Clinical trial results:
The Clinical Carbetocin Myocardium Trial

Summary

EudraCT number	2014-000507-27
Trial protocol	NO
Global end of trial date	19 February 2022

Results information

Result version number	v1 (current)
This version publication date	14 July 2023
First version publication date	14 July 2023

Trial information

Trial identification

Sponsor protocol code	CarbetocinHeart2014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03899961
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Box 4950 Nydalen, Oslo, Norway, 0424
Public contact	Department of Anesthesiology, Oslo University Hospital, 47 23073700, lrossela@ous-hf.no
Scientific contact	Department of Anesthesiology, Oslo University Hospital, 47 23073700, lrossela@ous-hf.no

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	08 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2022
Global end of trial reached?	Yes
Global end of trial date	19 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cardiac biomarkers may increase after injection of oxytocin. Carbetocin, a new synthetic oxytocin receptor agonist, may have similar effects. This study compares the two drugs in clinical use for treatment and prophylaxis of atonic uterine bleeding. The primary endpoint was group difference in troponin I.

Protection of trial subjects:

Both interventions are standard clinical practice in Norway and there is no reason to expect any additional risk of pain or discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	240
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potentially eligible participants were screened by the principal investigator for inclusion at their last midwife consultation before their scheduled delivery. Oral and written information was given to each woman at least 24 h before her delivery and written informed consent was obtained before randomization.

Pre-assignment

Screening details:

Inclusion:
- Healthy singleton pregnancy
- Gestational age > 36 weeks
- Age >=18 and <=50
- Understanding Norwegian

Exclusion:
- Pregnancy induced hypertension
- Invasive placenta
- Bleeding disorder
- Prolonged QT time or other serious cardiac disease
- Liver failure
- Renal failure
- Epilepsy
- Drug intolerance

Period 1

Period 1 title	Baseline
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To maintain treatment masking, both study drugs were diluted to 5 mL using normal saline by a trained member of staff otherwise uninvolved with the trial and labelled with the trial identification and randomization number according with ICH GCP and local regulations.

Arms

Are arms mutually exclusive?	Yes
Arm title	Carbetocin

Arm description:

Carbetocin 100µg iv

Arm type	Experimental
Investigational medicinal product name	carbetocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

carbetocin 100 µg

Arm title	Oxytocin

Arm description:

Oxytocin 2.5 U

Arm type	Active comparator

Investigational medicinal product name	Oxytocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxytocin 2.5 U

Number of subjects in period 1	Carbetocin	Oxytocin
Started	119	121
Exclusion prior to intervention	16 [1]	9 [2]
Completed	103	112
Not completed	16	9
Consent withdrawn by subject	1	1
Delivery prior to intervention	7	2
Required general anesthesia	2	1
Capacity reason	6	5

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Some patients were lost after inclusion but prior to set time for planned delivery

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Some patients were lost after inclusion but prior to set time for planned delivery

Period 2

Period 2 title	Treatment 0-30 min
Is this the baseline period?	Yes[3]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Carbetocin

Arm description:

Carbetocin 100µg iv

Arm type	Experimental
Investigational medicinal product name	carbetocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

carbetocin 100 µg

Arm title	Oxytocin
Arm description: Oxytocin 2.5 U	
Arm type	Active comparator
Investigational medicinal product name	Oxytocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Oxytocin 2.5 U	

Notes:

[3] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Some patients were lost after inclusion but prior to set time for planned delivery

Number of subjects in period 2[4]	Carbetocin	Oxytocin
Started	103	112
Completed	103	112

Notes:

[4] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Some patients were lost after inclusion but prior to set time for planned delivery

Period 3

Period 3 title	Follow-up 6-10 h
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Carbetocin
Arm description: Carbetocin 100µg iv	
Arm type	Experimental
Investigational medicinal product name	carbetocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: carbetocin 100 µg	
Arm title	Oxytocin
Arm description: Oxytocin 2.5 U	
Arm type	Active comparator

Investigational medicinal product name	Oxytocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:
Oxytocin 2.5 U

Number of subjects in period 3	Carbetocin	Oxytocin
Started	103	112
Completed	103	112

Period 4

Period 4 title	Followup 48 hours
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Carbetocin

Arm description:
Carbetocin 100µg iv

Arm type	Experimental
Investigational medicinal product name	carbetocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:
carbetocin 100 µg

Arm title	Oxytocin

Arm description:
Oxytocin 2.5 U

Arm type	Active comparator
Investigational medicinal product name	Oxytocin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:
Oxytocin 2.5 U

Number of subjects in period 4	Carbetocin	Oxytocin
Started	103	112
Completed	103	112

Baseline characteristics

Reporting groups	
Reporting group title	Carbetocin
Reporting group description: Carbetocin 100µg iv	
Reporting group title	Oxytocin
Reporting group description: Oxytocin 2.5 U	

Reporting group values	Carbetocin	Oxytocin	Total
Number of subjects	103	112	215
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	103	112	215
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	35.0	34.5	
full range (min-max)	24.1 to 47.5	23.4 to 50.9	-
Gender categorical Units: Subjects			
Female	103	112	215
Male	0	0	0
Parity Units: counts			
median	1	1	
full range (min-max)	0 to 4	0 to 5	-
Gestational age Units: weeks			
arithmetic mean	38.7	38.6	
standard deviation	± 0.9	± 0.8	-
Mean arterial pressure Units: mmHg			
arithmetic mean	100	100	
standard deviation	± 12	± 13	-
BMI			
body mass index			
Units: kg/m*m			
median	28.7	27.3	

full range (min-max)	20.4 to 51.6	22.0 to 45.0	-
Heart rate			
Units: beats/min			
arithmetic mean	88	90	
standard deviation	± 15	± 15	-
Troponin value at baseline			
Units: ng/L			
median	1.0	1.0	
full range (min-max)	1.0 to 19.2	1.0 to 48.7	-

