



Clinical trial results:

Phase III trial in IntrahepaTic CHolestasis of pregnancy (ICP) to Evaluate urSodeoxycholic acid (UDCA) in improving perinatal outcomes

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-004478-41 |
| Trial protocol | GB |
| Global end of trial date | 28 November 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 03 July 2019 |
| First version publication date | 03 July 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | LCC001 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|------------------------|
| ISRCTN number | ISRCTN91918806 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | REC number: 15/EE/0010 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | King's College London |
| Sponsor organisation address | The Strand, London, United Kingdom, WC2R 2LS |
| Public contact | Dr Lucy Chappell, King's College London, 0044 2071883639, lucy.chappell@kcl.ac.uk |
| Scientific contact | Dr Lucy Chappell, King's College London, 0044 2071883639, lucy.chappell@kcl.ac.uk |
| Sponsor organisation name | Guy's and St Thomas' NHS Foundation Trust |
| Sponsor organisation address | Great Maze Pond, London, United Kingdom, SE19RT |
| Public contact | Dr Lucy Chappell, Guy's and St Thomas' NHS Foundation Trust, 0044 2071883639, lucy.chappell@kcl.ac.uk |
| Scientific contact | Dr Lucy Chappell, Guy's and St Thomas' NHS Foundation Trust, 0044 2071883639, lucy.chappell@kcl.ac.uk |

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 | 06 December 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Intrahepatic cholestasis of pregnancy (ICP), or obstetric cholestasis (OC) is a liver condition of pregnancy. Pregnant women diagnosed with ICP are more at risk of suffering from in utero fetal death, stillbirth, perinatal death (under 7 days), preterm delivery (less than 37 weeks' gestation) and neonatal unit admission. The principal research question asks: does treatment with ursodeoxycholic acid (UDCA) in ICP women, increase the chance of having a healthy baby, by reducing the problems listed above?

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 01 September 2015 |
| 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 | United Kingdom: 605 |
| Worldwide total number of subjects | 605 |
| EEA total number of subjects | 605 |

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) | 605 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total assessed for eligibility: 2737

Excluded - not eligible: 1319

Total eligible: 1418

Excluded - declined to participate: 813

Total randomised: 605

Period 1

| | |
|------------------------------|---|
| Period 1 title | Trial entry (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Allocation code was held by MedSciNet (database provider) and trials programmers at NPEU CTU only.

Arms

| | |
|------------------------------|------|
| Are arms mutually exclusive? | Yes |
| Arm title | UDCA |

Arm description:

Active treatment - Ursodeoxycholic Acid

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

Dosage and administration details:

The starting dose will be 1,000 mg daily (500 mg bd), increased in increments of 500 mg per day every 3-14 days if there is no biochemical or clinical improvement, based on clinical decision, to a maximum of 2,000 mg per day. The dose of IMP may be reduced to 500mg daily.

IMP will be continued until delivery. Divided doses will be spread evenly throughout the day. There is no need to take with or without food. This will be left to participant preference.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Identical tablets administered in the same dose increments orally.

| | |
|--|----------|
| 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:

The starting dose will be 1,000 mg daily (500 mg bd), increased in increments of 500 mg per day every 3-14 days if there is no biochemical or clinical improvement, based on clinical decision, to a maximum of 2,000 mg per day. The dose of IMP may be reduced to 500mg daily.

IMP will be continued until delivery. Divided doses will be spread evenly throughout the day. There is no

need to take with or without
food. This will be left to participant preference.

| Number of subjects in period 1 | UDCA | Placebo |
|---------------------------------------|------|---------|
| Started | 305 | 300 |
| Completed | 304 | 300 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | UDCA |
| Reporting group description: | |
| Active treatment - Ursodeoxycholic Acid | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Identical tablets administered in the same dose increments orally. | |

| Reporting group values | UDCA | Placebo | Total |
|---|-------|---------|-------|
| Number of subjects | 305 | 300 | 605 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 30.5 | 30.8 | |
| standard deviation | ± 5.6 | ± 5.3 | - |
| Gender categorical Units: Subjects | | | |
| Female | 305 | 300 | 605 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|-------------------------------|
| Reporting group title | UDCA |
| Reporting group description: Active treatment - Ursodeoxycholic Acid | |
| Reporting group title | Placebo |
| Reporting group description: Identical tablets administered in the same dose increments orally. | |
| Subject analysis set title | UDCA - Infants |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All infants born to women randomised to the UDCA arm, excluding post-randomisation exclusions | |
| Subject analysis set title | Placebo - Infants |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All infants born to women randomised to the placebo arm, excluding post-randomisation exclusions | |
| Subject analysis set title | UDCA - Maternal population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Women included in analysis allocated to UDCA arm | |
| Subject analysis set title | Placebo - Maternal population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Women included in analysis allocated to placebo arm | |

Primary: Perinatal death, preterm delivery, or neonatal unit admission for at least 4 hours

| | |
|--|--|
| End point title | Perinatal death, preterm delivery, or neonatal unit admission for at least 4 hours |
| End point description: Perinatal death - Defined by in utero fetal death after randomisation or neonatal death up to 7 days. Preterm delivery - Less than 37 weeks' gestation. Neonatal unit (NNU) admission for at least 4 hours - Between infant delivery and hospital discharge. | |
| End point type | Primary |
| End point timeframe: Between randomisation and discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 74 | 85 | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Adjusted effect estimate |
| Statistical analysis description: Poisson regression, adjusted for minimisation factors bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.279 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.15 |

| | |
|---|------------------------------------|
| Statistical analysis title | Unadjusted effect estimate |
| Comparison groups | Placebo - Infants v UDCA - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.273 |
| Method | Regression, Logistic |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.13 |

Secondary: In utero fetal death after randomisation

| | |
|---|--|
| End point title | In utero fetal death after randomisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: After randomisation | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 1 | 2 | | |

Statistical analyses

| Statistical analysis title | Adjusted effect estimate |
|--|------------------------------------|
| Statistical analysis description: | |
| Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.598 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 6.25 |

Secondary: Pre-term delivery (less than 37 weeks' gestation)

| End point title | Pre-term delivery (less than 37 weeks' gestation) |
|------------------------------------|---|
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Between randomisation and delivery | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 54 | 65 | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Adjusted effect estimate |
| Statistical analysis description: Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.171 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 1.1 |

Secondary: Known neonatal death up to 7 days

| | |
|------------------------|-----------------------------------|
| End point title | Known neonatal death up to 7 days |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Prior to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NNU admission for at least 4 hours until infant hospital discharge

| | |
|------------------------|--|
| End point title | NNU admission for at least 4 hours until infant hospital discharge |
| End point description: | |
| End point type | Secondary |

End point timeframe:
Until infant hospital discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 45 | 54 | | |

Statistical analyses

| Statistical analysis title | Adjusted effect estimate |
|----------------------------|--------------------------|
|----------------------------|--------------------------|

Statistical analysis description:

Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins.

| | |
|---|------------------------------------|
| Comparison groups | Placebo - Infants v UDCA - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.212 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 1.13 |

Secondary: Known neonatal death up to 28 days

| | |
|-----------------|------------------------------------|
| End point title | Known neonatal death up to 28 days |
|-----------------|------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Prior to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Live birth

| | |
|-----------------|------------|
| End point title | Live birth |
|-----------------|------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation to delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 321 | 316 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mode of delivery

| | |
|-----------------|------------------|
| End point title | Mode of delivery |
|-----------------|------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Spontaneous vaginal (cephalic) | 193 | 182 | | |
| Spontaneous vaginal (breech) | 1 | 3 | | |
| Assisted vaginal – ventouse (cephalic) | 2 | 15 | | |
| Assisted vaginal – forceps (cephalic) | 19 | 20 | | |
| Assisted vaginal (breech) | 0 | 0 | | |
| Caesarean section | 36 | 36 | | |
| Pre-labour Caesarean section | 71 | 62 | | |

Statistical analyses

| Statistical analysis title | Spontaneous vaginal (cephalic) vs other modes |
|--|---|
| Statistical analysis description: | |
| Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.562 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.2 |

| Statistical analysis title | Caesarean section vs. other modes of delivery |
|--|---|
| Statistical analysis description: | |
| Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.995 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.46 |

Secondary: Gestational age at delivery (weeks)

| | |
|------------------------|-------------------------------------|
| End point title | Gestational age at delivery (weeks) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to delivery | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 37.6 (37.1 to 38.1) | 37.4 (37.0 to 38.1) | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Adjusted median difference |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.065 |
| Method | Quantile regression |
| Parameter estimate | Median difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.3 |

Secondary: Birth weight

| | |
|-----------------|--------------|
| End point title | Birth weight |
|-----------------|--------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: grams | | | | |
| median (inter-quartile range (Q1-Q3)) | 3105 (2775 to 3390) | 3040 (2660 to 3320) | | |

Statistical analyses

| | |
|----------------------------|-------------------|
| Statistical analysis title | Median difference |
|----------------------------|-------------------|

Statistical analysis description:

Adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy.

| | |
|---|------------------------------------|
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 |
| Method | Quantile regression |
| Parameter estimate | Median difference (final values) |
| Point estimate | 94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.7 |
| upper limit | 169.3 |

Secondary: Birth weight centile

| | |
|-----------------|----------------------|
| End point title | Birth weight centile |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: centile | | | | |
| arithmetic mean (standard deviation) | 59.3 (\pm 28.4) | 56.3 (\pm 27.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Birth weight centile - < 10th customised centile

| | |
|------------------------|--|
| End point title | Birth weight centile - < 10th customised centile |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At delivery | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 16 | 18 | | |

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Adjusted risk ratio |
| Statistical analysis description: | |
| Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.725 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.69 |

Secondary: Birth weight centile - < 3rd customised centile

| | |
|-----------------|---|
| End point title | Birth weight centile - < 3rd customised centile |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 7 | 7 | | |

Statistical analyses

| | |
|----------------------------|---------------------|
| Statistical analysis title | Adjusted risk ratio |
|----------------------------|---------------------|

Statistical analysis description:

Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins.

| | |
|---|------------------------------------|
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.877 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 3.12 |

Secondary: Presence of meconium

| | |
|-----------------|----------------------|
| End point title | Presence of meconium |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 34 | 52 | | |
| No | 286 | 264 | | |
| Missing | 2 | 2 | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Adjusted risk ratio |
| Statistical analysis description: Poisson regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 640 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.43 |
| upper limit | 0.98 |

Secondary: APGAR score at 5 minutes post-birth

| | |
|---|-------------------------------------|
| End point title | APGAR score at 5 minutes post-birth |
| End point description: In live births only | |
| End point type | Secondary |
| End point timeframe: 5 minutes post-birth | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 316 | | |
| Units: score | | | | |
| median (inter-quartile range (Q1-Q3)) | 9.0 (9 to 10) | 9 (9 to 10) | | |

Statistical analyses

| Statistical analysis title | Median difference (adjusted) |
|---|------------------------------------|
| Statistical analysis description: | |
| Adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 637 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Quantile regression |
| Parameter estimate | Median difference (final values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.4 |

Secondary: APGAR score at 5 minutes post-birth - < 7

| End point title | APGAR score at 5 minutes post-birth - < 7 |
|------------------------|---|
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 5 minutes post-birth | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 316 | | |
| Units: Number of infants | | | | |
| < 7 | 8 | 7 | | |
| >= 7 | 313 | 309 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Umbilical cord arterial pH - collected

| | |
|-----------------|--|
| End point title | Umbilical cord arterial pH - collected |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | 114 | 112 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Umbilical cord arterial pH

| | |
|-----------------|----------------------------|
| End point title | Umbilical cord arterial pH |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At delivery

| End point values | UDCA - Infants | Placebo - Infants | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 112 ^[1] | 102 ^[2] | | |
| Units: pH | | | | |
| arithmetic mean (standard deviation) | 7.2 (± 0.1) | 7.2 (± 0.1) | | |

Notes:

[1] - 114 collected, 2 values missing

[2] - 112 collected, 10 values missing

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Mean difference (adjusted) |
|----------------------------|----------------------------|

Statistical analysis description:

Linear regression adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple

pregnancy, and centre as a random effect. Standard errors allow for intraclass correlation to account for non-independence of twins.

| | |
|---|------------------------------------|
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 214 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.182 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.01 |

Secondary: Number of nights in each category of care - Intensive

| | |
|---|---|
| End point title | Number of nights in each category of care - Intensive |
| End point description: | |
| in survivors to discharge | |
| End point type | Secondary |
| End point timeframe: | |
| Between birth and discharge from hospital | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 10 ^[3] | 16 ^[4] | | |
| Units: Number of nights | | | | |
| median (inter-quartile range (Q1-Q3)) | 3 (2 to 3) | 2 (1 to 2.5) | | |

Notes:

[3] - 10 infants spent at least 1 night in intensive care

[4] - 16 infants spent at least 1 night in intensive care

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nights in each category of care - High dependency

| | |
|---------------------------|---|
| End point title | Number of nights in each category of care - High dependency |
| End point description: | |
| in survivors to discharge | |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 ^[5] | 17 ^[6] | | |
| Units: Number of nights | | | | |
| median (inter-quartile range (Q1-Q3)) | 2 (1 to 5.5) | 3 (1 to 5) | | |

Notes:

[5] - 20 infants spent at least one night in high dependency care

[6] - 17 infants spent at least one night in high dependency care

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nights in each category of care - Special care

| | |
|------------------------|--|
| End point title | Number of nights in each category of care - Special care |
| End point description: | (with carer not present). In survivors to discharge. |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 ^[7] | 45 ^[8] | | |
| Units: Number of nights | | | | |
| median (inter-quartile range (Q1-Q3)) | 5 (3 to 12.5) | 5 (2 to 16) | | |

Notes:

[7] - 40 infants spent at least one night in special care

[8] - 45 infants spent at least one night in special care

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nights in each category of care - Transitional

| | |
|------------------------|--|
| End point title | Number of nights in each category of care - Transitional |
| End point description: | (with carer present). In survivors to discharge. |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 ^[9] | 34 ^[10] | | |
| Units: Number of nights | | | | |
| median (inter-quartile range (Q1-Q3)) | 3 (1 to 4) | 2 (1 to 4) | | |

Notes:

[9] - 31 infants spent at least one night in transitional care

[10] - 34 infants spent at least one night in transitional care

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nights in each category of care - Normal

| | |
|---------------------------|--|
| End point title | Number of nights in each category of care - Normal |
| End point description: | |
| In survivors to discharge | |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 246 ^[11] | 226 ^[12] | | |
| Units: Number of nights | | | | |
| median (inter-quartile range (Q1-Q3)) | 1 (1 to 2) | 2 (1 to 3) | | |

Notes:

[11] - 246 infants spent at least one night in Normal care

[12] - 226 infants spent at least one night in Normal care

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of nights in neonatal unit

| | |
|---------------------------|---|
| End point title | Total number of nights in neonatal unit |
| End point description: | |
| In survivors to discharge | |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 ^[13] | 53 ^[14] | | |
| Units: Number of nights | | | | |
| median (inter-quartile range (Q1-Q3)) | 5.5 (3 to 13) | 6 (2 to 16) | | |

Notes:

[13] - 44 infants spent at least one night in a neonatal unit

[14] - 53 infants spent at least one night in a neonatal unit

Statistical analyses

| Statistical analysis title | Median difference (adjusted) |
|---|------------------------------------|
| Statistical analysis description: | |
| Adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy. | |
| Comparison groups | UDCA - Infants v Placebo - Infants |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Quantile regression |
| Parameter estimate | Median difference (final values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 3.2 |

Secondary: Main diagnosis for first NNU admission of at least 4 hours

| | |
|------------------------|--|
| End point title | Main diagnosis for first NNU admission of at least 4 hours |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 45 ^[15] | 54 ^[16] | | |
| Units: Number of infants | | | | |
| Congenital anomaly suspected/confirmed | 1 | 0 | | |
| Continuing care | 0 | 1 | | |
| Convulsions suspected/confirmed | 1 | 0 | | |
| HIE suspected/confirmed | 1 | 0 | | |
| Hypoglycaemia | 3 | 5 | | |
| Infection suspected/confirmed | 5 | 7 | | |
| IUGR/SGA | 0 | 1 | | |
| Jaundice | 0 | 1 | | |
| Monitoring | 0 | 5 | | |
| NAS suspected/confirmed | 1 | 0 | | |
| Poor condition at birth | 1 | 1 | | |
| Poor feeding or weight loss | 1 | 1 | | |
| Prematurity | 14 | 17 | | |
| Respiratory disease | 16 | 15 | | |
| Surgery | 1 | 0 | | |

Notes:

[15] - 45 infants had NNU admission of at least 4 hours

[16] - 54 infants had NNU admission of at least 4 hours

Statistical analyses

No statistical analyses for this end point

Secondary: Need for supplementary oxygen prior to discharge

| | |
|-----------------|--|
| End point title | Need for supplementary oxygen prior to discharge |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | | | | |
| Units: Number of infants | | | | |
| Yes | 16 | 20 | | |
| No | 306 | 296 | | |
| Missing | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Need for ventilation support

| | |
|-----------------|------------------------------|
| End point title | Need for ventilation support |
|-----------------|------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | | | | |
| Units: Number of infants | | | | |
| Yes | 15 | 18 | | |
| No | 307 | 298 | | |
| Missing | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Need for ventilation support - type

| | |
|-----------------|-------------------------------------|
| End point title | Need for ventilation support - type |
|-----------------|-------------------------------------|

End point description:

Not mutually exclusive

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 316 | | |
| Units: Number of infants | | | | |
| Endotracheal ventilation | 5 | 6 | | |
| CPAP | 9 | 12 | | |
| High-flow oxygen | 7 | 9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebral ultrasound scan performed

| | |
|-----------------|------------------------------------|
| End point title | Cerebral ultrasound scan performed |
|-----------------|------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 12 | 11 | | |
| No | 310 | 306 | | |
| Missing | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormalities found in cerebral ultrasound scan

| | |
|-----------------|---|
| End point title | Abnormalities found in cerebral ultrasound scan |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 317 ^[17] | | |
| Units: Number of infants | 3 | 3 | | |

Notes:

[17] - 1 missing ultrasound scan performed

Statistical analyses

No statistical analyses for this end point

Secondary: IVH - Grade 1

| | |
|-----------------|---------------|
| End point title | IVH - Grade 1 |
|-----------------|---------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 317 | | |
| Units: Number of infants | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ventricular dilatation

| | |
|-----------------|------------------------|
| End point title | Ventricular dilatation |
|-----------------|------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 317 | | |
| Units: Number of infants | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed sepsis

| | |
|-----------------|------------------|
| End point title | Confirmed sepsis |
|-----------------|------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 1 | 2 | | |
| No | 320 | 315 | | |
| Missing | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Necrotising Enterocolitis

| | |
|-----------------|---------------------------|
| End point title | Necrotising Enterocolitis |
|-----------------|---------------------------|

End point description:

Bell's stage 2 or 3

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 0 | 0 | | |
| No | 322 | 316 | | |
| Missing | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure prior to discharge

| | |
|-----------------|----------------------------|
| End point title | Seizure prior to discharge |
|-----------------|----------------------------|

| | |
|--|-----------|
| End point description: | |
| Confirmed by EEG or requiring anticonvulsant therapy | |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 0 | 0 | | |
| No | 321 | 317 | | |
| Missing | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Encephalopathy

| | |
|------------------------|----------------|
| End point title | Encephalopathy |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Delivery to discharge | |

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 2 | 0 | | |
| No | 320 | 317 | | |
| Missing | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Encephalopathy treated with hypothermia

| | |
|-----------------|---|
| End point title | Encephalopathy treated with hypothermia |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Infants | Placebo - Infants | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 322 | 318 | | |
| Units: Number of infants | | | | |
| Yes | 1 | 0 | | |
| No | 321 | 317 | | |
| Missing | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum dose of trial medication required

| | |
|-----------------|---|
| End point title | Maximum dose of trial medication required |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation to delivery

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|------------------------------|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 304 | 300 | | |
| Units: Number of women | | | | |
| One tablet once a day | 4 | 5 | | |
| One tablet twice a day | 203 | 198 | | |
| One tablet three times a day | 62 | 65 | | |
| Two tablets twice a day | 35 | 32 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Need for additional therapy for cholestasis

| | |
|-----------------|---|
| End point title | Need for additional therapy for cholestasis |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation to delivery

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|----------------------------------|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 304 | 300 | | |
| Units: Number of women | | | | |
| Yes | 134 | 125 | | |
| No | 127 | 120 | | |
| Delivered before first follow-up | 33 | 42 | | |
| Missing | 10 | 13 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Additional therapy for cholestasis

| | |
|-----------------|------------------------------------|
| End point title | Additional therapy for cholestasis |
|-----------------|------------------------------------|

End point description:

Not mutually exclusive

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation to delivery

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|-----------------------------|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 134 | 125 | | |
| Units: Number of women | | | | |
| Chlorphenamine | 97 | 105 | | |
| Aqueous cream | 17 | 27 | | |
| Menthol aqueous cream | 89 | 74 | | |
| Antihistamine | 6 | 1 | | |
| Topical emollient | 3 | 2 | | |
| Calamine | 7 | 1 | | |
| Vitamin K | 2 | 1 | | |

| | | | | |
|-----------------------------------|----|----|--|--|
| Rifampicin | 1 | 2 | | |
| Open-label UDCA (tablets stopped) | 17 | 21 | | |
| Other | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Gestational diabetes mellitus

| | |
|-----------------|-------------------------------|
| End point title | Gestational diabetes mellitus |
|-----------------|-------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Delivery to discharge

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|-----------------------------|----------------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 304 | 300 | | |
| Units: Number of women | | | | |
| Yes | 3 | 9 | | |
| No | 300 | 290 | | |
| Missing | 1 | 1 | | |

Statistical analyses

| | |
|----------------------------|-----------------------|
| Statistical analysis title | Risk ratio (adjusted) |
|----------------------------|-----------------------|

Statistical analysis description:

Adjusted for minimisation factors: bile acid, gestational age at randomisation, multiple pregnancy, and centre as a random effect.

| | |
|---|--|
| Comparison groups | UDCA - Maternal population v Placebo - Maternal population |
| Number of subjects included in analysis | 604 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.071 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 1.1 |

Secondary: Assessment of myometrial contractions by CTG approx. 1 week (3-14 days) post randomisation

| | |
|-----------------|--|
| End point title | Assessment of myometrial contractions by CTG approx. 1 week (3-14 days) post randomisation |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

3-14 days post-randomisation

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|--|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 304 | 300 | | |
| Units: Number of women | | | | |
| Yes | 165 | 153 | | |
| No | 93 | 96 | | |
| Delivered before first follow-up visit | 33 | 43 | | |
| Missing | 10 | 8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Bile acid (µmol/l) between randomisation and delivery

| | |
|-----------------|---|
| End point title | Bile acid (µmol/l) between randomisation and delivery |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between randomisation and delivery

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|--|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 256 ^[18] | 247 ^[19] | | |
| Units: µmol/l | | | | |
| geometric mean (confidence interval 95%) | 22.4 (21.4 to 23.5) | 18.5 (17.7 to 19.4) | | |

Notes:

[18] - With baseline and at least one post-randomisation measurement.

[19] - With baseline and at least one post-randomisation measurement.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Repeated measures ANCOVA |
| Statistical analysis description: | |
| Accounting for within-subject correlation between measures at the post-randomisation antenatal visits, adjusting for baseline measure and minimisation factors. | |
| Comparison groups | Placebo - Maternal population v UDCA - Maternal population |
| Number of subjects included in analysis | 503 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 |
| Method | ANCOVA |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.36 |

Secondary: Alanine transaminase (U/L) between randomisation and delivery

| | |
|------------------------------------|---|
| End point title | Alanine transaminase (U/L) between randomisation and delivery |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Between randomisation and delivery | |

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|---|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 242 ^[20] | 240 ^[21] | | |
| Units: U/L | | | | |
| geometric mean (inter-quartile range (Q1-Q3)) | 49.5 (43.8 to 55.8) | 58.0 (51.0 to 65.9) | | |

Notes:

[20] - With baseline and at least one post-randomisation measurement.

[21] - With baseline and at least one post-randomisation measurement.

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Repeated measures ANCOVA |
| Statistical analysis description: Accounting for within-subject correlation between measures at the post-randomisation antenatal visits, adjusting for baseline measure and minimisation factors. | |
| Comparison groups | UDCA - Maternal population v Placebo - Maternal population |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 0.83 |

Secondary: Aspartate transaminase (U/L) between randomisation and delivery

| | |
|--|---|
| End point title | Aspartate transaminase (U/L) between randomisation and delivery |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Between randomisation and delivery | |

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|--|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 ^[22] | 39 ^[23] | | |
| Units: U/L | | | | |
| geometric mean (confidence interval 95%) | 44.1 (35.7 to 54.5) | 64.3 (51.1 to 81.0) | | |

Notes:

[22] - With baseline and at least one post-randomisation measurement.

[23] - With baseline and at least one post-randomisation measurement.

Statistical analyses

No statistical analyses for this end point

Secondary: Bilirubin (µmol/l) between randomisation and delivery

| | |
|-----------------|---|
| End point title | Bilirubin (µmol/l) between randomisation and delivery |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between randomisation and delivery

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|--|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 246 ^[24] | 226 ^[25] | | |
| Units: µmol/l | | | | |
| geometric mean (confidence interval 95%) | 7.0 (6.6 to 7.5) | 8.6 (8.0 to 9.3) | | |

Notes:

[24] - With baseline and at least one post-randomisation measurement.

[25] - With baseline and at least one post-randomisation measurement.

Statistical analyses

No statistical analyses for this end point

Secondary: Gamma glutamyl transferase (U/L) between randomisation and delivery

| | |
|-----------------|---|
| End point title | Gamma glutamyl transferase (U/L) between randomisation and delivery |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Between randomisation and delivery

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|--|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 96 ^[26] | 100 ^[27] | | |
| Units: U/L | | | | |
| geometric mean (confidence interval 95%) | 18.3 (16.0 to 21.0) | 21.0 (18.8 to 23.4) | | |

Notes:

[26] - With baseline and at least one post-randomisation measurement.

[27] - With baseline and at least one post-randomisation measurement.

Statistical analyses

No statistical analyses for this end point

Secondary: Itch between randomisation and delivery (measured by worst episode of itch over past 24 hours)

| | |
|------------------------------------|--|
| End point title | Itch between randomisation and delivery (measured by worst episode of itch over past 24 hours) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Between randomisation and delivery | |

| End point values | UDCA - Maternal population | Placebo - Maternal population | | |
|--------------------------------------|----------------------------|-------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 241 ^[28] | 227 ^[29] | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 49.5 (± 12.9) | 56.9 (± 13.3) | | |

Notes:

[28] - With baseline and at least one post-randomisation measurement.

[29] - With baseline and at least one post-randomisation measurement.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Repeated measures ANCOVA |
| Comparison groups | UDCA - Maternal population v Placebo - Maternal population |
| Number of subjects included in analysis | 468 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -5.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.68 |
| upper limit | -1.68 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until discharge from hospital

Adverse event reporting additional description:

At each clinic visit, a member of the clinical or research team will ask the woman if she has had any adverse events, and will ensure that she has clinical monitoring (e.g. liver function tests and fetal monitoring) as routinely performed in each maternity unit.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-----|
| Dictionary name | N/A |
|-----------------|-----|

| | |
|--------------------|-----|
| Dictionary version | N/A |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | UDCA |
|-----------------------|------|

Reporting group description:

Active treatment - Ursodeoxycholic Acid

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Identical tablets administered in the same dose increments orally.

| Serious adverse events | UDCA | Placebo | |
|---|--|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 6 / 296 (2.03%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Congenital, familial and genetic disorders | | | |
| Downs syndrome | Additional description: Baby diagnosed with Downs syndrome | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Intrauterine fetal death | Additional description: Intrauterine fetal death at 35 weeks. CTG normal 2 days prior. FM normal. Latest scan normal. BA not above 21. Delivered. Mother making full physical recovery. | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vaginal haematoma | Additional description: Following a normal birth and perineal suturing participant went back to theatre for an evacuation of a vaginal haematoma. Given prophylactic antibiotics and analgesia, discharged home the next day, EBL = 600 mls. | | |

| | | | |
|---|---|-----------------|--|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 296 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Mild hypospadias | Additional description: Baby was diagnosed with mild hypospadias and a referral was made to the paediatricians. Baby was passing urine well, and testes were descended. Baby was seen by the paediatric team and no further action taken. | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Overdose | Additional description: Informed through the Pharmacy Department that participant was an inpatient having taken an overdose of Paracetamol. | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Sepsis | Additional description: Admitted with possible sepsis, raised respiratory rate, increased heart rate. Commenced sepsis pathway. Rhinovirus detected on throat swab. Home on oral antibiotics, no further follow up. Admitted for 5 days. | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic screen | Additional description: Maternal temperature 38.2 following delivery - septic screen performed on mother and baby, and treated with IV antibiotics. | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 296 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Urinary tract infection (possible) | Additional description: Participant was admitted to maternity unit feeling unwell and vomiting. Possible UTI, required management of diabetic ketoacidosis. | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | UDCA | Placebo | |
|---|---|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 300 (7.33%) | 34 / 296 (11.49%) | |
| Vascular disorders | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 296 (0.34%) | |
| occurrences (all) | 1 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Heart rate increased | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 296 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Unresponsive | Additional description: After Caesarean section | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences (all) | 0 | 1 | |
| Headache | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 296 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 296 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Intrapartum haemorrhage | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences (all) | 0 | 1 | |
| Postpartum haemorrhage | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 9 / 296 (3.04%) | |
| occurrences (all) | 4 | 9 | |
| Threatened pre-term labour | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 296 (0.34%) | |
| occurrences (all) | 1 | 1 | |
| Unwell | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 296 (0.34%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|----------------------|----------------------|--|
| Retained placenta or membranes subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Jaundice neonatal subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Previous pregnancy haemolytic strep B infection, prophylactic antibiotics administered subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Caesarean section wound haematoma subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Antepartum haemorrhage subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Third degree tear subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Vaginal haematoma subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Tightenings subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Pulmonary embolism (suspected) subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 3 / 296 (1.01%) 3 | |
| Haemoglobin low subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Low platelets | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Nosebleeds subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 2 / 300 (0.67%) 2 | 2 / 296 (0.68%) 2 | |
| Vomiting in pregnancy subjects affected / exposed occurrences (all) | 3 / 300 (1.00%) 3 | 3 / 296 (1.01%) 4 | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 2 / 296 (0.68%) 2 | |
| Stools abnormal subjects affected / exposed occurrences (all) | 3 / 300 (1.00%) 3 | 2 / 296 (0.68%) 2 | |
| Intestinal disorder subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Gastrooesophageal reflux subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Psychiatric disorders Panic attack subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Renal and urinary disorders Acute kidney injury (probable) subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Endocrine disorders | | | |

| | | | |
|---|----------------------|----------------------|--|
| Goitre (possible) subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Fall subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 1 / 296 (0.34%) 1 | |
| Hip pain subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Infections and infestations | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 1 / 296 (0.34%) 1 | |
| Dental abscess subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Sore throat subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Cough subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 296 (0.34%) 1 | |
| Urinary tract infection e. coli subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |
| Leg infection (suspected) subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 296 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 12 March 2018 | <p>Protocol v3.0</p> <p>Section 9.6 Withdrawal of Participants We have amended the wording to allow continued recruitment up to the number of women who discontinued the intervention or withdrew from the trial if there is sufficient time within the existing study time-line to do so.</p> <p>Removed: "There is no requirement to enrol extra participants to replace women who do not complete the study." Added: "If there is sufficient time within the existing study time-line, additional participants will be recruited up to the number of women who discontinued the intervention or withdrew".</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30482254>