



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	Protocol v3.0 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. 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".

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>