Subject analysis sets	
Subject analysis set title	Modified ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients included in the study having received the study drug

Reporting group values	Modified ITT		
Number of subjects	215		
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)	215		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median	34.8		
full range (min-max)	23.4 to 50.9		
Gender categorical			
Units: Subjects			
Female	215		
Male	0		
Parity			
Units: counts			
median	1		
full range (min-max)	0 to 5		
Gestational age			
Units: weeks			
arithmetic mean	38.6		
standard deviation	± 0.9		
Mean arterial pressure			
Units: mmHg			
arithmetic mean	100		
standard deviation	± 13		

BMI			
body mass index			
Units: kg/m*m			
median	28		
full range (min-max)	20.4 to 51.6		
Heart rate			
Units: beats/min			
arithmetic mean	89		
standard deviation	± 15		
Troponin value at baseline			
Units: ng/L			
median	1.0		
full range (min-max)	1.0 to 48.7		

End points

End points reporting groups

Reporting group title	Carbetocin

Reporting group description:
Carbetocin 100µg iv

Reporting group title	Oxytocin

Reporting group description:
Oxytocin 2.5 U

Reporting group title	Carbetocin

Reporting group description:
Carbetocin 100µg iv

Reporting group title	Oxytocin

Reporting group description:
Oxytocin 2.5 U

Reporting group title	Carbetocin

Reporting group description:
Carbetocin 100µg iv

Reporting group title	Oxytocin

Reporting group description:
Oxytocin 2.5 U

Reporting group title	Carbetocin

Reporting group description:
Carbetocin 100µg iv

Reporting group title	Oxytocin

Reporting group description:
Oxytocin 2.5 U

Subject analysis set title	Modified ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:
All patients included in the study having received the study drug

Primary: Troponin I

End point title	Troponin I

End point description:

End point type	Primary

End point timeframe:
at 6-10 hours

End point values	Carbetocin	Oxytocin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	109		
Units: ng/l				
median (full range (min-max))	1.2 (1.0 to 19.5)	1.2 (1.0 to 47.0)		

Statistical analyses

Statistical analysis title	median regression model
Statistical analysis description:	
median regression model for the change from baseline. model was adjusted for treatment. bootstrap was used for confidence intervals.	
Comparison groups	Carbetocin v Oxytocin
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	median regression
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	1.09

Secondary: Uterine tone at 5 minutes

End point title	Uterine tone at 5 minutes
End point description:	
End point type	Secondary
End point timeframe:	
5 minutes	

End point values	Carbetocin	Oxytocin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: 11 point scale 0-10				
median (full range (min-max))	8 (4 to 10)	7 (4 to 10)		

Statistical analyses

Statistical analysis title	Mann Whitney test
Comparison groups	Carbetocin v Oxytocin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Blood loss	
End point title	Blood loss
End point description:	
End point type	Secondary
End point timeframe:	
10 hours	

End point values	Carbetocin	Oxytocin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: ml				
arithmetic mean (standard deviation)	361 (± 435)	386 (± 369)		

Statistical analyses

Statistical analysis title	t test
Comparison groups	Carbetocin v Oxytocin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Time to end of surgery

End point title	Time to end of surgery

End point description:

End point type	Secondary

End point timeframe:

10 hours

End point values	Carbetocin	Oxytocin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: minute				
median (full range (min-max))	30 (14 to 58)	31 (14 to 91)		

Statistical analyses

Statistical analysis title	Mann Whitney test
Comparison groups	Carbetocin v Oxytocin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Need for rescue treatment

End point title	Need for rescue treatment

End point description:

End point type	Secondary

End point timeframe:

0-30 minutes

End point values	Carbetocin	Oxytocin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: Number of patients	23	50		

Statistical analyses

Statistical analysis title	Fisher mid p test
Comparison groups	Carbetocin v Oxytocin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Risk ratio (RR)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 hours	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	4
Reporting groups	
Reporting group title	Carbetocin
Reporting group description: Carbetocin 100µg iv	
Reporting group title	Oxytocin
Reporting group description: Oxytocin 2.5 U	

Serious adverse events	Carbetocin	Oxytocin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 103 (0.00%)	0 / 112 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Carbetocin	Oxytocin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 103 (53.40%)	50 / 112 (44.64%)	
Vascular disorders			
Flushing			
subjects affected / exposed	8 / 103 (7.77%)	11 / 112 (9.82%)	
occurrences (all)	8	11	
Cardiac disorders			
Chest pain			
subjects affected / exposed	4 / 103 (3.88%)	12 / 112 (10.71%)	
occurrences (all)	4	12	
Palpitations			

subjects affected / exposed	3 / 103 (2.91%)	7 / 112 (6.25%)	
occurrences (all)	3	7	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 103 (7.77%)	6 / 112 (5.36%)	
occurrences (all)	8	6	
General disorders and administration site conditions			
Feeling hot	Additional description: feeling of warmth		
subjects affected / exposed	27 / 103 (26.21%)	23 / 112 (20.54%)	
occurrences (all)	27	23	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	14 / 103 (13.59%)	1 / 112 (0.89%)	
occurrences (all)	14	1	
Nausea			
subjects affected / exposed	10 / 103 (9.71%)	8 / 112 (7.14%)	
occurrences (all)	10	8	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 103 (8.74%)	6 / 112 (5.36%)	
occurrences (all)	9	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported