuronide) compared with placebo. To evaluate the safety and tolerability of OCA treatment compared with placebo.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 22 June 2018 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Spain: 2         |
| Country: Number of subjects enrolled | Belgium: 1       |
| Country: Number of subjects enrolled | Estonia: 1       |
| Country: Number of subjects enrolled | Germany: 1       |
| Country: Number of subjects enrolled | Lithuania: 2     |
| Country: Number of subjects enrolled | United States: 8 |
| Country: Number of subjects enrolled | Australia: 1     |
| Country: Number of subjects enrolled | Brazil: 2        |
| Country: Number of subjects enrolled | Argentina: 4     |
| Worldwide total number of subjects   | 22               |
| EEA total number of subjects         | 7                |

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)                     | 12 |
| From 65 to 84 years                      | 10 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at study sites in the United States, Argentina, Belgium, Spain, Lithuania, Brazil, Australia, Germany, Estonia, Italy, Canada, and Hungary.

### Pre-assignment

Screening details:

A total of 31 participants were screened and 22 participants were randomized.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Double Blind (DB), up to Week 48       |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Participants received OCA matching placebo tablets orally once weekly or twice weekly for the duration of at least 48 Weeks.

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

Dosage and administration details:

OCA matching placebo was administered per schedule specified in the arm description.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Obeticholic Acid (OCA) |
|------------------|------------------------|

Arm description:

Participants initiated treatment with OCA 5 milligrams (mg) tablets orally once weekly. At Week 12, if there were no safety concerns, the dose was up-titrated to OCA 5 mg twice weekly. Every 6 weeks thereafter, based on tolerability assessments, further up-titration of dose was considered. At each titration visit, the participants started the higher dose regimen no earlier than 2 days after the prior dose. The maximum dose titration was OCA 10 mg twice weekly at least 3 days apart. The minimum treatment duration was 48 Weeks.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Obeticholic Acid |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

OCA was administered per dose and schedule specified in the arm description.

| Number of subjects in period 1                  | Placebo | Obeticholic Acid (OCA) |
|---|---------|------------------------|
| Started   | 12      | 10                     |
| Completed                                       | 4       | 6                      |
| Not completed                                   | 8       | 4                      |
| Consent withdrawn by subject                    | 1       | 1                      |
| Physician decision                              | 1       | -                      |
| Adverse event, non-fatal                        | -       | 1                      |
| Death   | 2       | 1                      |
| Multiple Serious AE and Drug Interruptions      | 1       | -                      |
| Study Terminated by Sponsor                     | 2       | 1                      |
| Liver Transplant During the Course of the Study | 1       | -                      |

## Period 2

|                              |  |
|------------------------------|--|
| Period 2 title               | DB Extension, Week 48 up to 3 Years    |
| Is this the baseline period? | No                                     |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

## Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

### Arm description:

Participants, who had completed their 48-week treatment, could continue the treatment until all randomized participants had completed their 48-week treatment period and the database for that period was locked (total duration: approximately up to 3 years).

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

### Dosage and administration details:

OCA matching placebo was administered per the schedule specified in the arm description.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Obeticholic Acid (OCA) |
|------------------|------------------------|

### Arm description:

Participants, who had completed their 48-week treatment, could continue the treatment until all randomized participants had completed their 48-week treatment period and the database for that period was locked (total duration: approximately up to 3 years).

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                  |
|--|------------------|
| Investigational medicinal product name | Obeticholic Acid |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

OCA was administered per dose and schedule specified in the arm description.

| <b>Number of subjects in period 2</b> | Placebo | Obeticholic Acid (OCA) |
|---------------------------------------|---------|------------------------|
| Started                               | 4       | 6                      |
| Completed                             | 0       | 0                      |
| Not completed                         | 4       | 6                      |
| Consent withdrawn by subject          | -       | 2                      |
| Physician decision                    | -       | 1                      |
| Death                                 | -       | 1                      |
| Study Terminated by Sponsor           | 3       | 2                      |
| Lost to follow-up                     | 1       | -                      |

## Baseline characteristics

### Reporting groups

|   |                        |
|---|------------------------|
| Reporting group title   | Placebo                |
| Reporting group description:  |                        |
| Participants received OCA matching placebo tablets orally once weekly or twice weekly for the duration of at least 48 Weeks.  |                        |
| Reporting group title   | Obeticholic Acid (OCA) |
| Reporting group description:  |                        |
| Participants initiated treatment with OCA 5 milligrams (mg) tablets orally once weekly. At Week 12, if there were no safety concerns, the dose was up-titrated to OCA 5 mg twice weekly. Every 6 weeks thereafter, based on tolerability assessments, further up-titration of dose was considered. At each titration visit, the participants started the higher dose regimen no earlier than 2 days after the prior dose. The maximum dose titration was OCA 10 mg twice weekly at least 3 days apart. The minimum treatment duration was 48 Weeks. |                        |

| Reporting group values  | Placebo | Obeticholic Acid (OCA) | Total |
|---|---------|------------------------|-------|
| Number of subjects  | 12      | 10                     | 22    |
| Age categorical<br>Units: Subjects  |         |                        |       |
| Age continuous<br>Units: years  |         |                        |       |
| arithmetic mean   | 62.5    | 60.5                   |       |
| standard deviation  | ± 9.10  | ± 10.19                | -     |
| Gender categorical<br>Units: Subjects   |         |                        |       |
| Female  | 10      | 6                      | 16    |
| Male  | 2       | 4                      | 6     |
| Ethnicity<br>Units: Subjects  |         |                        |       |
| Hispanic or Latino  | 6       | 4                      | 10    |
| Not Hispanic or Latino  | 6       | 6                      | 12    |
| Unknown or Not Reported   | 0       | 0                      | 0     |
| Race<br>Units: Subjects   |         |                        |       |
| American Indian or Alaska Native  | 1       | 0                      | 1     |
| Asian   | 0       | 0                      | 0     |
| Native Hawaiian or Other Pacific Islander   | 0       | 0                      | 0     |
| Black or African American   | 0       | 0                      | 0     |
| White   | 11      | 10                     | 21    |
| Child-Pugh Score Component Category (Ascites Categories)  |         |                        |       |
| Number of participants with Child-Pugh component - ascites categories of none, mild, and moderate-severe has been reported. The assessment of ascites was based on the investigator's discretion. |         |                        |       |
| Units: Subjects   |         |                        |       |
| None  | 6       | 5                      | 11    |
| Mild  | 5       | 3                      | 8     |
| Moderate to Severe  | 1       | 2                      | 3     |
| Child-Pugh Score Component Category   |         |                        |       |

|  |                |               |    |
|--|----------------|---------------|----|
| (Prothrombin Time Categories)  |                |               |    |
| Number of participants with Child-Pugh component - prothrombin time (measured as INR) in categories of <1.7, 1.7 - 2.3, and >2.3 has been reported.  |                |               |    |
| Units: Subjects  |                |               |    |
| <1.7   | 12             | 10            | 22 |
| 1.7-2.3  | 0              | 0             | 0  |
| >2.3   | 0              | 0             | 0  |
| Child-Pugh Score Component Category (Serum Albumin Categories)   |                |               |    |
| Number of participants with Child-Pugh component - serum albumin levels in categories of >35 gram per liter (g/L), 28-35 g/L, or <28 g/L has been reported.  |                |               |    |
| Units: Subjects  |                |               |    |
| >35 gram per liter (g/L)   | 3              | 4             | 7  |
| 28 - 35 g/L  | 8              | 5             | 13 |
| <28 g/L  | 1              | 1             | 2  |
| Child-Pugh Score Component Category (Total Bilirubin Categories)   |                |               |    |
| Number of participants with Child-Pugh component - total bilirubin levels in categories of <34 micromole per liter (μmol/L), 34-50 μmol/L, and >50 μmol/L has been reported.   |                |               |    |
| Units: Subjects  |                |               |    |
| <34 micromole per liter (μmol/L)   | 3              | 5             | 8  |
| 34-50 μmol/L   | 5              | 0             | 5  |
| >50 μmol/L   | 4              | 5             | 9  |
| Child-Pugh Score Component Category (Hepatic Encephalopathy Categories)  |                |               |    |
| Grade 0: normal consciousness, normal personality, normal neurological examination, normal electroencephalogram.<br>Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles, per second (cps) waves.<br>Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.<br>Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.<br>Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.      |                |               |    |
| Units: Subjects  |                |               |    |
| Grade 0  | 7              | 7             | 14 |
| Grade 1 or 2   | 5              | 3             | 8  |
| Grade 3 or 4   | 0              | 0             | 0  |
| Model of End-stage Liver Disease (MELD) Score  |                |               |    |
| The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is derived from the participant's serum total bilirubin, serum creatinine, and prothrombin international normalized ratio (INR): $3.78 \times \log \text{normal (ln) [total bilirubin (mg/deciliter [dL])]} + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$ . The MELD score ranges from 6 to 40 with higher scores indicating more severe liver disease and a worse outcome.                               |                |               |    |
| Units: Score on a scale  |                |               |    |
| median   | 11.75          | 12.75         |    |
| inter-quartile range (Q1-Q3)   | 10.60 to 13.50 | 9.50 to 16.00 | -  |
| MELD-Sodium (Na) Score   |                |               |    |
| The MELD-Na scoring system is used to assess the severity of chronic liver disease in the participants with an initial MELD(i) score greater than 11. MELD-Na score is derived from the participant's serum total bilirubin, serum creatinine, INR, and sodium. The MELD-Na score is re-calculated as follows: $\text{MELD-Na} = \text{MELD(i)} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD(i)} \times (137 - \text{Na})]$ . MELD score ranges from 6-40 with higher scores indicating more severe liver disease and a worse outcome. |                |               |    |
| Units: score on a scale  |                |               |    |
| median   | 11.75          | 13.25         |    |
| inter-quartile range (Q1-Q3)   | 10.60 to 14.25 | 9.50 to 16.00 | -  |
| Child-Pugh Score   |                |               |    |
| The Child-Pugh classification was a scoring system used for the classification of the severity of cirrhosis. It included three continuous variables (bilirubin, albumin, and INR) and two discrete variables (ascites  |                |               |    |



and encephalopathy). Each variable was scored 1-3 with 3 indicating most severe derangement. The determination of Child-Pugh score ranged from 5 to 15. The higher the score, the sicker the participant.

|  |                            |                            |   |
|--|----------------------------|----------------------------|---|
| Units: score on a scale<br>median<br>inter-quartile range (Q1-Q3)  | 8.0<br>7.0 to 8.0          | 8.0<br>7.0 to 8.0          | - |
| Total Bilirubin<br>Units: µmol/L<br>median<br>inter-quartile range (Q1-Q3)   | 45.38<br>34.57 to 55.79    | 41.50<br>19.00 to 106.88   | - |
| Direct Bilirubin<br>Units: µmol/L<br>median<br>inter-quartile range (Q1-Q3)  | 21.58<br>15.37 to 37.18    | 25.50<br>8.00 to 76.00     | - |
| Alkaline Phosphatase<br>Units: unit per liter (U/L)<br>median<br>inter-quartile range (Q1-Q3)  | 216.0<br>144.5 to 290.0    | 267.5<br>151.0 to 381.0    | - |
| Alanine Aminotransferase<br>Units: U/L<br>median<br>inter-quartile range (Q1-Q3)   | 47.5<br>31.0 to 60.5       | 38.0<br>27.0 to 56.0       | - |
| Aspartate Aminotransferase<br>Units: U/L<br>median<br>inter-quartile range (Q1-Q3)   | 60.0<br>45.5 to 95.5       | 65.5<br>46.0 to 104.0      | - |
| Gamma Glutamyl Transferase<br>Units: U/L<br>median<br>inter-quartile range (Q1-Q3)   | 98.0<br>36.0 to 152.0      | 103.0<br>53.0 to 191.0     | - |
| Prothrombin INR<br>Units: INR<br>median<br>inter-quartile range (Q1-Q3)  | 1.15<br>1.10 to 1.20       | 1.23<br>1.10 to 1.30       | - |
| Creatinine<br>Units: µmol/L<br>median<br>inter-quartile range (Q1-Q3)  | 60.000<br>51.000 to 96.732 | 60.172<br>55.000 to 95.472 | - |
| Albumin<br>Units: gram per liter (g/L)<br>median<br>inter-quartile range (Q1-Q3)   | 34.50<br>33.00 to 36.75    | 33.00<br>30.00 to 36.50    | - |
| Platelets  |                            |                            |   |
| Number analyzed (n) for Placebo arm = 11<br>Number analyzed (n) for OCA arm = 9  |                            |                            |   |
| Units: 10 <sup>9</sup> /L<br>median<br>inter-quartile range (Q1-Q3)  | 141.5<br>80.0 to 160.5     | 132.5<br>84.5 to 158.5     | - |
| Total Bile Acids Concentration   |                            |                            |   |
| Total bile acids (micromole [µM]) = total ursodeoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in µM + total chenodeoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in µM + total deoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in µM + total cholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in µM + total lithocholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in µM. |                            |                            |   |

|  |               |               |   |
|--|---------------|---------------|---|
| Number analyzed (n) for Placebo arm = 11   |               |               |   |
| Units: $\mu\text{M}$                       |               |               |   |
| median                                     | 149           | 127           |   |
| inter-quartile range (Q1-Q3)               | 90.3 to 307   | 65.3 to 176   | - |
| Total Endogenous Bile Acids Concentration  |               |               |   |
| Number analyzed (n) for Placebo arm = 11   |               |               |   |
| Units: $\mu\text{M}$                       |               |               |   |
| median                                     | 64.7          | 42.1          |   |
| inter-quartile range (Q1-Q3)               | 29.4 to 75.2  | 18.6 to 69.6  | - |
| 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4) |               |               |   |
| Number analyzed (n) for Placebo arm = 11   |               |               |   |
| Units: ng/mL                               |               |               |   |
| median                                     | 0.708         | 0.814         |   |
| inter-quartile range (Q1-Q3)               | 0.372 to 5.16 | 0.472 to 2.09 | - |
| Fibroblast Growth Factor-19 (FGF-19)       |               |               |   |
| Number analyzed (n) for Placebo arm = 11   |               |               |   |
| Units: picograms per milliliter (pg/mL)    |               |               |   |
| median                                     | 278           | 163           |   |
| inter-quartile range (Q1-Q3)               | 105 to 618    | 139 to 359    | - |

## End points

### End points reporting groups

|   |                        |
|---|------------------------|
| Reporting group title   | Placebo                |
| Reporting group description:<br>Participants received OCA matching placebo tablets orally once weekly or twice weekly for the duration of at least 48 Weeks.  |                        |
| Reporting group title   | Obeticholic Acid (OCA) |
| Reporting group description:<br>Participants initiated treatment with OCA 5 milligrams (mg) tablets orally once weekly. At Week 12, if there were no safety concerns, the dose was up-titrated to OCA 5 mg twice weekly. Every 6 weeks thereafter, based on tolerability assessments, further up-titration of dose was considered. At each titration visit, the participants started the higher dose regimen no earlier than 2 days after the prior dose. The maximum dose titration was OCA 10 mg twice weekly at least 3 days apart. The minimum treatment duration was 48 Weeks.   |                        |
| Reporting group title   | Placebo                |
| Reporting group description:<br>Participants, who had completed their 48-week treatment, could continue the treatment until all randomized participants had completed their 48-week treatment period and the database for that period was locked (total duration: approximately up to 3 years).   |                        |
| Reporting group title   | Obeticholic Acid (OCA) |
| Reporting group description:<br>Participants, who had completed their 48-week treatment, could continue the treatment until all randomized participants had completed their 48-week treatment period and the database for that period was locked (total duration: approximately up to 3 years).   |                        |
| Subject analysis set title  | OCA 5 mg Once Weekly   |
| Subject analysis set type   | Sub-group analysis     |
| Subject analysis set description:<br>Participants received OCA 5 mg tablets orally once weekly.   |                        |
| Subject analysis set title  | OCA 5 mg Twice Weekly  |
| Subject analysis set type   | Sub-group analysis     |
| Subject analysis set description:<br>Participants received OCA 5 mg tablets orally twice weekly.  |                        |
| Subject analysis set title  | OCA 10 mg Twice Weekly |
| Subject analysis set type   | Sub-group analysis     |
| Subject analysis set description:<br>Participants received OCA 10 mg tablets orally twice weekly.   |                        |
| Subject analysis set title  | Placebo                |
| Subject analysis set type   | Intention-to-treat     |
| Subject analysis set description:<br>Participants received OCA matching placebo tablets orally once weekly or twice weekly for the duration of at least 48 Weeks. Participants, who had completed their 48-Week treatment, could continue the treatment until all randomized participants had completed their 48-Week treatment period and the database for that period was locked (total duration: approximately up to 3 years).   |                        |
| Subject analysis set title  | Obeticholic Acid (OCA) |
| Subject analysis set type   | Intention-to-treat     |
| Subject analysis set description:<br>Participants initiated treatment with OCA 5 mg tablets orally once weekly. At Week 12, if there were no safety concerns, the dose was up-titrated to OCA 5 mg twice weekly. Every 6 weeks thereafter, based on tolerability assessments, further up-titration of dose was considered. At each titration visit, the participants started the higher dose regimen no earlier than 2 days after the prior dose. The maximum dose titration was OCA 10 mg twice weekly at least 3 days apart. The minimum treatment duration was 48 Weeks. Participants, who had completed their 48-Week treatment, could continue the treatment until all randomized participants had completed their 48-Week treatment period and the database for that period was locked (total duration: approximately up to 3 years). |                        |

**Primary: Maximum Observed Concentration (Cmax) of Total OCA at Week 12**

|                 |  |
|-----------------|--|
| End point title | Maximum Observed Concentration (Cmax) of Total OCA at Week 12 <sup>[1]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

Analysis population description (APD): PK Population: participants who received OCA and had adequate concentration-time profile to characterize OCA and its conjugates and must not have had any major protocol deviations that potentially affect exposure level. Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                       | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--|-------------------------|--------------------------|---------------------------|--|
| Subject group type                     | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed            | 5                       | 0 <sup>[2]</sup>         | 0 <sup>[3]</sup>          |  |
| Units: Nanogram per milliliter (ng/mL) |                         |                          |                           |  |
| arithmetic mean (standard deviation)   | 293 (± 189)             | ()                       | ()                        |  |

Notes:

[2] - No participant started OCA 5 mg twice weekly at Week 12.

[3] - No participant started OCA 10 mg twice weekly at Week 12.

**Statistical analyses**

No statistical analyses for this end point

**Primary: Time to Maximum Concentration (Tmax) of Total OCA at Week 12**

|                 |   |
|-----------------|---|
| End point title | Time to Maximum Concentration (Tmax) of Total OCA at Week 12 <sup>[4]</sup> |
|-----------------|---|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 5                       | 0 <sup>[5]</sup>         | 0 <sup>[6]</sup>          |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 2.02 (2.00 to 3.00)     | ( to )                   | ( to )                    |  |

Notes:

[5] - No participant started OCA 5 mg twice weekly at Week 12.

[6] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Trough Concentration (Ctough) of Total OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | Trough Concentration (Ctough) of Total OCA at Week 12 <sup>[7]</sup> |
|-----------------|--|

End point description:

Ctough was considered as the concentration at 24-hours post-dose at Week 12. Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 12

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                       | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--|-------------------------|--------------------------|---------------------------|--|
| Subject group type                     | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed            | 4                       | 0 <sup>[8]</sup>         | 0 <sup>[9]</sup>          |  |
| Units: nanogram per milliliter (ng/mL) |                         |                          |                           |  |
| arithmetic mean (standard deviation)   | 77.6 (± 49.7)           | ( )                      | ( )                       |  |

Notes:

[8] - No participant started OCA 5 mg twice weekly at week 12.

[9] - No participant started OCA 10 mg twice weekly at week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Area Under the Concentration Versus Time Curve From Zero Time to 24 Hours (AUC0-24h) of Total OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | Area Under the Concentration Versus Time Curve From Zero Time to 24 Hours (AUC0-24h) of Total OCA at Week 12 <sup>[10]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA. AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5

mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[11]</sup>        | 0 <sup>[12]</sup>         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 2970 (± 1650)           | ()                       | ()                        |  |

Notes:

[11] - No participant started OCA 5 mg twice weekly at Week 12.

[12] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: Cmax of Total OCA at Week 18

|                 |  |
|-----------------|--|
| End point title | Cmax of Total OCA at Week 18 <sup>[13]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[14]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 136 (± 77.6)            | 406 (± 120)              | ()                        |  |

Notes:

[14] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

**Primary: Tmax of Total OCA at Week 18**

|                 |  |
|-----------------|--|
| End point title | Tmax of Total OCA at Week 18 <sup>[15]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly  | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|--------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set     | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                        | 2                        | 0 <sup>[16]</sup>         |  |
| Units: hours                  |                          |                          |                           |  |
| median (full range (min-max)) | 0.750 (0.500<br>to 1.00) | 2.52 (2.00 to<br>3.03)   | ( to )                    |  |

Notes:

[16] - No participant started OCA 10 mg twice weekly at Week 18.

**Statistical analyses**

No statistical analyses for this end point

**Primary: Ctrough of Total OCA at Week 18**

|                 |   |
|-----------------|---|
| End point title | Ctrough of Total OCA at Week 18 <sup>[17]</sup> |
|-----------------|---|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 18. Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 18

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[18]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 28.7 (± 13.6)           | 187 (± 147)              | ( )                       |  |

Notes:

[18] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Total OCA at Week 18

|                 |  |
|-----------------|--|
| End point title | AUC0-24h of Total OCA at Week 18 <sup>[19]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA. AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[20]</sup>         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1380 (± 776)            | 5810 (± 3600)            | ()                        |  |

Notes:

[20] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Total OCA at Week 24

|                 |  |
|-----------------|--|
| End point title | Cmax of Total OCA at Week 24 <sup>[21]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24



Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[22]</sup>        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 263 (± 261)             | 195 (± 99999)            | 622 (± 117)               |  |

Notes:

[22] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Total OCA at Week 24

|                 |  |
|-----------------|--|
| End point title | Tmax of Total OCA at Week 24 <sup>[23]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 1                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 5.04 (4.00 to 6.08)     | 0.750 (0.750 to 0.750)   | 2.27 (2.00 to 2.53)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Total OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | Ctrough of Total OCA at Week 24 <sup>[24]</sup> |
|-----------------|---|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 24. Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| 24 hours post-dose at Week 24  |         |
| Notes:   |         |
| [24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |         |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.   |         |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[25]</sup>        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 132 (± 163)             | 41.4 (± 99999)           | 435 (± 28.6)              |  |

Notes:

[25] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

## Primary: AUC0-24h of Total OCA at Week 24

|   |  |
|---|--|
| End point title   | AUC0-24h of Total OCA at Week 24 <sup>[26]</sup> |
| End point description:  |  |
| Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA. AUC0-24h was calculated using the linear/linear trapezoidal rule. |  |

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24                                    |         |
| Notes:   |         |
| [26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |         |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.   |         |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[27]</sup>        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 4500 (± 4910)           | 2020 (± 99999)           | 11300 (± 2950)            |  |

Notes:

[27] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Total OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | Cmax of Total OCA at Week 30 <sup>[28]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[29]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 125 (± 99999)           | 277 (± 64.7)             | 674 (± 310)               |  |

Notes:

[29] - 99999: Standard deviation is not estimable as there is only one participant.

### Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Total OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | Tmax of Total OCA at Week 30 <sup>[30]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 1                       | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 1.00 (1.00 to 1.00)     | 4.52 (4.03 to 5.00)      | 3.77 (2.53 to 5.00)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Total OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | Ctrough of Total OCA at Week 30 <sup>[31]</sup> |
|-----------------|---|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 30. Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 30

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[32]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 22.3 (± 99999)          | 217 (± 15.7)             | 317 (± 248)               |  |

Notes:

[32] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Total OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | AUC0-24h of Total OCA at Week 30 <sup>[33]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA. AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[34]</sup>       | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1260 (± 99999)          | 5040 (± 855)             | 10500 (± 7000)            |  |

Notes:

[34] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Total OCA at Week 48

|                 |  |
|-----------------|--|
| End point title | Cmax of Total OCA at Week 48 <sup>[35]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[36]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 200 (± 15.1)             | 728 (± 27.5)              |  |

Notes:

[36] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Total OCA at Week 48

|                 |  |
|-----------------|--|
| End point title | Tmax of Total OCA at Week 48 <sup>[37]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg Once Weekly | OCA 5 mg Twice Weekly | OCA 10 mg Twice Weekly |  |
|-------------------------------|----------------------|-----------------------|------------------------|--|
| Subject group type            | Subject analysis set | Subject analysis set  | Subject analysis set   |  |
| Number of subjects analysed   | 0 <sup>[38]</sup>    | 2                     | 2                      |  |
| Units: hours                  |                      |                       |                        |  |
| median (full range (min-max)) | ( to )               | 1.73 (1.47 to 2.00)   | 4.03 (2.00 to 6.05)    |  |

Notes:

[38] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

## Primary: Ctrough of Total OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | Ctrough of Total OCA at Week 48 <sup>[39]</sup> |
|-----------------|---|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 48. Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 48

Notes:

[39] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg Once Weekly | OCA 5 mg Twice Weekly | OCA 10 mg Twice Weekly |  |
|--------------------------------------|----------------------|-----------------------|------------------------|--|
| Subject group type                   | Subject analysis set | Subject analysis set  | Subject analysis set   |  |
| Number of subjects analysed          | 0 <sup>[40]</sup>    | 2                     | 2                      |  |
| Units: ng/mL                         |                      |                       |                        |  |
| arithmetic mean (standard deviation) | ( )                  | 88.3 (± 29.9)         | 497 (± 135)            |  |

Notes:

[40] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Total OCA at Week 48

|                 |  |
|-----------------|--|
| End point title | AUC0-24h of Total OCA at Week 48 <sup>[41]</sup> |
|-----------------|--|

End point description:

Total OCA is molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA. AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[42]</sup>       | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 3210 (± 56.7)            | 13900 (± 452)             |  |

Notes:

[42] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Unconjugated OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | Cmax of Unconjugated OCA at Week 12 <sup>[43]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[44]</sup>        | 0 <sup>[45]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 107 (± 62.0)            | ( )                      | ( )                       |  |

Notes:

[44] - No participant started OCA 5 mg twice weekly at Week 12.

[45] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Unconjugated OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | Tmax of Unconjugated OCA at Week 12 <sup>[46]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[46] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 5                       | 0 <sup>[47]</sup>        | 0 <sup>[48]</sup>         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 1.43 (1.00 to 1.50)     | ( to )                   | ( to )                    |  |

Notes:

[47] - No participant started OCA 5 mg twice weekly at Week 12.

[48] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Unconjugated OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | Ctrough of Unconjugated OCA at Week 12 <sup>[49]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 12.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|



End point timeframe:

24 hours post-dose at Week 12

Notes:

[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[50]</sup>        | 0 <sup>[51]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 2.92 (± 2.51)           | ()                       | ()                        |  |

Notes:

[50] - No participant started OCA 5 mg twice weekly at Week 12.

[51] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: AUC0-24h of Unconjugated OCA at Week 12

End point title | AUC0-24h of Unconjugated OCA at Week 12<sup>[52]</sup>

End point description:

AUC0-24 was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

End point type | Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[52] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 3                       | 0 <sup>[53]</sup>        | 0 <sup>[54]</sup>         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 278 (± 142)             | ()                       | ()                        |  |

Notes:

[53] - No participant started OCA 5 mg twice weekly at Week 12.

[54] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: Cmax of Unconjugated OCA at Week 18

End point title | Cmax of Unconjugated OCA at Week 18<sup>[55]</sup>

End point description:

Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[55] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[56]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 107 (± 47.4)            | 109 (± 90.3)             | ( )                       |  |

Notes:

[56] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

## Primary: Tmax of Unconjugated OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | Tmax of Unconjugated OCA at Week 18 <sup>[57]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[57] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 2                        | 0 <sup>[58]</sup>         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 0.750 (0.500 to 1.00)   | 1.24 (1.00 to 1.48)      | ( to )                    |  |

Notes:

[58] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Unconjugated OCA at Week 18

End point title Ctrough of Unconjugated OCA at Week 18<sup>[59]</sup>

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 18.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

End point type Primary

End point timeframe:

24 hours post-dose at Week 18

Notes:

[59] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[60]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 3.38 (± 0.262)          | 3.56 (± 4.01)            | ()                        |  |

Notes:

[60] - No participant started OCA 10 mg twice weekly at Week 18.

### Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Unconjugated OCA at Week 18

End point title AUC0-24h of Unconjugated OCA at Week 18<sup>[61]</sup>

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

End point type Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[61] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[62]</sup>         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 191 (± 125)             | 263 (± 247)              | ()                        |  |

Notes:

[62] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Unconjugated OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | Cmax of Unconjugated OCA at Week 24 <sup>[63]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[63] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[64]</sup>        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 115 (± 98.2)            | 157 (± 99999)            | 168 (± 92.6)              |  |

Notes:

[64] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Unconjugated OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | Tmax of Unconjugated OCA at Week 24 <sup>[65]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[65] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 1                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 1.13 (0.750 to 1.50)    | 0.500 (0.500 to 0.500)   | 1.63 (1.58 to 1.67)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Unconjugated OCA at Week 24

|                 |  |
|-----------------|--|
| End point title | Ctrough of Unconjugated OCA at Week 24 <sup>[66]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 24.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 24

Notes:

[66] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[67]</sup>        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 2.46 (± 2.05)           | 5.18 (± 99999)           | 8.77 (± 11.4)             |  |

Notes:

[67] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Unconjugated OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Unconjugated OCA at Week 24 <sup>[68]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[68] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[69]</sup>        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 235 (± 130)             | 345 (± 99999)            | 480 (± 414)               |  |

Notes:

[69] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Unconjugated OCA at Week 30

|   |   |
|---|---|
| End point title   | Cmax of Unconjugated OCA at Week 30 <sup>[70]</sup> |
| End point description:  |   |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. |   |
| End point type  | Primary   |

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[70] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[71]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 92.6 (± 99999)          | 132 (± 24.0)             | 115 (± 40.9)              |  |

Notes:

[71] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Unconjugated OCA at Week 30

|   |   |
|---|---|
| End point title   | Tmax of Unconjugated OCA at Week 30 <sup>[72]</sup> |
| End point description:  |   |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. |   |
| End point type  | Primary   |

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24

hours post-dose at Week 30

Notes:

[72] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly   | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|---------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set      | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 1                         | 2                        | 2                         |  |
| Units: hours                  |                           |                          |                           |  |
| median (full range (min-max)) | 0.750 (0.750<br>to 0.750) | 1.17 (1.00 to<br>1.33)   | 1.75 (0.500 to<br>3.00)   |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Unconjugated OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | Ctrough of Unconjugated OCA at Week 30 <sup>[73]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 30.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 30

Notes:

[73] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[74]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 3.03 (± 99999)          | 4.27 (± 4.85)            | 3.20 (± 3.14)             |  |

Notes:

[74] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Unconjugated OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Unconjugated OCA at Week 30 <sup>[75]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who

received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[75] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[76]</sup>       | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 176 (± 99999)           | 304 (± 82.3)             | 473 (± 397)               |  |

Notes:

[76] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Unconjugated OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | Cmax of Unconjugated OCA at Week 48 <sup>[77]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[77] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[78]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ()                      | 131 (± 31.8)             | 284 (± 177)               |  |

Notes:

[78] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Unconjugated OCA at Week 48



|  |   |
|--|---|
| End point title  | Tmax of Unconjugated OCA at Week 48 <sup>[79]</sup> |
| End point description:   |   |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48  |   |
| Notes:   |   |
| [79] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.   |   |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.   |   |

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 0 <sup>[80]</sup>       | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | ( to )                  | 1.10 (0.700 to 1.50)     | 0.500 (0.500 to 0.500)    |  |

Notes:

[80] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

## Primary: Ctrough of Unconjugated OCA at Week 48

|  |  |
|--|--|
| End point title  | Ctrough of Unconjugated OCA at Week 48 <sup>[81]</sup> |
| End point description:   |  |
| Ctrough was considered as the concentration at 24-hours post-dose at Week 48.  |  |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| 24 hours post-dose at Week 48  |  |
| Notes:   |  |
| [81] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.   |  |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.   |  |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[82]</sup>       | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 3.43 (± 3.90)            | 4.72 (± 6.67)             |  |

Notes:

[82] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Unconjugated OCA at Week 48

End point title | AUC0-24h of Unconjugated OCA at Week 48<sup>[83]</sup>

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

End point type | Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[83] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[84]</sup>       | 2                        | 1 <sup>[85]</sup>         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 376 (± 118)              | 1190 (± 99999)            |  |

Notes:

[84] - No participant received OCA 5 mg once weekly at Week 48.

[85] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Glyco-OCA at Week 12

End point title | Cmax of Glyco-OCA at Week 12<sup>[86]</sup>

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

End point type | Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[86] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[87]</sup>        | 0 <sup>[88]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 117 (± 55.0)            | ( )                      | ( )                       |  |

Notes:

[87] - No participant started OCA 5 mg twice weekly at Week 12.

[88] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Glyco-OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | Tmax of Glyco-OCA at Week 12 <sup>[89]</sup> |
|-----------------|--|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[89] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 5                       | 0 <sup>[90]</sup>        | 0 <sup>[91]</sup>         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 5.00 (3.92 to 5.00)     | ( to )                   | ( to )                    |  |

Notes:

[90] - No participant started OCA 5 mg twice weekly at Week 12.

[91] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Glyco-OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | Ctrough of Glyco-OCA at Week 12 <sup>[92]</sup> |
|-----------------|---|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 12.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 12

Notes:

[92] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[93]</sup>        | 0 <sup>[94]</sup>         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 47.1 (± 31.1)           | ()                       | ()                        |  |

Notes:

[93] - No participant started OCA 5 mg twice weekly at Week 12.

[94] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: AUC0-24h of Glyco-OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | AUC0-24h of Glyco-OCA at Week 12 <sup>[95]</sup> |
|-----------------|--|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[95] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[96]</sup>        | 0 <sup>[97]</sup>         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1690 (± 947)            | ()                       | ()                        |  |

Notes:

[96] - No participant started OCA 5 mg twice weekly at Week 12.

[97] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: Metabolite to Parent Ratio of AUC-0-24h (MRAUC) of Glyco-OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | Metabolite to Parent Ratio of AUC-0-24h (MRAUC) of Glyco-OCA at Week 12 <sup>[98]</sup> |
|-----------------|---|

End point description:

MRAUC was the ratio of AUC0-24h of Glyco-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[98] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 3                       | 0 <sup>[99]</sup>        | 0 <sup>[100]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 4.36 (± 1.03)           | ()                       | ()                        |  |

Notes:

[99] - No participant started OCA 5 mg twice weekly at Week 12.

[100] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: Metabolite to Parent Ratio of Cmax (MRCmax) of Glyco-OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | Metabolite to Parent Ratio of Cmax (MRCmax) of Glyco-OCA at Week 12 <sup>[101]</sup> |
|-----------------|--|

End point description:

MRCmax was the ratio of Cmax of Glyco-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[101] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[102]</sup>       | 0 <sup>[103]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1.39 (± 1.38)           | ()                       | ()                        |  |

Notes:

[102] - No participant started OCA 5 mg twice weekly at Week 12.

[103] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Glyco-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | Cmax of Glyco-OCA at Week 18 <sup>[104]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[104] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[105]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 52.7 (± 4.31)           | 213 (± 22.6)             | ()                        |  |

Notes:

[105] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Glyco-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | Tmax of Glyco-OCA at Week 18 <sup>[106]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[106] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 2                        | 0 <sup>[107]</sup>        |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 4.25 (2.50 to 6.00)     | 2.52 (2.00 to 3.03)      | ( to )                    |  |

Notes:

[107] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Glyco-OCA at Week 18

|                 |  |
|-----------------|--|
| End point title | Ctrough of Glyco-OCA at Week 18 <sup>[108]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 18.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 18

Notes:

[108] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[109]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 13.3 (± 5.03)           | 98.1 (± 53.7)            | ( )                       |  |

Notes:

[109] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Glyco-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Glyco-OCA at Week 18 <sup>[110]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who

received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[110] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[111]</sup>        |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 625 (± 147)             | 3020 (± 1120)            | ()                        |  |

Notes:

[111] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses

No statistical analyses for this end point

## Primary: MRAUC of Glyco-OCA at Week 18

|                 |  |
|-----------------|--|
| End point title | MRAUC of Glyco-OCA at Week 18 <sup>[112]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC<sub>0-24h</sub> of Glyco-OCA (metabolite) to AUC<sub>0-24h</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where AUC<sub>0-24</sub> is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[112] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[113]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 3.39 (± 1.55)           | 21.2 (± 23.6)            | ()                        |  |

Notes:

[113] - No participant started OCA 10 mg twice weekly at Week 18.

## Statistical analyses



No statistical analyses for this end point

### Primary: MRCmax of Glyco-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | MRCmax of Glyco-OCA at Week 18 <sup>[114]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of Glyco-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[114] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[115]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.487 (± 0.250)         | 2.73 (± 2.44)            | ( )                       |  |

Notes:

[115] - No participant started OCA 10 mg twice weekly at Week 18.

### Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Glyco-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | Cmax of Glyco-OCA at Week 24 <sup>[116]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[116] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[117]</sup>       | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 166 (± 163)             | 56.2 (± 99999)           | 294 (± 70.0)              |  |

Notes:

[117] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Glyco-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | Tmax of Glyco-OCA at Week 24 <sup>[118]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[118] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 1                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 5.04 (4.00 to 6.08)     | 5.00 (5.00 to 5.00)      | 4.54 (4.08 to 5.00)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Glyco-OCA at Week 24

|                 |  |
|-----------------|--|
| End point title | Ctrough of Glyco-OCA at Week 24 <sup>[119]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 24.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 24

Notes:

[119] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[120]</sup>       | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 83.0 (± 106)            | 22.0 (± 99999)           | 239 (± 7.07)              |  |

Notes:

[120] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Glyco-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Glyco-OCA at Week 24 <sup>[121]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[121] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[122]</sup>       | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 2710 (± 3030)           | 936 (± 99999)            | 5550 (± 878)              |  |

Notes:

[122] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Glyco-OCA at Week 24

|                 |  |
|-----------------|--|
| End point title | MRAUC of Glyco-OCA at Week 24 <sup>[123]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of Glyco-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[123] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[124]</sup>       | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 8.26 (± 6.80)           | 2.39 (± 99999)           | 17.3 (± 16.5)             |  |

Notes:

[124] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Glyco-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | MRCmax of Glyco-OCA at Week 24 <sup>[125]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of Glyco-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[125] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[126]</sup>       | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1.17 (± 0.253)          | 0.315 (± 99999)          | 1.94 (± 1.44)             |  |

Notes:

[126] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Glyco-OCA at Week 30

End point title Cmax of Glyco-OCA at Week 30<sup>[127]</sup>

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included in the analysis.

End point type Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[127] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[128]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 83.0 (± 99999)          | 174 (± 75.0)             | 301 (± 86.3)              |  |

Notes:

[128] - 99999: Standard deviation is not estimable as there is only one participant.

### Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Glyco-OCA at Week 30

End point title Tmax of Glyco-OCA at Week 30<sup>[129]</sup>

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

End point type Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[129] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 1                       | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 6.00 (6.00 to 6.00)     | 14.0 (4.03 to 24.0)      | 4.51 (4.02 to 5.00)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Glyco-OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | Ctrough of Glyco-OCA at Week 30 <sup>[130]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 30.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 30

Notes:

[130] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[131]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 14.4 (± 99999)          | 143 (± 30.4)             | 156 (± 79.4)              |  |

Notes:

[131] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Glyco-OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Glyco-OCA at Week 30 <sup>[132]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[132] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[133]</sup>      | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 863 (± 99999)           | 3180 (± 1080)            | 5050 (± 2260)             |  |

Notes:

[133] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Glyco-OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | MRAUC of Glyco-OCA at Week 30 <sup>[134]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC<sub>0-24h</sub> of Glyco-OCA (metabolite) to AUC<sub>0-24h</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where AUC<sub>0-24</sub> is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[134] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[135]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 4.31 (± 99999)          | 10.0 (± 5.84)            | 17.2 (± 18.7)             |  |

Notes:

[135] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Glyco-OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | MRCmax of Glyco-OCA at Week 30 <sup>[136]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of C<sub>max</sub> of Glyco-OCA (metabolite) to C<sub>max</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where C<sub>max</sub> is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[136] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[137]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.789 (± 99999)         | 1.23 (± 0.723)           | 2.58 (± 1.58)             |  |

Notes:

[137] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Glyco-OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | Cmax of Glyco-OCA at Week 48 <sup>[138]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[138] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[139]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ()                      | 123 (± 34.0)             | 354 (± 37.5)              |  |

Notes:

[139] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Glyco-OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | Tmax of Glyco-OCA at Week 48 <sup>[140]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily.



mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:  |         |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48 |         |

Notes:

[140] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 0 <sup>[141]</sup>      | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | ( to )                  | 5.00 (5.00 to 5.00)      | 4.03 (2.00 to 6.05)       |  |

Notes:

[141] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

## Primary: Ctrough of Glyco-OCA at Week 48

|                 |  |
|-----------------|--|
| End point title | Ctrough of Glyco-OCA at Week 48 <sup>[142]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 48.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 48

Notes:

[142] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[143]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 65.9 (± 10.2)            | 280 (± 62.2)              |  |

Notes:

[143] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

**Primary: AUC0-24h of Glyco-OCA at Week 48**

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Glyco-OCA at Week 48 <sup>[144]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[144] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[145]</sup>      | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 2120 (± 442)             | 6950 (± 648)              |  |

Notes:

[145] - No participant received OCA 5 mg once weekly at Week 48.

**Statistical analyses**

No statistical analyses for this end point

**Primary: MRAUC of Glyco-OCA at Week 48**

|                 |  |
|-----------------|--|
| End point title | MRAUC of Glyco-OCA at Week 48 <sup>[146]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of Glyco-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[146] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[147]</sup>      | 2                        | 1 <sup>[148]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ()                      | 5.39 (± 2.69)            | 4.79 (± 99999)            |  |

Notes:

[147] - No participant received OCA 5 mg once weekly at Week 48.

[148] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Glyco-OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | MRCmax of Glyco-OCA at Week 48 <sup>[149]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of Glyco-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Glyco-OCA, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[149] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[150]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ()                      | 0.826 (± 0.0280)         | 1.41 (± 1.00)             |  |

Notes:

[150] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Tauro-OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | Cmax of Tauro-OCA at Week 12 <sup>[151]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[151] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[152]</sup>       | 0 <sup>[153]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 201 (± 213)             | ( )                      | ( )                       |  |

Notes:

[152] - No participant started OCA 5 mg twice weekly at Week 12.

[153] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Tauro-OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | Tmax of Tauro-OCA at Week 12 <sup>[154]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[154] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 5                       | 0 <sup>[155]</sup>       | 0 <sup>[156]</sup>        |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 5.00 (3.00 to 5.00)     | ( to )                   | ( to )                    |  |

Notes:

[155] - No participant started OCA 5 mg twice weekly at Week 12.

[156] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Tauro-OCA at Week 12

|   |  |
|---|--|
| End point title   | Ctrough of Tauro-OCA at Week 12 <sup>[157]</sup> |
| End point description:  |  |
| Ctrough was considered as the concentration at 24-hours post-dose at Week 12.   |  |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| 24 hours post-dose at Week 12   |  |
| Notes:  |  |
| [157] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.   |  |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.  |  |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[158]</sup>       | 0 <sup>[159]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 41.6 (± 33.0)           | ()                       | ()                        |  |

Notes:

[158] - No participant started OCA 5 mg twice weekly at Week 12.

[159] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

## Primary: AUC0-24h of Tauro-OCA at Week 12

|   |   |
|---|---|
| End point title   | AUC0-24h of Tauro-OCA at Week 12 <sup>[160]</sup> |
| End point description:  |   |
| AUC0-24h was calculated using the linear/linear trapezoidal rule.   |   |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12   |   |
| Notes:  |   |
| [160] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.   |   |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.  |   |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[161]</sup>       | 0 <sup>[162]</sup>        |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1580 (± 1260)           | ()                       | ()                        |  |

Notes:

[161] - No participant started OCA 5 mg twice weekly at Week 12.

[162] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Tauro-OCA at Week 12

|                 |  |
|-----------------|--|
| End point title | MRAUC of Tauro-OCA at Week 12 <sup>[163]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC<sub>0-24h</sub> of Tauro-OCA (metabolite) to AUC<sub>0-24h</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where AUC<sub>0-24</sub> is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[163] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 3                       | 0 <sup>[164]</sup>       | 0 <sup>[165]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 3.13 (± 1.08)           | ()                       | ()                        |  |

Notes:

[164] - No participant started OCA 5 mg twice weekly at Week 12.

[165] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Tauro-OCA at Week 12

|                 |   |
|-----------------|---|
| End point title | MRCmax of Tauro-OCA at Week 12 <sup>[166]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of C<sub>max</sub> of Tauro-OCA (metabolite) to C<sub>max</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where C<sub>max</sub> is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[166] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[167]</sup>       | 0 <sup>[168]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 2.24 (± 2.46)           | ()                       | ()                        |  |

Notes:

[167] - No participant started OCA 5 mg twice weekly at Week 12.

[168] - No participant started OCA 10 mg twice weekly at Week 12.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Tauro-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | Cmax of Tauro-OCA at Week 18 <sup>[169]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[169] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[170]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 63.2 (± 46.9)           | 221 (± 188)              | ()                        |  |

Notes:

[170] - No participant started OCA 10 mg twice weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Tauro-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | Tmax of Tauro-OCA at Week 18 <sup>[171]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who

received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[171] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 2                        | 0 <sup>[172]</sup>        |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 5.00 (5.00 to 5.00)     | 2.52 (2.00 to 3.03)      | ( to )                    |  |

Notes:

[172] - No participant started OCA 10 mg twice weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Tauro-OCA at Week 18

|                 |  |
|-----------------|--|
| End point title | Ctrough of Tauro-OCA at Week 18 <sup>[173]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 18.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 18

Notes:

[173] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[174]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 17.0 (± 11.2)           | 122 (± 130)              | ( )                       |  |

Notes:

[174] - No participant started OCA 10 mg twice weekly at Week 18

## Statistical analyses

No statistical analyses for this end point



### Primary: AUC0-24h of Tauro-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Tauro-OCA at Week 18 <sup>[175]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[175] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[176]</sup>        |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 799 (± 654)             | 3630 (± 3600)            | ( )                       |  |

Notes:

[176] - No participant started OCA 10 mg twice weekly at Week 18

### Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Tauro-OCA at Week 18

|                 |  |
|-----------------|--|
| End point title | MRAUC of Tauro-OCA at Week 18 <sup>[177]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of Tauro-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[177] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[178]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 3.11 (± 0.685)          | 28.8 (± 37.9)            | ( )                       |  |

Notes:

[178] - No participant started OCA 10 mg twice weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Tauro-OCA at Week 18

|                 |   |
|-----------------|---|
| End point title | MRCmax of Tauro-OCA at Week 18 <sup>[179]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of Tauro-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where Cmax is the maximum observed concentration.

Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[179] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[180]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.434 (± 0.156)         | 3.32 (± 4.12)            | ( )                       |  |

Notes:

[180] - No participant started OCA 10 mg twice weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Tauro-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | Cmax of Tauro-OCA at Week 24 <sup>[181]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[181] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[182]</sup>       | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 142 (± 144)             | 65.5 (± 99999)           | 430 (± 142)               |  |

Notes:

[182] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Tauro-OCA at Week 24

|   |   |
|---|---|
| End point title   | Tmax of Tauro-OCA at Week 24 <sup>[183]</sup> |
| End point description:  |   |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. |   |
| End point type  | Primary                                       |
| End point timeframe:  |   |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24   |   |

Notes:

[183] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 1                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 5.54 (5.00 to 6.08)     | 9.00 (9.00 to 9.00)      | 4.05 (3.10 to 5.00)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Tauro-OCA at Week 24

|   |  |
|---|--|
| End point title   | Ctrough of Tauro-OCA at Week 24 <sup>[184]</sup> |
| End point description:  |  |
| Ctrough was considered as the concentration at 24-hours post-dose at Week 24.   |  |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. |  |
| End point type  | Primary  |

End point timeframe:

24 hours post-dose at Week 24

Notes:

[184] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[185]</sup>       | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 71.0 (± 90.5)           | 21.2 (± 99999)           | 271 (± 58.0)              |  |

Notes:

[185] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Tauro-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Tauro-OCA at Week 24 <sup>[186]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[186] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[187]</sup>       | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 2360 (± 2650)           | 1060 (± 99999)           | 7470 (± 3260)             |  |

Notes:

[187] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Tauro-OCA at Week 24

|                 |  |
|-----------------|--|
| End point title | MRAUC of Tauro-OCA at Week 24 <sup>[188]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of Tauro-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[188] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[189]</sup>       | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 6.51 (± 5.40)           | 2.46 (± 99999)           | 23.4 (± 25.6)             |  |

Notes:

[189] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Tauro-OCA at Week 24

|                 |   |
|-----------------|---|
| End point title | MRCmax of Tauro-OCA at Week 24 <sup>[190]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of Tauro-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[190] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[191]</sup>       | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.881 (± 0.249)         | 0.332 (± 99999)          | 2.63 (± 2.13)             |  |

Notes:

[191] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Tauro-OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | Cmax of Tauro-OCA at Week 30 <sup>[192]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[192] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[193]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 38.6 (± 99999)          | 141 (± 13.4)             | 460 (± 342)               |  |

Notes:

[193] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Tauro-OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | Tmax of Tauro-OCA at Week 30 <sup>[194]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[194] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 1                       | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 6.00 (6.00 to 6.00)     | 4.52 (4.03 to 5.00)      | 4.03 (3.05 to 5.00)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Tauro-OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | Ctrough of Tauro-OCA at Week 30 <sup>[195]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 30.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 30

Notes:

[195] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[196]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 8.21 (± 99999)          | 110 (± 7.78)             | 222 (± 228)               |  |

Notes:

[196] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Tauro-OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Tauro-OCA at Week 30 <sup>[197]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[197] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[198]</sup>      | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 408 (± 99999)           | 2430 (± 18.1)            | 7020 (± 6780)             |  |

Notes:

[198] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Tauro-OCA at Week 30

|                 |  |
|-----------------|--|
| End point title | MRAUC of Tauro-OCA at Week 30 <sup>[199]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of Tauro-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[199] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[200]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1.84 (± 99999)          | 6.61 (± 1.74)            | 25.7 (± 33.0)             |  |

Notes:

[200] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of Tauro-OCA at Week 30

|                 |   |
|-----------------|---|
| End point title | MRCmax of Tauro-OCA at Week 30 <sup>[201]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of Tauro-OCA (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where Cmax is the maximum observed



concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[201] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[202]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.332 (± 99999)         | 0.855 (± 0.0746)         | 3.85 (± 3.73)             |  |

Notes:

[202] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of Tauro-OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | Cmax of Tauro-OCA at Week 48 <sup>[203]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[203] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[204]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ()                      | 72.5 (± 15.1)            | 485 (± 20.5)              |  |

Notes:

[204] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of Tauro-OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | Tmax of Tauro-OCA at Week 48 <sup>[205]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[205] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 0 <sup>[206]</sup>      | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | ( to )                  | 6.50 (6.00 to 7.00)      | 2.57 (2.00 to 3.13)       |  |

Notes:

[206] - No participant received OCA 5 mg once weekly at Week 48.

### Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of Tauro-OCA at Week 48

|                 |  |
|-----------------|--|
| End point title | Ctrough of Tauro-OCA at Week 48 <sup>[207]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 48.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 48

Notes:

[207] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[208]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 33.7 (± 21.4)            | 309 (± 109)               |  |

Notes:

[208] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of Tauro-OCA at Week 48

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of Tauro-OCA at Week 48 <sup>[209]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[209] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[210]</sup>      | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 1220 (± 389)             | 8890 (± 696)              |  |

Notes:

[210] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of Tauro-OCA at Week 48

|                 |  |
|-----------------|--|
| End point title | MRAUC of Tauro-OCA at Week 48 <sup>[211]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of Tauro-OCA (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:  |         |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48                                     |         |
| Notes:  |         |
| [211] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |         |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.  |         |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[212]</sup>      | 2                        | 1 <sup>[213]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 2.59 (± 0.00903)         | 5.60 (± 99999)            |  |

Notes:

[212] - No participant received OCA 5 mg once weekly at Week 48.

[213] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

## Primary: MRCmax of Tauro-OCA at Week 48

|  |   |
|--|---|
| End point title  | MRCmax of Tauro-OCA at Week 48 <sup>[214]</sup> |
| End point description:   |   |
| MRCmax was the ratio of Cmax of Tauro-OCA (metabolite) to Cmax of OCA (parent drug) * ratio of molecular weight of OCA to molecular weight of Tauro-OCA, where Cmax is the maximum observed concentration.   |   |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48  |   |
| Notes:   |   |
| [214] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.  |   |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.   |   |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[215]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 0.468 (± 0.206)          | 1.67 (± 0.989)            |  |

Notes:

[215] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of OCA-glucuronide at Week 12

|                 |   |
|-----------------|---|
| End point title | Cmax of OCA-glucuronide at Week 12 <sup>[216]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[216] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[217]</sup>       | 0 <sup>[218]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 47.0 (± 24.7)           | ( )                      | ( )                       |  |

Notes:

[217] - No participant started OCA 5 mg Twice Weekly at Week 12

[218] - No participant started OCA 10 mg Twice Weekly at Week 12

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of OCA-glucuronide at Week 12

|                 |   |
|-----------------|---|
| End point title | Tmax of OCA-glucuronide at Week 12 <sup>[219]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

Pharmacokinetic of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[219] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 5                       | 0 <sup>[220]</sup>       | 0 <sup>[221]</sup>        |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 2.50 (1.50 to 3.00)     | ( to )                   | ( to )                    |  |

Notes:

[220] - No participant started OCA 5 mg Twice Weekly at Week 12

[221] - No participant started OCA 10 mg Twice Weekly at Week 12

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of OCA-glucuronide at Week 12

|                 |  |
|-----------------|--|
| End point title | Ctrough of OCA-glucuronide at Week 12 <sup>[222]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 12.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 12

Notes:

[222] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[223]</sup>       | 0 <sup>[224]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 20.7 (± 15.4)           | ( )                      | ( )                       |  |

Notes:

[223] - No participant started OCA 5 mg Twice Weekly at Week 12

[224] - No participant started OCA 10 mg Twice Weekly at Week 12

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of OCA-glucuronide at Week 12

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of OCA-glucuronide at Week 12 <sup>[225]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. Pharmacokinetic of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[225] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 4                       | 0 <sup>[226]</sup>       | 0 <sup>[227]</sup>        |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 593 (± 388)             | ()                       | ()                        |  |

Notes:

[226] - No participant started OCA 5 mg Twice Weekly at Week 12

[227] - No participant started OCA 10 mg Twice Weekly at Week 12

## Statistical analyses

No statistical analyses for this end point

## Primary: MRAUC of OCA-glucuronide at Week 12

|                 |  |
|-----------------|--|
| End point title | MRAUC of OCA-glucuronide at Week 12 <sup>[228]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC<sub>0-24h</sub> of OCA-glucuronide (metabolite) to AUC<sub>0-24h</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where AUC<sub>0-24</sub> is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[228] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 3                       | 0 <sup>[229]</sup>       | 0 <sup>[230]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1.17 (± 0.638)          | ()                       | ()                        |  |

Notes:

[229] - No participant started OCA 5 mg Twice Weekly at Week 12

[230] - No participant started OCA 10 mg Twice Weekly at Week 12

## Statistical analyses

No statistical analyses for this end point

**Primary: MRCmax of OCA-glucuronide at Week 12**

|                 |   |
|-----------------|---|
| End point title | MRCmax of OCA-glucuronide at Week 12 <sup>[231]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of OCA-glucuronide (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg twice weekly or 10 mg twice weekly at Week 12 are not applicable as no participant started 5 mg twice weekly or 10 mg twice weekly at Week 12.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 12

Notes:

[231] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 5                       | 0 <sup>[232]</sup>       | 0 <sup>[233]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.384 (±<br>0.275)      | ( )                      | ( )                       |  |

Notes:

[232] - No participant started OCA 5 mg Twice Weekly at Week 12

[233] - No participant started OCA 10 mg Twice Weekly at Week 12

**Statistical analyses**

No statistical analyses for this end point

**Primary: Cmax of OCA-glucuronide at Week 18**

|                 |   |
|-----------------|---|
| End point title | Cmax of OCA-glucuronide at Week 18 <sup>[234]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[234] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.



| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[235]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 39.2 (± 30.3)           | 74.9 (± 38.4)            | ( )                       |  |

Notes:

[235] - No participant started OCA 10 mg Twice Weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of OCA-glucuronide at Week 18

|                 |   |
|-----------------|---|
| End point title | Tmax of OCA-glucuronide at Week 18 <sup>[236]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[236] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 2                        | 0 <sup>[237]</sup>        |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 1.25 (1.00 to 1.50)     | 2.73 (1.50 to 3.97)      | ( to )                    |  |

Notes:

[237] - No participant started OCA 10 mg Twice Weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of OCA-glucuronide at Week 18

|                 |  |
|-----------------|--|
| End point title | Ctrough of OCA-glucuronide at Week 18 <sup>[238]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 18.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 18

Notes:

[238] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[239]</sup>        |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 11.7 (± 7.55)           | 40.9 (± 43.9)            | ( )                       |  |

Notes:

[239] - No participant started OCA 10 mg Twice Weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of OCA-glucuronide at Week 18

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of OCA-glucuronide at Week 18 <sup>[240]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[240] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[241]</sup>        |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 390 (± 278)             | 1120 (± 989)             | ( )                       |  |

Notes:

[241] - No participant started OCA 10 mg Twice Weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of OCA-glucuronide at Week 18

|                 |  |
|-----------------|--|
| End point title | MRAUC of OCA-glucuronide at Week 18 <sup>[242]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of OCA-glucuronide (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[242] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[243]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 1.41 ( $\pm$ 0.101)     | 7.58 ( $\pm$ 9.76)       | ()                        |  |

Notes:

[243] - No participant started OCA 10 mg Twice Weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

## Primary: MRCmax of OCA-glucuronide at Week 18

|                 |   |
|-----------------|---|
| End point title | MRCmax of OCA-glucuronide at Week 18 <sup>[244]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of OCA-glucuronide (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where Cmax is the maximum observed concentration.

Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 10 mg twice weekly at Week 18 is not applicable as no participant started 10 mg twice weekly at Week 18.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 18

Notes:

[244] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 2                        | 0 <sup>[245]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.236 ( $\pm$ 0.0942)   | 0.891 ( $\pm$ 0.985)     | ()                        |  |

Notes:

[245] - No participant started OCA 10 mg Twice Weekly at Week 18

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of OCA-glucuronide at Week 24

|                 |   |
|-----------------|---|
| End point title | Cmax of OCA-glucuronide at Week 24 <sup>[246]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[246] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[247]</sup>       | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 20.2 (± 7.42)           | 58.1 (± 99999)           | 127 (± 71.0)              |  |

Notes:

[247] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of OCA-glucuronide at Week 24

|                 |   |
|-----------------|---|
| End point title | Tmax of OCA-glucuronide at Week 24 <sup>[248]</sup> |
|-----------------|---|

End point description:

Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[248] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 2                       | 1                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 2.54 (2.08 to 3.00)     | 1.00 (1.00 to 1.00)      | 2.27 (2.00 to 2.53)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of OCA-glucuronide at Week 24

|                 |  |
|-----------------|--|
| End point title | Ctrough of OCA-glucuronide at Week 24 <sup>[249]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 24.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 24

Notes:

[249] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[250]</sup>       | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 11.6 (± 6.43)           | 14.5 (± 99999)           | 84.2 (± 81.7)             |  |

Notes:

[250] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of OCA-glucuronide at Week 24

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of OCA-glucuronide at Week 24 <sup>[251]</sup> |
|-----------------|---|

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[251] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[252]</sup>       | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 330 (± 191)             | 602 (± 99999)            | 2120 (± 1920)             |  |

Notes:

[252] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of OCA-glucuronide at Week 24

|                 |  |
|-----------------|--|
| End point title | MRAUC of OCA-glucuronide at Week 24 <sup>[253]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC<sub>0-24h</sub> of OCA-glucuronide (metabolite) to AUC<sub>0-24h</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where AUC<sub>0-24</sub> is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[253] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[254]</sup>       | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.983 (± 0.0286)        | 1.23 (± 99999)           | 6.87 (± 8.74)             |  |

Notes:

[254] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of OCA-glucuronide at Week 24

|                 |   |
|-----------------|---|
| End point title | MRCmax of OCA-glucuronide at Week 24 <sup>[255]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of C<sub>max</sub> of OCA-glucuronide (metabolite) to C<sub>max</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where C<sub>max</sub> is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 24

Notes:

[255] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 2                       | 1 <sup>[256]</sup>       | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.165 (± 0.0959)        | 0.261 (± 99999)          | 0.727 (± 0.701)           |  |

Notes:

[256] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of OCA-glucuronide at Week 30

|                 |   |
|-----------------|---|
| End point title | Cmax of OCA-glucuronide at Week 30 <sup>[257]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by dose regimen. Participants who received planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[257] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[258]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 13.7 (± 99999)          | 51.9 (± 49.4)            | 148 (± 117)               |  |

Notes:

[258] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of OCA-glucuronide at Week 30

|                 |   |
|-----------------|---|
| End point title | Tmax of OCA-glucuronide at Week 30 <sup>[259]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:  |         |
| Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30                                     |         |
| Notes:  |         |
| [259] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |         |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.  |         |

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 1                       | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | 1.50 (1.50 to 1.50)     | 2.26 (1.50 to 3.02)      | 4.51 (4.02 to 5.00)       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of OCA-glucuronide at Week 30

|   |  |
|---|--|
| End point title   | Ctrough of OCA-glucuronide at Week 30 <sup>[260]</sup> |
| End point description:  |  |
| Ctrough was considered as the concentration at 24-hours post-dose at Week 30.   |  |
| APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| 24 hours post-dose at Week 30   |  |
| Notes:  |  |
| [260] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.                           |  |
| Justification: Per protocol, statistical analysis was not planned for this endpoint.  |  |

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[261]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 5.57 (± 99999)          | 19.7 (± 13.8)            | 89.0 (± 107)              |  |

Notes:

[261] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of OCA-glucuronide at Week 30

|                 |   |
|-----------------|---|
| End point title | AUC0-24h of OCA-glucuronide at Week 30 <sup>[262]</sup> |
|-----------------|---|



End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[262] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[263]</sup>      | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 170 (± 99999)           | 641 (± 482)              | 2200 (± 2100)             |  |

Notes:

[263] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

## Primary: MRAUC of OCA-glucuronide at Week 30

|                 |  |
|-----------------|--|
| End point title | MRAUC of OCA-glucuronide at Week 30 <sup>[264]</sup> |
|-----------------|--|

End point description:

MRAUC was the ratio of AUC0-24h of OCA-glucuronide (metabolite) to AUC0-24h of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where AUC0-24 is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[264] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[265]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.680 (± 99999)         | 1.39 (± 0.742)           | 7.10 (± 9.09)             |  |

Notes:

[265] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRCmax of OCA-glucuronide at Week 30

|                 |   |
|-----------------|---|
| End point title | MRCmax of OCA-glucuronide at Week 30 <sup>[266]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of Cmax of OCA-glucuronide (metabolite) to Cmax of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where Cmax is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 30

Notes:

[266] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 1 <sup>[267]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | 0.104 (± 99999)         | 0.257 (± 0.217)          | 1.11 (± 1.11)             |  |

Notes:

[267] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of OCA-glucuronide at Week 48

|                 |   |
|-----------------|---|
| End point title | Cmax of OCA-glucuronide at Week 48 <sup>[268]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[268] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[269]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 66.0 (± 63.6)            | 134 (± 71.3)              |  |

Notes:

[269] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Tmax of OCA-glucuronide at Week 48

|                 |   |
|-----------------|---|
| End point title | Tmax of OCA-glucuronide at Week 48 <sup>[270]</sup> |
|-----------------|---|

End point description:

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[270] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values              | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|-------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type            | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed   | 0 <sup>[271]</sup>      | 2                        | 2                         |  |
| Units: hours                  |                         |                          |                           |  |
| median (full range (min-max)) | ( to )                  | 1.73 (1.47 to 2.00)      | 1.54 (1.50 to 1.58)       |  |

Notes:

[271] - No participant OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: Ctrough of OCA-glucuronide at Week 48

|                 |  |
|-----------------|--|
| End point title | Ctrough of OCA-glucuronide at Week 48 <sup>[272]</sup> |
|-----------------|--|

End point description:

Ctrough was considered as the concentration at 24-hours post-dose at Week 48.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 hours post-dose at Week 48

Notes:

[272] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[273]</sup>      | 2                        | 2                         |  |
| Units: ng/mL                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 39.2 (± 35.7)            | 89.2 (± 73.3)             |  |

Notes:

[273] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-24h of OCA-glucuronide at Week 48

End point title AUC0-24h of OCA-glucuronide at Week 48<sup>[274]</sup>

End point description:

AUC0-24h was calculated using the linear/linear trapezoidal rule.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

End point type Primary

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[274] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[275]</sup>      | 2                        | 2                         |  |
| Units: ng*h/mL                       |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 952 (± 833)              | 2490 (± 1520)             |  |

Notes:

[275] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

### Primary: MRAUC of OCA-glucuronide at Week 48

End point title MRAUC of OCA-glucuronide at Week 48<sup>[276]</sup>

End point description:

MRAUC was the ratio of AUC<sub>0-24h</sub> of OCA-glucuronide (metabolite) to AUC<sub>0-24h</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where AUC<sub>0-24</sub> is the area under the plasma concentration time profile from time 0 to 24 hours.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[276] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[277]</sup>      | 2                        | 1 <sup>[278]</sup>        |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 1.62 (± 1.05)            | 0.833 (± 99999)           |  |

Notes:

[277] - No participant received OCA 5 mg once weekly at Week 48.

[278] - 99999: Standard deviation is not estimable as there is only one participant.

## Statistical analyses

No statistical analyses for this end point

## Primary: MRCmax of OCA-glucuronide at Week 48

|                 |   |
|-----------------|---|
| End point title | MRCmax of OCA-glucuronide at Week 48 <sup>[279]</sup> |
|-----------------|---|

End point description:

MRCmax was the ratio of C<sub>max</sub> of OCA-glucuronide (metabolite) to C<sub>max</sub> of OCA (parent drug) \* ratio of molecular weight of OCA to molecular weight of OCA-glucuronide, where C<sub>max</sub> is the maximum observed concentration.

APD: Results of PK were planned to be listed by the dose regimen. Participants in the PK population who received the planned dose regimen and had available data were included in the analysis. PK of OCA 5 mg once weekly at Week 48 is not applicable as participants received either OCA 5 mg twice daily or 10 mg twice daily and no participant received OCA 5 mg once weekly at Week 48.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (30 minutes before administration) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose at Week 48

Notes:

[279] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | OCA 5 mg<br>Once Weekly | OCA 5 mg<br>Twice Weekly | OCA 10 mg<br>Twice Weekly |  |
|--------------------------------------|-------------------------|--------------------------|---------------------------|--|
| Subject group type                   | Subject analysis set    | Subject analysis set     | Subject analysis set      |  |
| Number of subjects analysed          | 0 <sup>[280]</sup>      | 2                        | 2                         |  |
| Units: ratio                         |                         |                          |                           |  |
| arithmetic mean (standard deviation) | ( )                     | 0.411 (±<br>0.444)       | 0.482 (±<br>0.479)        |  |

Notes:

[280] - No participant received OCA 5 mg once weekly at Week 48.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) <sup>[281]</sup> |
|-----------------|--|

End point description:

An adverse event (AE) was any unfavorable & unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with use of study drug, whether or not related to study drug. An SAE was any AE that resulted in death, was life-threatening, resulted in a persistent or significant disability/incapacity, resulted in in-patient hospitalization or prolonged an existing hospitalization, was a congenital anomaly/birth defect, or was an important medical event that could jeopardize participant or could have required medical intervention to prevent one of the outcomes listed above. TEAE was defined as any AE if it met one or more of the following criteria: 1)An AE started on or after first study drug dose & within 30 days after last dose of study drug, 2)An AE occurred prior to first study drug dose that worsens after the first study drug dose.

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline up to approximately 3 years

Notes:

[281] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values            | Placebo              | Obeticholic<br>Acid (OCA) |  |  |
|-----------------------------|----------------------|---------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set      |  |  |
| Number of subjects analysed | 12                   | 10                        |  |  |
| Units: Participants         |                      |                           |  |  |
| Any TEAE                    | 12                   | 10                        |  |  |
| SAE                         | 9                    | 7                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Model of End-stage Liver Disease (MELD) Score at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the Model of End-stage Liver Disease |
|-----------------|--|

## End point description:

The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is derived from the participant's serum total bilirubin, serum creatinine, and prothrombin international normalized ratio (INR):  $3.78 \times \log \text{normal (ln)} [\text{total bilirubin (mg/deciliter [dL])}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$ . The MELD score ranges from 6 to 40 with higher scores indicating more severe liver disease and a worse outcome.

APD: Intent-to-treat (ITT) population included all randomized participants who received any amount of investigational product (OCA or placebo). Participants with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

|  |
|--|
| Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|--|

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed             | 11 <sup>[282]</sup>    | 10 <sup>[283]</sup>    |  |  |
| Units: Score on a scale                 |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 11, 10)           | 0.50 (-0.50 to 1.00)   | 0.00 (-1.50 to 2.00)   |  |  |
| Change at Week 6 (n = 9, 8)             | 0.50 (0.00 to 2.50)    | 0.00 (-0.75 to 1.25)   |  |  |
| Change at Week 12 (n = 6, 7)            | 0.75 (0.00 to 2.50)    | 0.00 (-1.00 to 1.00)   |  |  |
| Change at Week 18 (n = 8, 8)            | 0.65 (-0.25 to 3.00)   | -0.75 (-2.00 to 1.00)  |  |  |
| Change at Week 24 (n = 4, 5)            | 0.15 (0.00 to 0.40)    | -1.50 (-2.00 to 0.00)  |  |  |
| Change at Week 30 (n = 6, 6)            | 0.15 (-0.50 to 0.50)   | -1.25 (-2.00 to 0.00)  |  |  |
| Change at Week 36 (n = 6, 6)            | 0.15 (-1.00 to 1.50)   | 0.25 (-1.50 to 1.00)   |  |  |
| Change at Week 42 (n = 6, 6)            | 0.65 (-0.50 to 1.50)   | 0.50 (0.00 to 1.50)    |  |  |
| Change at Week 48 (n = 6, 4)            | 0.65 (0.00 to 1.50)    | -1.75 (-2.50 to -0.50) |  |  |
| Change at Extension Month 3 (n = 5, 5)  | 0.50 (0.50 to 4.30)    | -1.00 (-1.50 to -0.50) |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 0.00 (-1.00 to 3.50)   | 0.25 (0.00 to 0.50)    |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | 0.75 (-1.00 to 2.50)   |  |  |
| Change at Extension Month 12 (n = 1, 1) | -1.00 (-1.00 to -1.00) | 4.50 (4.50 to 4.50)    |  |  |
| Change at Extension Month 15 (n = 1, 0) | -1.00 (-1.00 to -1.00) | 99999 (99999 to 99999) |  |  |

## Notes:

[282] - 99999 denotes data not available as there were no participants at specified timepoint.

[283] - 99999 denotes data not available as there were no participants at specified timepoint.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in MELD-Sodium (Na) Score at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in MELD-Sodium (Na) Score at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

### End point description:

The MELD-Na scoring system is used to assess the severity of chronic liver disease in the participants with an initial MELD(i) score greater than 11. MELD-Na score is derived from the participant's serum total bilirubin, serum creatinine, INR, and sodium. The MELD-Na score is re-calculated as follows:  $MELD-Na = MELD(i) + 1.32 \times (137 - Na) - [0.033 \times MELD(i) \times (137 - Na)]$ . MELD score ranges from 6-40 with higher scores indicating more severe liver disease and a worse outcome.

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

### End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 11 <sup>[284]</sup>    | 10 <sup>[285]</sup>    |  |  |
| Units: Score on a Scale                 |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 11, 10)           | 0.00 (-0.50 to 1.00)   | 0.50 (-1.50 to 2.00)   |  |  |
| Change at Week 6 (n = 9, 8)             | 0.50 (0.00 to 2.00)    | -0.25 (-0.75 to 1.50)  |  |  |
| Change at Week 12 (n = 6, 7)            | 0.50 (0.00 to 3.50)    | 0.50 (-1.50 to 2.00)   |  |  |
| Change at Week 18 (n = 8, 8)            | 0.65 (-0.25 to 2.75)   | -0.75 (-2.50 to 0.50)  |  |  |
| Change at Week 24 (n = 4, 5)            | 0.15 (0.00 to 0.40)    | -2.00 (-2.50 to 1.00)  |  |  |
| Change at Week 30 (n = 6, 6)            | 0.15 (-0.50 to 0.50)   | -0.75 (-2.00 to 0.50)  |  |  |
| Change at Week 36 (n = 6, 6)            | 0.15 (-1.00 to 1.50)   | -0.25 (-1.50 to 1.00)  |  |  |
| Change at Week 42 (n = 5, 6)            | 0.00 (-0.50 to 1.30)   | 0.50 (0.00 to 0.50)    |  |  |
| Change at Week 48 (n = 6, 4)            | 0.65 (0.00 to 2.50)    | -1.75 (-3.00 to 0.00)  |  |  |
| Change at Extension Month 3 (n = 5, 5)  | 2.50 (0.50 to 4.30)    | -1.00 (-2.50 to -0.50) |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 0.00 (-1.00 to 3.50)   | 1.75 (0.50 to 3.00)    |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | 0.75 (-1.00 to 2.50)   |  |  |
| Change at Extension Month 12 (n = 1, 1) | -1.00 (-1.00 to -1.00) | 4.50 (4.50 to 4.50)    |  |  |
| Change at Extension Month 15 (n = 1, 0) | -1.00 (-1.00 to -1.00) | 99999 (99999 to 99999) |  |  |

### Notes:

[284] - 99999 denotes data not available as there were no participants.

[285] - 99999 denotes data not available as there were no participants.

## Statistical analyses



**Secondary: Change From Baseline in Child-Pugh Score at Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Child-Pugh Score at Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

## End point description:

The Child-Pugh classification was a scoring system used for the classification of the severity of cirrhosis. It included three continuous variables (bilirubin, albumin, and INR) and two discrete variables (ascites and encephalopathy). Each variable was scored 1-3 with 3 indicating most severe derangement. The determination of child-pugh score ranged from 5 to 15. The higher the score, the sicker the participant.

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline, Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 12 <sup>[286]</sup>    | 10 <sup>[287]</sup>    |  |  |
| Units: Score on a Scale                 |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Day 1 (n = 12, 10)            | 0.0 (-0.5 to 0.0)      | 0.0 (0.0 to 0.0)       |  |  |
| Change at Week 6 (n = 9, 8)             | 0.0 (-1.0 to 0.0)      | 0.0 (-0.5 to 0.5)      |  |  |
| Change at Week 12 (n = 6, 7)            | -0.5 (-1.0 to 1.0)     | 0.0 (-1.0 to 1.0)      |  |  |
| Change at Week 18 (n = 8, 8)            | 0.0 (-1.0 to 0.0)      | -0.5 (-2.0 to 0.0)     |  |  |
| Change at Week 24 (n = 5, 5)            | -1.0 (-1.0 to 0.0)     | 0.0 (-1.0 to 0.0)      |  |  |
| Change at Week 30 (n = 6, 6)            | -0.5 (-1.0 to 0.0)     | -1.0 (-2.0 to 0.0)     |  |  |
| Change at Week 36 (n = 6, 6)            | -1.0 (-1.0 to 0.0)     | -0.5 (-1.0 to 0.0)     |  |  |
| Change at Week 48 (n = 6, 6)            | -0.5 (-1.0 to 0.0)     | 0.0 (-2.0 to 0.0)      |  |  |
| Change at Extension Month 3 (n = 6, 5)  | 0.0 (-1.0 to 0.0)      | 0.0 (-1.0 to 1.0)      |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 1.0 (-2.0 to 3.0)      | 0.0 (0.0 to 0.0)       |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | 0.0 (-1.0 to 1.0)      |  |  |
| Change at Extension Month 12 (n = 1, 1) | 1.0 (1.0 to 1.0)       | 0.0 (0.0 to 0.0)       |  |  |
| Change at Extension Month 15 (n = 1, 0) | 1.0 (1.0 to 1.0)       | 99999 (99999 to 99999) |  |  |

## Notes:

[286] - 99999 denotes data not available as there were no participants.

[287] - 99999 denotes data not available as there were no participants.

**Statistical analyses**

**Secondary: Number of Participants by Child-Pugh Score Component (Ascites Categories)**

|  |   |
|--|---|
| End point title  | Number of Participants by Child-Pugh Score Component (Ascites Categories) |
| End point description:   |   |
| Number of participants with Child-Pugh component - ascites categories of none, mild, and moderate-severe has been reported. The ascites categories were defined per investigator's discretion. |   |
| APD: Participants in the ITT population with available data were analyzed.   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15   |   |

| End point values                              | Placebo              | Obeticholic Acid (OCA) |  |  |
|---|----------------------|------------------------|--|--|
| Subject group type                            | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed                   | 12                   | 10                     |  |  |
| Units: Participants                           |                      |                        |  |  |
| Day 1: None (n =12, 10)                       | 6                    | 5                      |  |  |
| Day 1: Mild (n =12, 10)                       | 5                    | 4                      |  |  |
| Day 1: Moderate-Severe (n =12, 10)            | 1                    | 1                      |  |  |
| Week 6: None (n = 9, 9)                       | 7                    | 4                      |  |  |
| Week 6: Mild (n = 9, 9)                       | 2                    | 5                      |  |  |
| Week 6: Moderate-Severe (n = 9, 9)            | 0                    | 0                      |  |  |
| Week 12: None (n = 6, 7)                      | 4                    | 4                      |  |  |
| Week 12: Mild (n = 6, 7)                      | 2                    | 3                      |  |  |
| Week 12: Moderate-Severe (n = 6, 7)           | 0                    | 0                      |  |  |
| Week 18: None (n = 8, 8)                      | 6                    | 5                      |  |  |
| Week 18: Mild (n = 8, 8)                      | 2                    | 3                      |  |  |
| Week 18: Moderate-Severe (n = 8, 8)           | 0                    | 0                      |  |  |
| Week 24: None (n = 6, 6)                      | 6                    | 3                      |  |  |
| Week 24: Mild (n = 6, 6)                      | 0                    | 3                      |  |  |
| Week 24: Moderate-Severe (n = 6, 6)           | 0                    | 0                      |  |  |
| Week 30: None (n = 6, 6)                      | 6                    | 4                      |  |  |
| Week 30: Mild (n = 6, 6)                      | 0                    | 2                      |  |  |
| Week 30: Moderate-Severe (n = 6, 6)           | 0                    | 0                      |  |  |
| Week 36: None (n = 6, 6)                      | 6                    | 4                      |  |  |
| Week 36: Mild (n = 6, 6)                      | 0                    | 2                      |  |  |
| Week 36: Moderate-Severe (n = 6, 6)           | 0                    | 0                      |  |  |
| Week 48: None (n = 6, 6)                      | 6                    | 4                      |  |  |
| Week 48: Mild (n = 6, 6)                      | 0                    | 1                      |  |  |
| Week 48: Moderate-Severe (n = 6, 6)           | 0                    | 1                      |  |  |
| Extension Month 3: None (n = 6, 5)            | 6                    | 2                      |  |  |
| Extension Month 3: Mild (n = 6, 5)            | 0                    | 1                      |  |  |
| Extension Month 3: Moderate-Severe (n = 6, 5) | 0                    | 2                      |  |  |
| Extension Month 6: None (n = 3, 2)            | 1                    | 1                      |  |  |
| Extension Month 6: Mild (n = 3, 2)            | 1                    | 1                      |  |  |

|  |   |   |  |  |
|--|---|---|--|--|
| Extension Month 6: Moderate-Severe (n = 3, 2)  | 1 | 0 |  |  |
| Extension Month 9: None (n = 0, 2)             | 0 | 1 |  |  |
| Extension Month 9: Mild (n = 0, 2)             | 0 | 1 |  |  |
| Extension Month 9: Moderate-Severe (n = 0, 2)  | 0 | 0 |  |  |
| Extension Month 12: None (n = 1, 1)            | 0 | 0 |  |  |
| Extension Month 12: Mild (n = 1, 1)            | 1 | 1 |  |  |
| Extension Month 12: Moderate-Severe (n = 1, 1) | 0 | 0 |  |  |
| Extension Month 15: None (n = 1, 1)            | 0 | 0 |  |  |
| Extension Month 15: Mild (n = 1, 1)            | 1 | 1 |  |  |
| Extension Month 15: Moderate-Severe (n = 1, 1) | 0 | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants by Child-Pugh Score Component (Prothrombin Time Categories)

|                 |  |
|-----------------|--|
| End point title | Number of Participants by Child-Pugh Score Component (Prothrombin Time Categories) |
|-----------------|--|

End point description:

Number of participants with Child-Pugh component - prothrombin time (measured as INR) in categories of <1.7, 1.7 - 2.3, and >2.3 has been reported.

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values              | Placebo              | Obeticholic Acid (OCA) |  |  |
|-------------------------------|----------------------|------------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed   | 12                   | 10                     |  |  |
| Units: Participants           |                      |                        |  |  |
| Day 1: <1.7 (n = 12, 10)      | 12                   | 10                     |  |  |
| Day 1: 1.7 - 2.3 (n = 12, 10) | 0                    | 0                      |  |  |
| Day 1: >2.3 (n = 12, 10)      | 0                    | 0                      |  |  |
| Week 6: <1.7 (n = 9, 9)       | 9                    | 9                      |  |  |
| Week 6: 1.7 - 2.3 (n = 9, 9)  | 0                    | 0                      |  |  |
| Week 6: >2.3 (n = 9, 9)       | 0                    | 0                      |  |  |
| Week 12: <1.7 (n = 6, 7)      | 6                    | 7                      |  |  |
| Week 12: 1.7 - 2.3 (n = 6, 7) | 0                    | 0                      |  |  |
| Week 12: >2.3 (n = 6, 7)      | 0                    | 0                      |  |  |
| Week 18: <1.7 (n = 8, 8)      | 8                    | 8                      |  |  |
| Week 18: 1.7 - 2.3 (n = 8, 8) | 0                    | 0                      |  |  |
| Week 18: >2.3 (n = 8, 8)      | 0                    | 0                      |  |  |

|  |   |   |  |  |
|--|---|---|--|--|
| Week 24: <1.7 (n = 5, 5)                 | 4 | 5 |  |  |
| Week 24: 1.7 - 2.3 (n = 5, 5)            | 1 | 0 |  |  |
| Week 24: >2.3 (n = 5, 5)                 | 0 | 0 |  |  |
| Week 30: <1.7 (n = 6, 6)                 | 6 | 6 |  |  |
| Week 30: 1.7 - 2.3 (n = 6, 6)            | 0 | 0 |  |  |
| Week 30: >2.3 (n = 6, 6)                 | 0 | 0 |  |  |
| Week 36: <1.7 (n = 6, 6)                 | 6 | 6 |  |  |
| Week 36: 1.7 - 2.3 (n = 6, 6)            | 0 | 0 |  |  |
| Week 36: >2.3 (n = 6, 6)                 | 0 | 0 |  |  |
| Week 48: <1.7 (n = 6, 6)                 | 6 | 6 |  |  |
| Week 48: 1.7 - 2.3 (n = 6, 6)            | 0 | 0 |  |  |
| Week 48: >2.3 (n = 6, 6)                 | 0 | 0 |  |  |
| Extension Month 3: <1.7 (n = 6, 5)       | 6 | 5 |  |  |
| Extension Month 3: 1.7 - 2.3 (n = 6, 5)  | 0 | 0 |  |  |
| Extension Month 3: >2.3 (n = 6, 5)       | 0 | 0 |  |  |
| Extension Month 6: <1.7 (n = 3, 2)       | 3 | 2 |  |  |
| Extension Month 6: 1.7 - 2.3 (n = 3, 2)  | 0 | 0 |  |  |
| Extension Month 6: >2.3 (n = 3, 2)       | 0 | 0 |  |  |
| Extension Month 9: <1.7 (n = 0, 2)       | 0 | 2 |  |  |
| Extension Month 9: 1.7 - 2.3 (n = 0, 2)  | 0 | 0 |  |  |
| Extension Month 9: >2.3 (n = 0, 2)       | 0 | 0 |  |  |
| Extension Month 12: <1.7 (n = 1, 1)      | 1 | 1 |  |  |
| Extension Month 12: 1.7 - 2.3 (n = 1, 1) | 0 | 0 |  |  |
| Extension Month 12: >2.3 (n = 1, 1)      | 0 | 0 |  |  |
| Extension Month 15: <1.7 (n = 1, 0)      | 1 | 0 |  |  |
| Extension Month 15: 1.7 - 2.3 (n = 1, 0) | 0 | 0 |  |  |
| Extension Month 12: >2.3 (n = 1, 0)      | 0 | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants by Child-Pugh Score Component (Serum Albumin Categories)

|                 |   |
|-----------------|---|
| End point title | Number of Participants by Child-Pugh Score Component (Serum Albumin Categories) |
|-----------------|---|

End point description:

Number of participants with Child-Pugh component - serum albumin levels in categories of >35 gram per liter (g/L), 28-35 g/L, or <28 g/L has been reported.

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                         | Placebo              | Obeticholic Acid (OCA) |  |  |
|--|----------------------|------------------------|--|--|
| Subject group type                       | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed              | 12                   | 10                     |  |  |
| Units: Participants                      |                      |                        |  |  |
| Day 1: >35 g/L (n = 12, 10)              | 3                    | 4                      |  |  |
| Day 1: 28-35 g/L (n = 12, 10)            | 9                    | 4                      |  |  |
| Day 1: <28 g/L (n = 12, 10)              | 0                    | 2                      |  |  |
| Week 6: >35 g/L (n = 9, 9)               | 2                    | 4                      |  |  |
| Week 6: 28-35 g/L (n = 9, 9)             | 7                    | 3                      |  |  |
| Week 6: <28 g/L (n = 9, 9)               | 0                    | 2                      |  |  |
| Week 12: >35 g/L (n = 6, 7)              | 1                    | 3                      |  |  |
| Week 12: 28-35 g/L (n = 6, 7)            | 5                    | 3                      |  |  |
| Week 12: <28 g/L (n = 6, 7)              | 0                    | 1                      |  |  |
| Week 18: >35 g/L (n = 8, 8)              | 2                    | 5                      |  |  |
| Week 18: 28-35 g/L (n = 8, 8)            | 6                    | 3                      |  |  |
| Week 18: <28 g/L (n = 8, 8)              | 0                    | 0                      |  |  |
| Week 24: >35 g/L (n = 6, 6)              | 1                    | 3                      |  |  |
| Week 24: 28-35 g/L (n = 6, 6)            | 5                    | 3                      |  |  |
| Week 24: <28 g/L (n = 6, 6)              | 0                    | 0                      |  |  |
| Week 30: >35 g/L (n = 6, 6)              | 1                    | 3                      |  |  |
| Week 30: 28-35 g/L (n = 6, 6)            | 5                    | 3                      |  |  |
| Week 30: <28 g/L (n = 6, 6)              | 0                    | 0                      |  |  |
| Week 36: >35 g/L (n = 6, 6)              | 1                    | 2                      |  |  |
| Week 36: 28-35 g/L (n = 6, 6)            | 5                    | 4                      |  |  |
| Week 36: <28 g/L (n = 6, 6)              | 0                    | 0                      |  |  |
| Week 48: >35 g/L (n = 6, 6)              | 2                    | 3                      |  |  |
| Week 48: 28-35 g/L (n = 6, 6)            | 4                    | 3                      |  |  |
| Week 48: <28 g/L (n = 6, 6)              | 0                    | 0                      |  |  |
| Extension Month 3: >35 g/L (n = 6, 5)    | 1                    | 2                      |  |  |
| Extension Month 3: 28-35 g/L (n = 6, 5)  | 5                    | 3                      |  |  |
| Extension Month 3: <28 g/L (n = 6, 5)    | 0                    | 0                      |  |  |
| Extension Month 6: >35 g/L (n = 3, 2)    | 1                    | 1                      |  |  |
| Extension Month 6: 28-35 g/L (n = 3, 2)  | 2                    | 1                      |  |  |
| Extension Month 6: <28 g/L (n = 3, 2)    | 0                    | 0                      |  |  |
| Extension Month 9: >35 g/L (n = 0, 2)    | 0                    | 0                      |  |  |
| Extension Month 9: 28-35 g/L (n = 0, 2)  | 0                    | 2                      |  |  |
| Extension Month 9: <28 g/L (n = 0, 2)    | 0                    | 0                      |  |  |
| Extension Month 12: >35 g/L (n = 1, 1)   | 0                    | 1                      |  |  |
| Extension Month 12: 28-35 g/L (n = 1, 1) | 1                    | 0                      |  |  |
| Extension Month 12: <28 g/L (n = 1, 1)   | 0                    | 0                      |  |  |
| Extension Month 15: >35 g/L (n = 1, 1)   | 0                    | 0                      |  |  |
| Extension Month 15: 28-35 g/L (n = 1, 1) | 1                    | 1                      |  |  |
| Extension Month 15: <28 g/L (n = 1, 1)   | 0                    | 0                      |  |  |

## Statistical analyses

**Secondary: Number of Participants by Child-Pugh Score Component (Total Bilirubin Categories)**

|  |   |
|--|---|
| End point title  | Number of Participants by Child-Pugh Score Component (Total Bilirubin Categories) |
| End point description:<br>Number of participants with Child-Pugh component - total bilirubin levels in categories of <34 micromole per liter ( $\mu\text{mol/L}$ ), 34-50 $\mu\text{mol/L}$ , and >50 $\mu\text{mol/L}$ has been reported. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15   |   |

| End point values                                      | Placebo              | Obeticholic Acid (OCA) |  |  |
|---|----------------------|------------------------|--|--|
| Subject group type                                    | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed                           | 12                   | 10                     |  |  |
| Units: Participants                                   |                      |                        |  |  |
| Day 1: <34 $\mu\text{mol/L}$ (n = 12, 10)             | 3                    | 5                      |  |  |
| Day 1: 34-50 $\mu\text{mol/L}$ (n = 12, 10)           | 5                    | 0                      |  |  |
| Day 1: >50 $\mu\text{mol/L}$ (n = 12, 10)             | 4                    | 5                      |  |  |
| Week 6: <34 $\mu\text{mol/L}$ (n = 9, 8)              | 4                    | 4                      |  |  |
| Week 6: 34-50 $\mu\text{mol/L}$ (n = 9, 8)            | 1                    | 0                      |  |  |
| Week 6: >50 $\mu\text{mol/L}$ (n = 9, 8)              | 4                    | 4                      |  |  |
| Week 12: <34 $\mu\text{mol/L}$ (n = 6, 7)             | 2                    | 4                      |  |  |
| Week 12: 34-50 $\mu\text{mol/L}$ (n = 6, 7)           | 3                    | 0                      |  |  |
| Week 12: >50 $\mu\text{mol/L}$ (n = 6, 7)             | 1                    | 3                      |  |  |
| Week 18: <34 $\mu\text{mol/L}$ (n = 8, 8)             | 2                    | 5                      |  |  |
| Week 18: 34-50 $\mu\text{mol/L}$ (n = 8, 8)           | 3                    | 0                      |  |  |
| Week 18: >50 $\mu\text{mol/L}$ (n = 8, 8)             | 3                    | 3                      |  |  |
| Week 24: <34 $\mu\text{mol/L}$ (n = 6, 6)             | 2                    | 4                      |  |  |
| Week 24: 34-50 $\mu\text{mol/L}$ (n = 6, 6)           | 3                    | 0                      |  |  |
| Week 24: >50 $\mu\text{mol/L}$ (n = 6, 6)             | 1                    | 2                      |  |  |
| Week 30: <34 $\mu\text{mol/L}$ (n = 6, 6)             | 3                    | 4                      |  |  |
| Week 30: 34-50 $\mu\text{mol/L}$ (n = 6, 6)           | 1                    | 1                      |  |  |
| Week 30: >50 $\mu\text{mol/L}$ (n = 6, 6)             | 2                    | 1                      |  |  |
| Week 36: <34 $\mu\text{mol/L}$ (n = 6, 6)             | 3                    | 4                      |  |  |
| Week 36: 34-50 $\mu\text{mol/L}$ (n = 6, 6)           | 1                    | 0                      |  |  |
| Week 36: >50 $\mu\text{mol/L}$ (n = 6, 6)             | 2                    | 2                      |  |  |
| Week 48: <34 $\mu\text{mol/L}$ (n = 6, 6)             | 2                    | 4                      |  |  |
| Week 48: 34-50 $\mu\text{mol/L}$ (n = 6, 6)           | 1                    | 0                      |  |  |
| Week 48: >50 $\mu\text{mol/L}$ (n = 6, 6)             | 3                    | 2                      |  |  |
| Extension Month 3: <34 $\mu\text{mol/L}$ (n = 6, 5)   | 2                    | 3                      |  |  |
| Extension Month 3: 34-50 $\mu\text{mol/L}$ (n = 6, 5) | 1                    | 1                      |  |  |
| Extension Month 3: >50 $\mu\text{mol/L}$ (n = 6, 5)   | 3                    | 1                      |  |  |
| Extension Month 6: <34 $\mu\text{mol/L}$ (n = 3, 2)   | 1                    | 1                      |  |  |

|   |   |   |  |  |
|---|---|---|--|--|
| Extension Month 6: 34-50 µmol/L (n = 3, 2)  | 1 | 0 |  |  |
| Extension Month 6: >50 µmol/L (n = 3, 2)    | 1 | 1 |  |  |
| Extension Month 9: <34 µmol/L (n = 0, 2)    | 0 | 1 |  |  |
| Extension Month 9: 34-50 µmol/L (n = 0, 2)  | 0 | 1 |  |  |
| Extension Month 9: >50 µmol/L (n = 0, 2)    | 0 | 0 |  |  |
| Extension Month 12: <34 µmol/L (n = 1, 1)   | 0 | 1 |  |  |
| Extension Month 12: 34-50 µmol/L (n = 1, 1) | 1 | 0 |  |  |
| Extension Month 12: >50 µmol/L (n = 1, 1)   | 0 | 0 |  |  |
| Extension Month 15: <34 µmol/L (n = 1, 1)   | 0 | 1 |  |  |
| Extension Month 15: 34-50 µmol/L (n = 1, 1) | 1 | 0 |  |  |
| Extension Month 15: >50 µmol/L (n = 1, 1)   | 0 | 0 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants by Child-Pugh Score Component (Hepatic Encephalopathy Categories)

|                 |  |
|-----------------|--|
| End point title | Number of Participants by Child-Pugh Score Component (Hepatic Encephalopathy Categories) |
|-----------------|--|

End point description:

Number of participants with Child-Pugh component - Hepatic encephalopathy in categories of Grade 0, Grade 1 or 2, and Grade 3 and 4 has been reported.

Grade 0: normal consciousness, normal personality, normal neurological examination, normal electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles, per second (cps) waves.

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                            | Placebo              | Obeticholic Acid (OCA) |  |  |
|---|----------------------|------------------------|--|--|
| Subject group type                          | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed                 | 12                   | 10                     |  |  |
| Units: Participants                         |                      |                        |  |  |
| Day 1: Grade 0 (n = 12, 10)                 | 8                    | 8                      |  |  |
| Day 1: Grade 1 or 2 (n = 12, 10)            | 4                    | 2                      |  |  |
| Day 1: Grade 3 or 4 (n = 12, 10)            | 0                    | 0                      |  |  |
| Week 6: Grade 0 (n = 9, 9)                  | 6                    | 6                      |  |  |
| Week 6: Grade 1 or 2 (n = 9, 9)             | 3                    | 3                      |  |  |
| Week 6: Grade 3 or 4 (n = 9, 9)             | 0                    | 0                      |  |  |
| Week 12: Grade 0 (n = 6, 7)                 | 4                    | 5                      |  |  |
| Week 12: Grade 1 or 2 (n = 6, 7)            | 2                    | 2                      |  |  |
| Week 12: Grade 3 or 4 (n = 6, 7)            | 0                    | 0                      |  |  |
| Week 18: Grade 0 (n = 8, 8)                 | 6                    | 7                      |  |  |
| Week 18: Grade 1 or 2 (n = 8, 8)            | 2                    | 1                      |  |  |
| Week 18: Grade 3 or 4 (n = 8, 8)            | 0                    | 0                      |  |  |
| Week 24: Grade 0 (n = 6, 6)                 | 6                    | 5                      |  |  |
| Week 24: Grade 1 or 2 (n = 6, 6)            | 0                    | 1                      |  |  |
| Week 24: Grade 3 or 4 (n = 6, 6)            | 0                    | 0                      |  |  |
| Week 30: Grade 0 (n = 6, 6)                 | 5                    | 5                      |  |  |
| Week 30: Grade 1 or 2 (n = 6, 6)            | 1                    | 1                      |  |  |
| Week 30: Grade 3 or 4 (n = 6, 6)            | 0                    | 0                      |  |  |
| Week 36: Grade 0 (n = 6, 6)                 | 6                    | 5                      |  |  |
| Week 36: Grade 1 or 2 (n = 6, 6)            | 0                    | 1                      |  |  |
| Week 36: Grade 3 or 4 (n = 6, 6)            | 0                    | 0                      |  |  |
| Week 48: Grade 0 (n = 6, 6)                 | 5                    | 5                      |  |  |
| Week 48: Grade 1 or 2 (n = 6, 6)            | 1                    | 1                      |  |  |
| Week 48: Grade 3 or 4 (n = 6, 6)            | 0                    | 0                      |  |  |
| Extension Month 3: Grade 0 (n = 6, 5)       | 5                    | 4                      |  |  |
| Extension Month 3: Grade 1 or 2 (n = 6, 5)  | 1                    | 1                      |  |  |
| Extension Month 3: Grade 3 or 4 (n = 6, 5)  | 0                    | 0                      |  |  |
| Extension Month 6: Grade 0 (n = 3, 2)       | 3                    | 1                      |  |  |
| Extension Month 6: Grade 1 or 2 (n = 3, 2)  | 0                    | 1                      |  |  |
| Extension Month 6: Grade 3 or 4 (n = 3, 2)  | 0                    | 0                      |  |  |
| Extension Month 9: Grade 0 (n = 0, 2)       | 0                    | 1                      |  |  |
| Extension Month 9: Grade 1 or 2 (n = 0, 2)  | 0                    | 1                      |  |  |
| Extension Month 9: Grade 3 or 4 (n = 0, 2)  | 0                    | 0                      |  |  |
| Extension Month 12: Grade 0 (n = 1, 1)      | 1                    | 0                      |  |  |
| Extension Month 12: Grade 1 or 2 (n = 1, 1) | 0                    | 1                      |  |  |
| Extension Month 12: Grade 3 or 4 (n = 1, 1) | 0                    | 0                      |  |  |
| Extension Month 15: Grade 0 (n = 1, 1)      | 1                    | 0                      |  |  |
| Extension Month 15: Grade 1 or 2 (n = 1, 1) | 0                    | 1                      |  |  |
| Extension Month 15: Grade 3 or 4 (n = 1, 1) | 0                    | 0                      |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Total Bilirubin at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Total Bilirubin at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|---|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                   | Obeticholic Acid (OCA) |  |  |
|---|---------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set      | Subject analysis set   |  |  |
| Number of subjects analysed             | 11 <sup>[288]</sup>       | 10                     |  |  |
| Units: µmol/L                           |                           |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                           |                        |  |  |
| Change at Week 3 (n = 11, 10)           | 0.86 (-13.0 to 6.50)      | -3.25 (-4.00 to 24.00) |  |  |
| Change at Week 6 (n = 9, 8)             | 3.00 (-1.50 to 5.99)      | -2.14 (-3.43 to 26.75) |  |  |
| Change at Week 12 (n = 7, 7)            | 0.86 (-4.28 to 9.00)      | -1.71 (-6.00 to 17.96) |  |  |
| Change at Week 18 (n = 8, 8)            | 1.08 (-4.70 to 16.05)     | -4.03 (-9.00 to 3.21)  |  |  |
| Change at Week 24 (n = 5, 7)            | 2.67 (-1.50 to 20.40)     | -3.50 (-10.00 to 1.71) |  |  |
| Change at Week 30 (n = 6, 6)            | 2.08 (-2.57 to 31.34)     | -8.49 (-9.00 to -5.50) |  |  |
| Change at Week 36 (n = 6, 6)            | 4.25 (-11.12 to 9.67)     | -3.53 (-7.00 to 3.42)  |  |  |
| Change at Week 42 (n = 6, 7)            | 6.58 (-7.70 to 12.00)     | 1.71 (-2.85 to 6.00)   |  |  |
| Change at Week 48 (n = 6, 6)            | 6.25 (-2.57 to 23.67)     | -3.75 (-6.27 to -0.57) |  |  |
| Change at Extension Month 3 (n = 6, 5)  | 2.25 (0.86 to 60.67)      | 0.50 (-16.00 to 0.57)  |  |  |
| Change at Extension Month 6 (n = 3, 2)  | -1.50 (-12.83 to 21.38)   | -0.22 (-1.00 to 0.57)  |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999)    | -7.86 (-18.00 to 2.28) |  |  |
| Change at Extension Month 12 (n = 1, 1) | -14.54 (-14.54 to -14.54) | 9.12 (9.12 to 9.12)    |  |  |

|   |                           |                        |  |  |
|---|---------------------------|------------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | -12.83 (-12.83 to -12.83) | 24.51 (24.51 to 24.51) |  |  |
|---|---------------------------|------------------------|--|--|

Notes:

[288] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Direct Bilirubin at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Direct Bilirubin at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 11 <sup>[289]</sup>    | 10                     |  |  |
| Units: µmol/L                           |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 11, 10)           | 0.00 (-6.04 to 1.50)   | -1.07 (-1.50 to 15.00) |  |  |
| Change at Week 6 (n = 8, 8)             | 2.53 (0.00 to 7.25)    | -1.32 (-4.61 to 18.50) |  |  |
| Change at Week 12 (n = 7, 7)            | 4.28 (0.00 to 12.50)   | -1.14 (-3.00 to 1.71)  |  |  |
| Change at Week 18 (n = 8, 8)            | 2.99 (0.50 to 14.20)   | -1.82 (-3.25 to 2.00)  |  |  |
| Change at Week 24 (n = 5, 6)            | 1.00 (-1.00 to 15.00)  | -1.75 (-2.85 to 0.00)  |  |  |
| Change at Week 30 (n = 6, 5)            | 0.93 (-1.00 to 6.10)   | -2.50 (-4.00 to -1.71) |  |  |
| Change at Week 36 (n = 6, 6)            | 0.00 (-4.28 to 3.37)   | -1.57 (-2.50 to 0.00)  |  |  |
| Change at Week 42 (n = 6, 7)            | 2.50 (-2.57 to 9.37)   | -1.71 (-2.66 to 1.50)  |  |  |
| Change at Week 48 (n = 6, 6)            | 3.61 (-1.00 to 15.00)  | -2.36 (-6.08 to -1.14) |  |  |
| Change at Extension Month 3 (n = 5, 5)  | 3.37 (0.00 to 4.28)    | -2.00 (-15.00 to 1.50) |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 0.00 (-5.99 to 19.67)  | -1.00 (-6.00 to 3.99)  |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -3.79 (-15.00 to 7.41) |  |  |
| Change at Extension Month 12 (n = 1, 1) | -9.41 (-9.41 to -9.41) | 7.41 (7.41 to 7.41)    |  |  |

|   |                        |                        |  |  |
|---|------------------------|------------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | -5.99 (-5.99 to -5.99) | 12.54 (12.54 to 12.54) |  |  |
|---|------------------------|------------------------|--|--|

Notes:

[289] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Alkaline Phosphatase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Alkaline Phosphatase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 11 <sup>[290]</sup>    | 10                     |  |  |
| Units: unit per liter (U/ L)            |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 11, 10)           | -21.0 (-48.0 to 6.0)   | -9.0 (-48.0 to 0.0)    |  |  |
| Change at Week 6 (n = 9, 9)             | -7.0 (-22.0 to 19.0)   | 5.0 (-12.0 to 15.0)    |  |  |
| Change at Week 12 (n = 7, 7)            | -1.0 (-54.0 to 12.0)   | -17.0 (-32.0 to 6.0)   |  |  |
| Change at Week 18 (n = 8, 8)            | -20.5 (-35.5 to 16.5)  | -4.5 (-37.5 to 1.5)    |  |  |
| Change at Week 24 (n = 5, 7)            | -30.0 (-66.0 to 16.0)  | -5.0 (-100.0 to 4.0)   |  |  |
| Change at Week 30 (n = 6, 6)            | -34.5 (-76.0 to -19.0) | -20.0 (-33.0 to -7.0)  |  |  |
| Change at Week 36 (n = 6, 8)            | -26.0 (-64.0 to -6.0)  | -4.0 (-89.5 to 4.0)    |  |  |
| Change at Week 42 (n = 6, 7)            | -24.0 (-45.0 to -17.0) | 5.0 (-87.0 to 9.0)     |  |  |
| Change at Week 48 (n = 6, 5)            | -29.0 (-63.0 to -17.0) | 8.0 (-3.0 to 13.0)     |  |  |
| Change at Extension Month 3 (n = 6, 5)  | -24.0 (-48.0 to -7.0)  | 10.0 (-14.0 to 26.0)   |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 6.0 (-33.0 to 7.0)     | -46.0 (-133.0 to 41.0) |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -66.5 (-148.0 to 15.0) |  |  |
| Change at Extension Month 12 (n = 1, 1) | -72.0 (-72.0 to -72.0) | 122.0 (122.0 to 122.0) |  |  |

|   |                        |                     |  |  |
|---|------------------------|---------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | -83.0 (-83.0 to -83.0) | 10.0 (10.0 to 10.0) |  |  |
|---|------------------------|---------------------|--|--|

Notes:

[290] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Alanine Aminotransferase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Alanine Aminotransferase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 11 <sup>[291]</sup>    | 10                     |  |  |
| Units: U/L                              |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 11, 10)           | -5.0 (-9.0 to -1.0)    | -2.0 (-9.0 to 1.0)     |  |  |
| Change at Week 6 (n = 9, 8)             | -5.0 (-9.0 to 1.0)     | 2.5 (-1.0 to 12.5)     |  |  |
| Change at Week 12 (n = 7, 7)            | 1.0 (-9.0 to 5.0)      | 10.0 (1.0 to 19.0)     |  |  |
| Change at Week 18 (n = 8, 8)            | -6.5 (-12.5 to -3.5)   | -0.5 (-5.0 to 1.5)     |  |  |
| Change at Week 24 (n = 5, 6)            | -4.0 (-5.0 to 4.0)     | -4.0 (-8.0 to 3.0)     |  |  |
| Change at Week 30 (n = 6, 6)            | -6.0 (-12.0 to 3.0)    | 1.5 (-2.0 to 3.0)      |  |  |
| Change at Week 36 (n = 6, 7)            | 11.5 (-6.0 to 24.0)    | -3.0 (-5.0 to 5.0)     |  |  |
| Change at Week 42 (n = 6, 7)            | -9.0 (-12.0 to -3.0)   | -1.0 (-6.0 to 1.0)     |  |  |
| Change at Week 48 (n = 6, 6)            | -6.0 (-7.0 to -2.0)    | 1.0 (-1.0 to 2.0)      |  |  |
| Change at Extension Month 3 (n = 6, 5)  | -8.0 (-12.0 to -3.0)   | -1.0 (-7.0 to 7.0)     |  |  |
| Change at Extension Month 6 (n = 3, 2)  | -12.0 (-27.0 to -1.0)  | -1.5 (-6.0 to 3.0)     |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -6.0 (-11.0 to 1.0)    |  |  |
| Change at Extension Month 12 (n = 1, 1) | -34.0 (-34.0 to -34.0) | -2.0 (-2.0 to -2.0)    |  |  |

|   |                        |                  |  |  |
|---|------------------------|------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | -32.0 (-32.0 to -32.0) | 1.0 (1.0 to 1.0) |  |  |
|---|------------------------|------------------|--|--|

Notes:

[291] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Aspartate Aminotransferase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Aspartate Aminotransferase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 11 <sup>[292]</sup>    | 10                     |  |  |
| Units: U/L                              |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 11, 10)           | -4.0 (-11.0 to 3.0)    | -1.0 (-13.0 to 6.0)    |  |  |
| Change at Week 6 (n = 8, 8)             | -4.0 (-12.0 to 0.5)    | 10.5 (-3.5 to 23.5)    |  |  |
| Change at Week 12 (n = 7, 7)            | 0.0 (-5.0 to 19.0)     | 18.0 (-3.0 to 29.0)    |  |  |
| Change at Week 18 (n = 8, 8)            | -1.5 (-7.5 to 5.5)     | -5.0 (-10.5 to 4.5)    |  |  |
| Change at Week 24 (n = 5, 6)            | -7.0 (-13.0 to -2.0)   | -2.0 (-7.0 to 1.0)     |  |  |
| Change at Week 30 (n = 6, 6)            | -10.0 (-12.0 to -3.0)  | 1.0 (-2.0 to 9.0)      |  |  |
| Change at Week 36 (n = 6, 7)            | 19.5 (-10.0 to 34.0)   | 2.0 (-4.0 to 15.0)     |  |  |
| Change at Week 42 (n = 6, 7)            | -3.5 (-14.0 to 8.0)    | 1.0 (-2.0 to 39.0)     |  |  |
| Change at Week 48 (n = 6, 6)            | -12.0 (-22.0 to 7.0)   | 0.5 (-15.0 to 20.0)    |  |  |
| Change at Extension Month 3 (n = 6, 5)  | -6.5 (-11.0 to 6.0)    | -12.0 (-15.0 to 6.0)   |  |  |
| Change at Extension Month 6 (n = 3, 2)  | -16.0 (-32.0 to 1.0)   | -0.5 (-21.0 to 20.0)   |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -8.5 (-33.0 to 16.0)   |  |  |
| Change at Extension Month 12 (n = 1, 1) | -33.0 (-33.0 to -33.0) | 19.0 (19.0 to 19.0)    |  |  |

|   |                        |                     |  |  |
|---|------------------------|---------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | -34.0 (-34.0 to -34.0) | 16.0 (16.0 to 16.0) |  |  |
|---|------------------------|---------------------|--|--|

Notes:

[292] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Gamma Glutamyl Transferase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Gamma Glutamyl Transferase at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 10 <sup>[293]</sup>    | 10                     |  |  |
| Units: U/L                              |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 10, 10)           | -12.5 (-27.0 to -2.0)  | -13.5 (-54.0 to -1.0)  |  |  |
| Change at Week 6 (n = 9, 9)             | -11.0 (-28.0 to -3.0)  | 0.0 (-31.0 to 4.0)     |  |  |
| Change at Week 12 (n = 7, 7)            | -13.0 (-32.0 to -3.0)  | -2.0 (-44.0 to 7.0)    |  |  |
| Change at Week 18 (n = 8, 8)            | -9.5 (-28.0 to 0.5)    | -3.5 (-38.5 to 1.5)    |  |  |
| Change at Week 24 (n = 5, 7)            | 8.0 (-37.0 to 25.0)    | -14.0 (-70.0 to -5.0)  |  |  |
| Change at Week 30 (n = 5, 6)            | -9.0 (-22.0 to 5.0)    | -12.5 (-27.0 to 5.0)   |  |  |
| Change at Week 36 (n = 6, 8)            | -5.5 (-12.0 to 24.0)   | -10.5 (-90.0 to 4.5)   |  |  |
| Change at Week 42 (n = 6, 7)            | -12.0 (-26.0 to 5.0)   | -4.0 (-154.0 to 17.0)  |  |  |
| Change at Week 48 (n = 6, 6)            | -9.0 (-21.0 to 6.0)    | -15.0 (-112.0 to 9.0)  |  |  |
| Change at Extension Month 3 (n = 6, 5)  | -9.5 (-48.0 to 1.0)    | 9.0 (-14.0 to 22.0)    |  |  |
| Change at Extension Month 6 (n = 3, 2)  | -10.0 (-35.0 to -9.0)  | -58.5 (-137.0 to 20.0) |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -57.0 (-128.0 to 14.0) |  |  |
| Change at Extension Month 12 (n = 1, 1) | -74.0 (-74.0 to -74.0) | 8.0 (8.0 to 8.0)       |  |  |

|   |                        |                  |  |  |
|---|------------------------|------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | -63.0 (-63.0 to -63.0) | 2.0 (2.0 to 2.0) |  |  |
|---|------------------------|------------------|--|--|

Notes:

[293] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Prothrombin INR at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Prothrombin INR at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|---|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo              | Obeticholic Acid (OCA) |  |  |
|---|----------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed             | 11                   | 10 <sup>[294]</sup>    |  |  |
| Units: INR                              |                      |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                      |                        |  |  |
| Change at Week 3 (n = 11, 10)           | 0.00 (0.00 to 0.10)  | 0.00 (0.00 to 0.10)    |  |  |
| Change at Week 6 (n = 9, 9)             | 0.00 (-0.03 to 0.00) | 0.00 (-0.05 to 0.00)   |  |  |
| Change at Week 12 (n = 6, 7)            | 0.08 (0.00 to 0.15)  | -0.05 (-0.10 to 0.00)  |  |  |
| Change at Week 18 (n = 8, 8)            | 0.09 (0.00 to 0.10)  | -0.05 (-0.13 to 0.05)  |  |  |
| Change at Week 24 (n = 4, 5)            | 0.03 (-0.02 to 0.08) | -0.05 (-0.10 to 0.05)  |  |  |
| Change at Week 30 (n = 6, 6)            | 0.03 (-0.03 to 0.10) | 0.00 (-0.10 to 0.00)   |  |  |
| Change at Week 36 (n = 6, 8)            | 0.05 (0.00 to 0.10)  | -0.10 (-0.18 to 0.03)  |  |  |
| Change at Week 42 (n = 6, 7)            | 0.05 (0.00 to 0.07)  | 0.00 (-0.10 to 0.05)   |  |  |
| Change at Week 48 (n = 6, 5)            | 0.00 (-0.03 to 0.05) | -0.10 (-0.15 to 0.00)  |  |  |
| Change at Extension Month 3 (n = 6, 5)  | 0.06 (0.00 to 0.10)  | -0.10 (-0.10 to -0.10) |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 0.05 (-0.10 to 0.15) | -0.05 (-0.10 to 0.00)  |  |  |
| Change at Extension Month 9 (n = 1, 2)  | 0.15 (0.15 to 0.15)  | 0.00 (0.00 to 0.00)    |  |  |
| Change at Extension Month 12 (n = 1, 1) | 0.05 (0.05 to 0.05)  | 0.10 (0.10 to 0.10)    |  |  |

|   |                     |                        |  |  |
|---|---------------------|------------------------|--|--|
| Change at Extension Month 15 (n = 1, 0) | 0.05 (0.05 to 0.05) | 99999 (99999 to 99999) |  |  |
|---|---------------------|------------------------|--|--|

Notes:

[294] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Creatinine at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Creatinine at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                   | Obeticholic Acid (OCA)    |  |  |
|---|---------------------------|---------------------------|--|--|
| Subject group type                      | Subject analysis set      | Subject analysis set      |  |  |
| Number of subjects analysed             | 11 <sup>[295]</sup>       | 10                        |  |  |
| Units: µmol/L                           |                           |                           |  |  |
| median (inter-quartile range (Q1-Q3))   |                           |                           |  |  |
| Change at Week 3 (n = 11, 10)           | 0.884 (-3.000 to 5.000)   | -0.308 (-2.000 to 1.768)  |  |  |
| Change at Week 6 (n = 9, 9)             | 5.000 (0.388 to 5.746)    | 0.884 (-1.000 to 4.000)   |  |  |
| Change at Week 12 (n = 7, 7)            | -0.496 (-4.000 to 13.500) | 2.500 (-1.000 to 5.000)   |  |  |
| Change at Week 18 (n = 8, 8)            | -2.431 (-4.958 to 7.250)  | 0.942 (-6.170 to 5.036)   |  |  |
| Change at Week 24 (n = 5, 7)            | -1.000 (-4.000 to -0.496) | -2.652 (-11.492 to 5.000) |  |  |
| Change at Week 30 (n = 6, 6)            | -0.663 (-4.032 to 1.768)  | -2.250 (-6.188 to 3.000)  |  |  |
| Change at Week 36 (n = 6, 8)            | 1.500 (-1.326 to 7.000)   | 2.466 (-1.960 to 33.586)  |  |  |
| Change at Week 42 (n = 6, 7)            | 2.000 (-1.326 to 4.000)   | 6.236 (-2.652 to 28.000)  |  |  |
| Change at Week 48 (n = 6, 6)            | 2.221 (-3.536 to 6.000)   | 0.466 (-3.000 to 20.000)  |  |  |
| Change at Extension Month 3 (n = 6, 5)  | 3.884 (0.000 to 6.630)    | 0.000 (-1.500 to 12.000)  |  |  |
| Change at Extension Month 6 (n = 3, 2)  | 2.652 (-4.000 to 12.818)  | 4.648 (-7.500 to 16.796)  |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999)    | 15.068 (4.500 to 25.636)  |  |  |
| Change at Extension Month 12 (n = 1, 1) | 10.608 (10.608 to 10.608) | 27.404 (27.404 to 27.404) |  |  |



|   |                        |                           |  |  |
|---|------------------------|---------------------------|--|--|
| Change at Extension Month 15 (n = 1, 1) | 4.420 (4.420 to 4.420) | 29.172 (29.172 to 29.172) |  |  |
|---|------------------------|---------------------------|--|--|

Notes:

[295] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Albumin at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Albumin at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
|-----------------|---|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

| End point values                        | Placebo                | Obeticholic Acid (OCA)    |  |  |
|---|------------------------|---------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set      |  |  |
| Number of subjects analysed             | 10 <sup>[296]</sup>    | 10                        |  |  |
| Units: g/L                              |                        |                           |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                           |  |  |
| Change at Week 3 (n = 10, 10)           | -2.25 (-2.50 to -1.00) | -0.50 (-1.70 to 0.00)     |  |  |
| Change at Week 6 (n = 9, 9)             | -1.00 (-3.00 to 0.00)  | 0.00 (-1.00 to 1.30)      |  |  |
| Change at Week 12 (n = 7, 7)            | -2.00 (-4.00 to -1.50) | -0.70 (-1.00 to 1.50)     |  |  |
| Change at Week 18 (n = 8, 8)            | -4.25 (-5.00 to -1.50) | 0.00 (-1.60 to 0.50)      |  |  |
| Change at Week 24 (n = 5, 7)            | -2.50 (-4.00 to -1.00) | -2.50 (-2.70 to 1.00)     |  |  |
| Change at Week 30 (n = 6, 6)            | -2.50 (-4.00 to -2.00) | 0.15 (-1.50 to 1.00)      |  |  |
| Change at Week 36 (n = 6, 8)            | -2.00 (-3.00 to -2.00) | 0.50 (-2.35 to 2.25)      |  |  |
| Change at Week 42 (n = 6, 7)            | -1.25 (-4.00 to 0.00)  | -0.70 (-1.00 to 2.00)     |  |  |
| Change at Week 48 (n = 6, 6)            | -0.50 (-2.00 to 1.00)  | 0.50 (-4.70 to 1.00)      |  |  |
| Change at Extension Month 3 (n = 6, 5)  | -2.50 (-3.00 to -1.00) | 1.00 (-2.70 to 2.50)      |  |  |
| Change at Extension Month 6 (n = 3, 2)  | -2.00 (-3.00 to -1.00) | -0.35 (-1.70 to 1.00)     |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -1.35 (-3.70 to 1.00)     |  |  |
| Change at Extension Month 12 (n = 1, 1) | -1.00 (-1.00 to -1.00) | -2.70 (-2.70 to -2.70)    |  |  |
| Change at Extension Month 15 (n = 1, 1) | -1.00 (-1.00 to -1.00) | -11.70 (-11.70 to -11.70) |  |  |

Notes:

[296] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Platelets at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15

|  |   |
|--|---|
| End point title  | Change From Baseline in Platelets at Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |
| End point description:   |   |
| APD: Participants in the ITT population with available data were analyzed.                     |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and Extension Months 3, 6, 9, 12, and 15 |   |

| End point values                        | Placebo                | Obeticholic Acid (OCA) |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed             | 10 <sup>[297]</sup>    | 9                      |  |  |
| Units: 10 <sup>9</sup> /L               |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                        |                        |  |  |
| Change at Week 3 (n = 10, 9)            | -6.2 (-21.0 to -3.0)   | -7.5 (-12.0 to 8.5)    |  |  |
| Change at Week 6 (n = 8, 6)             | -12.0 (-28.8 to -2.3)  | 15.0 (1.0 to 26.5)     |  |  |
| Change at Week 12 (n = 6, 5)            | -10.5 (-31.0 to 7.5)   | -15.0 (-15.0 to -1.5)  |  |  |
| Change at Week 18 (n = 6, 7)            | -15.0 (-21.9 to -8.5)  | 7.5 (-10.0 to 38.5)    |  |  |
| Change at Week 24 (n = 5, 6)            | 4.5 (-14.4 to 17.0)    | -1.5 (-25.0 to 25.5)   |  |  |
| Change at Week 30 (n = 6, 5)            | -11.4 (-23.5 to 15.0)  | -5.5 (-9.0 to 6.5)     |  |  |
| Change at Week 36 (n = 6, 6)            | -16.5 (-20.5 to -12.0) | 9.8 (-6.5 to 39.5)     |  |  |
| Change at Week 42 (n = 6, 6)            | -16.2 (-37.5 to -10.0) | 9.0 (6.5 to 11.0)      |  |  |
| Change at Week 48 (n = 5, 5)            | 4.0 (-41.5 to 23.0)    | -9.0 (-11.5 to 14.5)   |  |  |
| Change at Extension Month 3 (n = 6, 5)  | -5.0 (-24.0 to 16.5)   | -11.5 (-24.0 to -8.5)  |  |  |
| Change at Extension Month 6 (n = 3, 1)  | 48.5 (14.0 to 78.0)    | -0.5 (-0.5 to -0.5)    |  |  |
| Change at Extension Month 9 (n = 0, 2)  | 99999 (99999 to 99999) | -4.5 (-5.5 to -3.5)    |  |  |
| Change at Extension Month 12 (n = 1, 1) | -2.0 (-2.0 to -2.0)    | -3.5 (-3.5 to -3.5)    |  |  |
| Change at Extension Month 15 (n = 1, 1) | -9.0 (-9.0 to -9.0)    | -22.5 (-22.5 to -22.5) |  |  |

Notes:

[297] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Total Bile Acids Concentration at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Total Bile Acids Concentration at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3 |
|-----------------|--|

End point description:

Total bile acids (micromole [ $\mu\text{M}$ ]) = total ursodeoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$  + total chenodeoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$  + total deoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$  + total cholic acid (unconjugated, glyco-conjugate, tauroconjugate) in  $\mu\text{M}$  + total lithocholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$ .

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 6, 12, 18, 24, 30, 36, 48; and Extension Month 3

| End point values                       | Placebo                | Obeticholic Acid (OCA) |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                     | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed            | 7 <sup>[298]</sup>     | 8                      |  |  |
| Units: $\mu\text{M}$                   |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))  |                        |                        |  |  |
| Change at Week 6 (n = 7, 8)            | 16.3 (-7.68 to 37.4)   | 8.09 (-15.9 to 37.1)   |  |  |
| Change at Week 12 (n = 6, 6)           | 0.863 (-21.0 to 88.4)  | 5.55 (-58.4 to 13.7)   |  |  |
| Change at Week 18 (n = 7, 7)           | 17.7 (-56.0 to 160)    | 12.8 (-169 to 36.0)    |  |  |
| Change at Week 24 (n = 4, 4)           | 3.29 (-76.6 to 30.6)   | -3.14 (-14.5 to 21.3)  |  |  |
| Change at Week 30 (n = 4, 6)           | 26.0 (-56.0 to 98.5)   | 16.1 (-7.06 to 38.7)   |  |  |
| Change at Week 36 (n = 5, 8)           | -15.2 (-79.4 to 10.0)  | -1.54 (-22.9 to 24.6)  |  |  |
| Change at Week 48 (n = 4, 5)           | 63.2 (16.7 to 132)     | 0.876 (-4.07 to 19.5)  |  |  |
| Change at Extension Month 3 (n = 0, 1) | 99999 (99999 to 99999) | -32.9 (-32.9 to -32.9) |  |  |

Notes:

[298] - 99999 denotes data not available as there were no participants.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Total Endogenous Bile Acids Concentration at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Total Endogenous Bile Acids Concentration at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3 |
|-----------------|---|

End point description:

Total endogenous bile acids ( $\mu\text{M}$ ) = total chenodeoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$  + total deoxycholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$  + total cholic acid (unconjugated, glycoconjugate, tauro-conjugate) in  $\mu\text{M}$  + total lithocholic acid (unconjugated, glyco-conjugate, tauro-conjugate) in  $\mu\text{M}$ .

APD: Participants in the ITT population with available data were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3

| End point values                       | Placebo                 | Obeticholic Acid (OCA) |  |  |
|--|-------------------------|------------------------|--|--|
| Subject group type                     | Subject analysis set    | Subject analysis set   |  |  |
| Number of subjects analysed            | 7 <sup>[299]</sup>      | 9                      |  |  |
| Units: $\mu\text{M}$                   |                         |                        |  |  |
| median (inter-quartile range (Q1-Q3))  |                         |                        |  |  |
| Change at Week 6 (n = 7, 9)            | -4.98 (-6.88 to 36.2)   | 3.58 (-5.64 to 14.0)   |  |  |
| Change at Week 12 (n = 6, 6)           | -3.97 (-13.3 to 63.9)   | 1.46 (-5.43 to 4.81)   |  |  |
| Change at Week 18 (n = 7, 7)           | -5.00 (-20.2 to 51.0)   | 3.98 (-18.3 to 7.21)   |  |  |
| Change at Week 24 (n = 4, 6)           | -6.76 (-18.5 to -1.25)  | 3.18 (-2.53 to 15.2)   |  |  |
| Change at Week 30 (n = 5, 6)           | 6.74 (-6.22 to 7.44)    | 1.47 (-3.87 to 13.6)   |  |  |
| Change at Week 36 (n = 6, 8)           | -5.74 (-24.9 to -0.576) | -2.69 (-14.4 to 9.66)  |  |  |
| Change at Week 48 (n = 6, 6)           | 10.9 (6.32 to 19.8)     | 4.18 (-2.08 to 9.82)   |  |  |
| Change at Extension Month 3 (n = 0, 1) | 99999 (99999 to 99999)  | -9.57 (-9.57 to -9.57) |  |  |

Notes:

[299] - 99999 denotes data not available as there were no participants.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4) at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4) at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3 |
|-----------------|--|

End point description:

APD: Participants in the ITT population with available data were analyzed.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3 |           |

| End point values                       | Placebo                      | Obeticholic Acid (OCA)   |  |  |
|--|------------------------------|--------------------------|--|--|
| Subject group type                     | Subject analysis set         | Subject analysis set     |  |  |
| Number of subjects analysed            | 8 <sup>[300]</sup>           | 9                        |  |  |
| Units: ng/mL                           |                              |                          |  |  |
| median (inter-quartile range (Q1-Q3))  |                              |                          |  |  |
| Change at Week 6 (n = 8, 9)            | 0.0990 (-0.0445 to 0.296)    | 0.0770 (-0.110 to 0.450) |  |  |
| Change at Week 12 (n = 6, 7)           | -0.0275 (-0.0690 to 0.156)   | -0.289 (-1.31 to 0.0100) |  |  |
| Change at Week 18 (n = 7, 8)           | -0.0470 (-0.278 to 0.205)    | -0.267 (-0.965 to 0.805) |  |  |
| Change at Week 24 (n = 4, 6)           | -0.00100 (-0.00700 to 0.692) | -0.141 (-1.67 to 1.07)   |  |  |
| Change at Week 30 (n = 5, 6)           | 0.0890 (0.0500 to 0.355)     | -0.386 (-1.77 to 2.50)   |  |  |
| Change at Week 36 (n = 6, 8)           | 0.118 (-0.104 to 0.240)      | -0.476 (-3.53 to 5.41)   |  |  |
| Change at Week 48 (n = 6, 6)           | -0.170 (-0.491 to -0.0140)   | -0.510 (-1.83 to 5.20)   |  |  |
| Change at Extension Month 3 (n = 0, 1) | 99999 (99999 to 99999)       | 1.36 (1.36 to 1.36)      |  |  |

Notes:

[300] - 99999 denotes data not available as there were no participants.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Fibroblast Growth Factor-19 (FGF-19) Concentrations at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3

|  |   |
|--|---|
| End point title  | Change From Baseline in Fibroblast Growth Factor-19 (FGF-19) Concentrations at Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3 |
| End point description:   |   |
| APD: Participants in the ITT population with available data were analyzed. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Weeks 6, 12, 18, 24, 30, 36, and 48; and Extension Month 3       |   |

| <b>End point values</b>                 | Placebo              | Obeticholic Acid (OCA) |  |  |
|---|----------------------|------------------------|--|--|
| Subject group type                      | Subject analysis set | Subject analysis set   |  |  |
| Number of subjects analysed             | 8                    | 9                      |  |  |
| Units: picograms per milliliter (pg/mL) |                      |                        |  |  |
| median (inter-quartile range (Q1-Q3))   |                      |                        |  |  |
| Change at Week 6 (n = 8, 9)             | -50.7 (-142 to 33.0) | 26.0 (4.50 to 101)     |  |  |
| Change at Week 12 (n = 6, 7)            | -14.0 (-220 to 19.0) | 119 (-25.6 to 174)     |  |  |
| Change at Week 18 (n = 7, 8)            | -57.0 (-118 to 40.0) | 136 (-28.3 to 298)     |  |  |
| Change at Week 24 (n = 4, 6)            | -33.0 (-152 to 402)  | 16.6 (-24.0 to 219)    |  |  |
| Change at Week 30 (n = 5, 6)            | -83.0 (-123 to 43.0) | 142 (-45.0 to 168)     |  |  |
| Change at Week 36 (n = 6, 8)            | 26.0 (-34.0 to 102)  | 15.0 (-97.4 to 201)    |  |  |
| Change at Week 48 (n = 6, 6)            | -28.5 (-161 to 84.5) | 69.6 (8.00 to 145)     |  |  |
| Change at Extension Month 3 (n = 1, 1)  | -117 (-117 to -117)  | 0 (0 to 0)             |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 3 years

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Obeticholic Acid (OCA) |
|-----------------------|------------------------|

Reporting group description:

Participants initiated treatment with OCA 5 mg tablets orally once weekly. At Week 12, if there were no safety concerns, the dose was up-titrated to OCA 5 mg twice weekly. Every 6 weeks thereafter, based on tolerability assessments, further up-titration of dose was considered. At each titration visit, the participants started the higher dose regimen no earlier than 2 days after the prior dose. The maximum dose titration was OCA 10 mg twice weekly at least 3 days apart. The minimum treatment duration was 48 Weeks. Participants, who had completed their 48 Week treatment, could continue the treatment until all randomized participants had completed their 48 Week treatment period and the database for that period was locked (total duration: approximately up to 3 years).

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received OCA matching placebo tablets orally once weekly or twice weekly for the duration of at least 48 Weeks. Participants, who had completed their 48 Week treatment, could continue the treatment until all randomized participants had completed their 48 Week treatment period and the database for that period was locked (total duration: approximately up to 3 years).

| Serious adverse events                            | Obeticholic Acid (OCA) | Placebo         |  |
|---|------------------------|-----------------|--|
| Total subjects affected by serious adverse events |                        |                 |  |
| subjects affected / exposed                       | 7 / 10 (70.00%)        | 9 / 12 (75.00%) |  |
| number of deaths (all causes)                     | 2                      | 2               |  |
| number of deaths resulting from adverse events    |                        |                 |  |
| Vascular disorders                                |                        |                 |  |
| Aortic aneurysm rupture                           |                        |                 |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)         | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all   | 0 / 0                  | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0                  | 0 / 1           |  |
| Cardiac disorders                                 |                        |                 |  |
| Acute myocardial infarction                       |                        |                 |  |
| subjects affected / exposed                       | 1 / 10 (10.00%)        | 0 / 12 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1                  | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0                  | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Cardiac arrest                                       |                 |                 |  |
| subjects affected / exposed                          | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Liver transplant                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                             |                 |                 |  |
| Hepatic encephalopathy                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 2 / 12 (16.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| General disorders and administration site conditions |                 |                 |  |
| Pyrexia  |                 |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Blood and lymphatic system disorders                 |                 |                 |  |
| Pancytopenia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                           |                 |                 |  |
| Abdominal pain                                       |                 |                 |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 2 / 12 (16.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Ascites  |                 |                 |  |



|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Upper gastrointestinal haemorrhage              |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Oesophageal varices haemorrhage                 |                 |                |  |
| subjects affected / exposed                     | 3 / 10 (30.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatobiliary disorders                         |                 |                |  |
| Hepatic failure                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatic function abnormal                       |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Pneumonia aspiration                            |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hydrothorax                                     |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal and urinary disorders                     |                 |                |  |
| Acute kidney injury                             |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Infections and infestations                     |                 |                |  |
| COVID-19  |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pneumonia                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Obeticholic Acid (OCA) | Placebo          |  |
|---|------------------------|------------------|--|
| Total subjects affected by non-serious adverse events               |                        |                  |  |
| subjects affected / exposed   | 10 / 10 (100.00%)      | 10 / 12 (83.33%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                  |  |
| Pituitary tumour benign   |                        |                  |  |
| subjects affected / exposed   | 1 / 10 (10.00%)        | 0 / 12 (0.00%)   |  |
| occurrences (all)   | 1                      | 0                |  |
| Vascular disorders  |                        |                  |  |
| Peripheral coldness   |                        |                  |  |
| subjects affected / exposed   | 1 / 10 (10.00%)        | 0 / 12 (0.00%)   |  |
| occurrences (all)   | 1                      | 0                |  |
| Haematoma   |                        |                  |  |
| subjects affected / exposed   | 0 / 10 (0.00%)         | 1 / 12 (8.33%)   |  |
| occurrences (all)   | 0                      | 2                |  |
| Haemorrhage   |                        |                  |  |
| subjects affected / exposed   | 0 / 10 (0.00%)         | 1 / 12 (8.33%)   |  |
| occurrences (all)   | 0                      | 1                |  |
| General disorders and administration site conditions                |                        |                  |  |
| Fatigue   |                        |                  |  |
| subjects affected / exposed   | 2 / 10 (20.00%)        | 1 / 12 (8.33%)   |  |
| occurrences (all)   | 3                      | 1                |  |
| Chest discomfort  |                        |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Disease progression                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 4 / 12 (33.33%) |  |
| occurrences (all)                               | 1               | 4               |  |
| Asthenia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                               | 0               | 4               |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Vaginal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Breast pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 10 (20.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 2               | 0               |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Haemoptysis                                     |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Investigations   |                      |                      |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 10 (10.00%)<br>1 | 1 / 12 (8.33%)<br>1  |  |
| Blood urea increased<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Cardiac murmur<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Injury, poisoning and procedural complications   |                      |                      |  |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 10 (10.00%)<br>1 | 2 / 12 (16.67%)<br>2 |  |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 10 (0.00%)<br>0  | 2 / 12 (16.67%)<br>2 |  |
| Cardiac disorders  |                      |                      |  |
| Coronary artery disease<br>subjects affected / exposed<br>occurrences (all)              | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Nervous system disorders   |                      |                      |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 10 (20.00%)<br>2 | 1 / 12 (8.33%)<br>1  |  |

|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| Burning sensation                    |                 |                 |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Balance disorder                     |                 |                 |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Encephalopathy                       |                 |                 |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 1               | 1               |  |
| Hypoaesthesia                        |                 |                 |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 1               | 1               |  |
| Hepatic encephalopathy               |                 |                 |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Neuralgia                            |                 |                 |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Memory impairment                    |                 |                 |  |
| subjects affected / exposed          | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Headache                             |                 |                 |  |
| subjects affected / exposed          | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Sciatica                             |                 |                 |  |
| subjects affected / exposed          | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Blood and lymphatic system disorders |                 |                 |  |
| Anaemia                              |                 |                 |  |
| subjects affected / exposed          | 3 / 10 (30.00%) | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 3               | 1               |  |
| Iron deficiency anaemia              |                 |                 |  |
| subjects affected / exposed          | 0 / 10 (0.00%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                    | 0               | 2               |  |
| Ear and labyrinth disorders          |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Ear pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Eye disorders  |                      |                      |  |
| Vitreous floaters<br>subjects affected / exposed<br>occurrences (all)    | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)       | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Gastrointestinal disorders   |                      |                      |  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)              | 6 / 10 (60.00%)<br>6 | 4 / 12 (33.33%)<br>4 |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 2 / 10 (20.00%)<br>2 | 3 / 12 (25.00%)<br>3 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 2 / 10 (20.00%)<br>3 | 1 / 12 (8.33%)<br>2  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 2 / 10 (20.00%)<br>3 | 2 / 12 (16.67%)<br>3 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 2 / 10 (20.00%)<br>4 | 1 / 12 (8.33%)<br>1  |  |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>3 | 1 / 12 (8.33%)<br>1  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)           | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Frequent bowel movements   |                      |                      |  |

|                                 |                 |                 |
|---------------------------------|-----------------|-----------------|
| subjects affected / exposed     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |
| occurrences (all)               | 1               | 0               |
| Haematemesis                    |                 |                 |
| subjects affected / exposed     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |
| occurrences (all)               | 1               | 0               |
| Haemorrhoids                    |                 |                 |
| subjects affected / exposed     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |
| occurrences (all)               | 1               | 0               |
| Melaena                         |                 |                 |
| subjects affected / exposed     | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |
| occurrences (all)               | 1               | 0               |
| Abdominal pain lower            |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Abdominal pain upper            |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Constipation                    |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 2 / 12 (16.67%) |
| occurrences (all)               | 0               | 2               |
| Dry mouth                       |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Gastric antral vascular ectasia |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Gastric polyps                  |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Irritable bowel syndrome        |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Toothache                       |                 |                 |
| subjects affected / exposed     | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)               | 0               | 1               |
| Large intestine polyp           |                 |                 |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Portal hypertensive gastropathy<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Varices oesophageal<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 10 (20.00%)<br>3 | 1 / 12 (8.33%)<br>1  |  |
| Hepatobiliary disorders<br>Portal vein thrombosis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 10 (20.00%)<br>2 | 1 / 12 (8.33%)<br>1  |  |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | 3 / 10 (30.00%)<br>4 | 2 / 12 (16.67%)<br>4 |  |
| Skin mass<br>subjects affected / exposed<br>occurrences (all)  | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Palmar erythema<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all) | 2 / 10 (20.00%)<br>3 | 1 / 12 (8.33%)<br>3  |  |
| Endocrine disorders<br>Thyroid mass<br>subjects affected / exposed<br>occurrences (all)                | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue  |                      |                      |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| disorders                              |                 |                 |  |
| Pain in extremity                      |                 |                 |  |
| subjects affected / exposed            | 2 / 10 (20.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 3               | 0               |  |
| Arthralgia                             |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 2 / 12 (16.67%) |  |
| occurrences (all)                      | 2               | 3               |  |
| Limb mass                              |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Muscular weakness                      |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Rhabdomyolysis                         |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Back pain                              |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                      | 0               | 2               |  |
| Muscle spasms                          |                 |                 |  |
| subjects affected / exposed            | 0 / 10 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Infections and infestations            |                 |                 |  |
| Pneumonia                              |                 |                 |  |
| subjects affected / exposed            | 2 / 10 (20.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 2               | 0               |  |
| Urinary tract infection                |                 |                 |  |
| subjects affected / exposed            | 3 / 10 (30.00%) | 2 / 12 (16.67%) |  |
| occurrences (all)                      | 3               | 2               |  |
| Oesophageal candidiasis                |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Cytomegalovirus infection reactivation |                 |                 |  |
| subjects affected / exposed            | 1 / 10 (10.00%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1               | 0               |  |
| Herpes zoster                          |                 |                 |  |

|                                    |                 |                |  |
|------------------------------------|-----------------|----------------|--|
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |
| Upper respiratory tract infection  |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |
| Cellulitis                         |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Peritonitis bacterial              |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |
| Influenza                          |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Ear infection                      |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Fungal infection                   |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Skin infection                     |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Metabolism and nutrition disorders |                 |                |  |
| Hyperglycaemia                     |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |
| Hyperkalaemia                      |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                  | 1               | 1              |  |
| Hypokalaemia                       |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |
| Type 2 diabetes mellitus           |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                  | 1               | 0              |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| Dehydration                 |                |                |  |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)           | 0              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 22 May 2017      | <p>The changes in Version 2 were incorporated based on Food and Drug Administration (FDA) review of Version 1 of the protocol:</p> <ul style="list-style-type: none"><li>• Background information was included to estimate the exposure difference between healthy subjects and subjects with moderate hepatic impairment to support the rationale for dose selection</li><li>• Additional PK sampling times were added to adequately characterize the PK of OCA and its active metabolites at steady state in subjects with moderate and severe impairment when dosing weekly to biweekly</li><li>• The period between screening and Day 1 was extended to at least 14 days to establish a baseline for serum biomarkers with at least two samples two weeks apart</li><li>• The Week 3 contact Visit by email/telephone was changed to a Safety Visit to assess evidence of early hepatotoxicity</li><li>• Guidelines were added to assess subjects for evidence of hepatotoxicity at each visit</li></ul>  |
| 04 January 2018  | <ul style="list-style-type: none"><li>• The Introduction was revised to highlight the need for close monitoring specifically in subjects with clinical evidence of hepatic decompensation and other complications due to advanced cirrhosis.</li><li>• Dosing regimens were updated to modify dosing to one regimen for subjects with moderate and severe hepatic impairment [e.g., same for child-pugh B and child-pugh C ], not to exceed 10 mg twice weekly, to align with label dosing guidelines. Titration was then only based on tolerability and not CP score.</li><li>• Reference to an option for open-label treatment was removed. An open-label extension was to be considered only after review of blinded safety and PK data from the double-blind treatment period.</li><li>• Protocol was updated with discontinuation criteria for decompensation events and biochemical thresholds. A plan for monitoring and drug-induced liver injury algorithm was included to ensure careful monitoring and drug interruption/discontinuation. Analysis of decompensation events as adverse events of interest was added. Additionally, "Close Observation" per FDA Guidance for Industry on Drug Induced Liver Injury (DILI) was clearly defined in the protocol to ensure that subjects who experienced a potential DILI underwent a full evaluation.</li><li>• Guidance was added that subjects should have been instructed to contact the site promptly upon awareness if they developed signs and symptoms of potential hepatic decompensation.</li><li>• Guidance was added that the Investigator should have contacted the study Medical Monitor upon awareness when any signs and symptoms of hepatic decompensation were observed in any subject.</li><li>• Guidance was added for monitoring amylase and lipase levels in subjects with suspected acute pancreatitis.</li><li>• Gallbladder assessments were added at Screening or Day 1.</li></ul> |
| 15 February 2019 | <ul style="list-style-type: none"><li>• Updated clinical development data based on IB Version 18 (31 Jan 2019).</li><li>• Exclusion criteria were updated to mitigate the inclusion of subjects who may have been pregnant or breastfeeding as an additional safety precaution or who had a known history of human immunodeficiency syndrome infection.</li><li>• Exclusion criteria and prohibited medications sections were updated to prevent the concomitant use of fibrates and OCA. The primary objective of this study was to characterize the PK of OCA in subjects with PBC and mild to severe hepatic impairment. The drug-drug interactions of OCA with fibrates were not yet fully characterized in any population and were being restricted in this study as an additional safety precaution until data were available in a less advanced population.</li></ul>  |

|             |  |
|-------------|--|
| 19 May 2020 | <ul style="list-style-type: none"> <li>Addendum was issued to multiple countries to describe the requirements and processes under which subjects who were unable to return to study sites during the COVID-19 pandemic may have completed protocol specified assessments and continued to receive investigational product until in-person site visits could resume.</li> </ul> |
|-------------|--|

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported