Clinical trial results:
Assisted reproduction and the early luteal phase
The effect of ovulation induction on the endocrine profile

Summary

EudraCT number	2013-003304-39
Trial protocol	DK
Global end of trial date	28 August 2020

Results information

Result version number	v1 (current)
This version publication date	21 January 2022
First version publication date	21 January 2022

Trial information

Trial identification

Sponsor protocol code	13.010

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	Kløvervænget 23, Odense, Denmark,
Public contact	Fertilitycenter, Odense University Hospital, 0045 20342687, Peter.Humaidan@midt.rm.dk
Scientific contact	Fertilitycenter, Odense University Hospital, 0045 20342687, Peter.Humaidan@midt.rm.dk

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	30 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2020
Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the endocrine hormone levels in the luteal phase during fertility treatment.

Protection of trial subjects:

Ethics Committee of Southern of Denmark, the Danish Health and Medicines Authority, the Danish Data Protection Agency and Local Good Clinical Practice Unit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2014
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	Denmark: 222
Worldwide total number of subjects	222
EEA total number of subjects	222

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)	222
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fertility Clinic, Patients in fertility treatment.

Pre-assignment

Screening details:

Healthy women in infertility treatment, 18-40 years, healthy with normal screening blood samples
RCT I: In total ≤ 11 follicles ≤ 12 mm, on both ovaries at the last ultrasonography before oocyte retrieval
RCT II: In total ≥ 12 or ≤ 25 follicles ≤ 12 mm, on both ovaries at the last ultrasonography before oocyte retrieval

Period 1

Period 1 title	overall periode
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RCT I, group 1

Arm description:

5.000 IU (urinary hCG) + 17α OH P4

Arm type	Active comparator
Investigational medicinal product name	Lentogest
Investigational medicinal product code	G03DA03
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

341 mg every 3.th day

Arm title	RCT I, group 2

Arm description:

6.500 IU (recombinant hCG) + 17α OH P4

Arm type	Active comparator
Investigational medicinal product name	Lentogest
Investigational medicinal product code	G03DA03
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

341 mg every 3.th day

Arm title	RCT I, group 3

Arm description:

10.000 IU (urinary hCG) + 17α OH P4

Arm type	Active comparator

Investigational medicinal product name	Lentogest
Investigational medicinal product code	G03DA03
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:
341 mg every 3.th day

Arm title	RCT I, group 4

Arm description:
6500 IU (recombinant hCG) + P4

Arm type	control
Investigational medicinal product name	Progesterone, Crinone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:
180 mg every day

Arm title	RCT II, group 1

Arm description:
Trigger: 6.500 IU hCG. Luteal support: P4

Arm type	control
Investigational medicinal product name	Progesterone, Crinone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:
180 mg every day

Arm title	RCT II, group 2

Arm description:
Trigger: GnRh agonist 0.5 mg. Luteal support: 1500 IU hCG at OPU, P4

Arm type	Active comparator
Investigational medicinal product name	Progesterone, Crinone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:
180 mg every day

Arm title	RCT II, group 3

Arm description:
Trigger: GnRha agonist 0.5 mg. Luteal support: 1000 IU hCG at OPU, 500 IU hCG at OPU+5, P4

Arm type	Active comparator
Investigational medicinal product name	Progesterone, Crinone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:
180 mg every day

Number of subjects in period 1	RCT I, group 1	RCT I, group 2	RCT I, group 3
Started	30	33	32
Completed	21	22	25
Not completed	9	11	7
Consent withdrawn by subject	1	1	1
missed blood samples	1	1	-
Adverse event, non-fatal	-	-	1
missing ovary	-	-	-
total freeze	-	2	1
wrong medicine	-	-	-
no oocytes	2	1	1
cancelled transfer	-	3	3
endocrinological diseases	-	3	-
transfer cancelled	5	-	-

Number of subjects in period 1	RCT I, group 4	RCT II, group 1	RCT II, group 2
Started	32	33	32
Completed	26	25	22
Not completed	6	8	10
Consent withdrawn by subject	1	1	-
missed blood samples	1	-	1
Adverse event, non-fatal	-	-	-
missing ovary	-	-	1
total freeze	3	1	5
wrong medicine	-	-	1
no oocytes	-	-	-
cancelled transfer	1	6	2
endocrinological diseases	-	-	-
transfer cancelled	-	-	-

Number of subjects in period 1	RCT II, group 3
Started	30

Completed	22
Not completed	8
Consent withdrawn by subject	-
missed blood samples	3
Adverse event, non-fatal	-
missing ovary	-
total freeze	1
wrong medicine	-
no oocytes	1
cancelled transfer	3
endocrinological diseases	-
transfer cancelled	-

Baseline characteristics

Reporting groups	
Reporting group title	RCT I, group 1
Reporting group description:	
5.000 IU (urinary hCG) + 17α OH P4	

Reporting group title	RCT I, group 2
Reporting group description:	
6.500 IU (recombinant hCG) + 17α OH P4	
Reporting group title	RCT I, group 3
Reporting group description:	
10.000 IU (urinary hCG) + 17α OH P4	
Reporting group title	RCT I, group 4
Reporting group description:	
6500 IU (recombinant hCG) + P4	
Reporting group title	RCT II, group 1
Reporting group description:	
Trigger: 6.500 IU hCG. Luteal support: P4	
Reporting group title	RCT II, group 2
Reporting group description:	
Trigger: GnRh agonist 0.5 mg. Luteal support: 1500 IU hCG at OPU, P4	
Reporting group title	RCT II, group 3
Reporting group description:	
Trigger: GnRha agonist 0.5 mg. Luteal support: 1000 IU hCG at OPU, 500 IU hCG at OPU+5, P4	

Reporting group values	RCT I, group 1	RCT I, group 2	RCT I, group 3
Number of subjects	30	33	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29.1	31.1	30.1
standard deviation	± 5.0	± 4.44	± 4.4
Gender categorical Units: Subjects			
Female	30	33	32
Male	0	0	0

Reporting group values	RCT I, group 4	RCT II, group 1	RCT II, group 2
Number of subjects	32	33	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	31.7	30.9	31.0

standard deviation	± 4.3	± 3.6	± 4.2

Gender categorical Units: Subjects			
Female	32	33	32
Male	0	0	0

Reporting group values	RCT II, group 3	Total	
Number of subjects	30	222	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	30.1		
standard deviation	± 3.9	-	
Gender categorical Units: Subjects			
Female	30	222	
Male	0	0	

End points

End points reporting groups	
Reporting group title	RCT I, group 1
Reporting group description: 5.000 IU (urinary hCG) + 17α OH P4	

Reporting group title	RCT I, group 2
Reporting group description: 6.500 IU (recombinant hCG) + 17α OH P4	
Reporting group title	RCT I, group 3
Reporting group description: 10.000 IU (urinary hCG) + 17α OH P4	
Reporting group title	RCT I, group 4
Reporting group description: 6500 IU (recombinant hCG) + P4	
Reporting group title	RCT II, group 1
Reporting group description: Trigger: 6.500 IU hCG. Luteal support: P4	
Reporting group title	RCT II, group 2
Reporting group description: Trigger: GnRh agonist 0.5 mg. Luteal support: 1500 IU hCG at OPU, P4	
Reporting group title	RCT II, group 3
Reporting group description: Trigger: GnRha agonist 0.5 mg. Luteal support: 1000 IU hCG at OPU, 500 IU hCG at OPU+5, P4	

Primary: Progesterone	
End point title	Progesterone
End point description:	

End point type	Primary
End point timeframe: At randomization	

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	25	25
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	1.9 (1.5 to 2.3)	2.1 (1.3 to 2.9)	1.6 (1.0 to 2.4)	2.3 (1.6 to 2.7)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	22	22	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	2.5 (2.0 to 3.9)	2.7 (1.7 to 3.5)	2.9 (2.1 to 3.6)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: Progesterone

End point title	Progesterone

End point description:

End point type	Primary

End point timeframe:

Oocyte pick up (OPU)

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	22	25	26
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	20.4 (15.7 to 28)	21.4 (17.7 to 35.0)	16.8 (11.1 to 25.7)	21.0 (17.3 to 31.0)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	22	22	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	35.0 (27.2 to 38.5)	17.3 (14.5 to 27.8)	23.4 (17.2 to 26.1)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: Progesterone

End point title	Progesterone
End point description:	

End point type	Primary
End point timeframe:	
OPU+2	

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	21	25	26
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	79.5 (60.7 to 110.0)	104.0 (74.4 to 168.0)	94.1 (58.2 to 177.0)	125.5 (70.0 to 246.0)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	22	22	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	208.0 (114.0 to 266.0)	204.5 (113.0 to 261.0)	241.0 (119.0 to 282.0)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: Progesterone

End point title	Progesterone

End point description:

End point type	Primary

End point timeframe:

OPU+4

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	21	24	26
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	122 (105.0 to 281.0)	228 (104.0 to 287.0)	234.5 (120.0 to 364.0)	286.5 (125.0 to 382.0)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	21	22	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	385.0 (290.0 to 442.0)	363.0 (256.0 to 385.0)	278.0 (186.0 to 417.0)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: Progesterone	
End point title	Progesterone
End point description:	

End point type	Primary
End point timeframe:	
OPU+6	

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	25	26
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	61.7 (36.0 to 181.0)	171.5 (89.7 to 285.0)	216 (125.0 to 299.0)	207.0 (82.7 to 278.0)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	22	22	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	234.0 (183.0 to 300.0)	112.5 (57.9 to 236.0)	354.5 (177.0 to 541.0)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: progesterone	
End point title	progesterone
End point description:	

End point type	Primary
End point timeframe:	
OPU+8	

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	22	25	26
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	8.4 (6.4 to 24.5)	19.1 (13.0 to 59.1)	47.4 (31.4 to 116.0)	47.2 (33.1 to 63.6)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	21	21	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	46.1 (34.7 to 55.8)	42.0 (34.0 to 46.7)	230.0 (75.7 to 321.0)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: progesterone

End point title	progesterone

End point description:

End point type	Primary

End point timeframe:

OPU+10

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	22	24	24
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	3.8 (1.2 to 7.4)	5.8 (3.5 to 10.4)	11.7 (7.1 to 56.0)	36.1 (28.0 to 45.8)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	22	21	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	30.7 (26.2 to 45.1)	31.9 (27.0 to 51.2)	42.9 (32.4 to 252.0)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 2 v RCT I, group 1 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Primary: Progesterone

End point title	Progesterone

End point description:

End point type	Primary

End point timeframe:

OPU+14

End point values	RCT I, group 1	RCT I, group 2	RCT I, group 3	RCT I, group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	23	25
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	1.6 (1.2 to 7.4)	1.5 (1.1 to 4.4)	2.6 (1.1 to 90.3)	34.0 (27.1 to 48.0)

End point values	RCT II, group 1	RCT II, group 2	RCT II, group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	22	21	
Units: nmol/l				
median (inter-quartile range (Q1-Q3))	31.3 (25.3 to 53.8)	33.2 (25.5 to 58.8)	29.1 (24.0 to 461.0)	

Statistical analyses

Statistical analysis title	progesterone levels
Comparison groups	RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 14 dec. 2014 until 29. aug 2020, for each patient from randomization until OPU+14 or ultrasonography in gestational week 7.	
Assessment type	Systematic
Dictionary used	
Dictionary name	none
Dictionary version	0
Reporting groups	
Reporting group title	RCT I
Reporting group description: Group 1, 2, 3, 4	
Reporting group title	RCT II
Reporting group description: Group 5, 6, 7	

Serious adverse events	RCT I	RCT II	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 127 (0.00%)	0 / 95 (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	RCT I	RCT II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 127 (21.26%)	20 / 95 (21.05%)	
General disorders and administration site conditions			
Local reaction	Additional description: Pain at the injection site		
subjects affected / exposed	13 / 127 (10.24%)	0 / 95 (0.00%)	
occurrences (all)	13	0	
OHSS	Additional description: ovarian hyperstimulation syndrome		
subjects affected / exposed	5 / 127 (3.94%)	7 / 95 (7.37%)	
occurrences (all)	5	7	
bloated stomach			

subjects affected / exposed occurrences (all)	8 / 127 (6.30%) 3	12 / 95 (12.63%) 8	
Endocrine disorders sore breasts subjects affected / exposed occurrences (all)	 1 / 127 (0.79%) 1	 5 / 95 (5.26%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2015	Before randomization of the first patient into group 4-5-6-7, Prolutex was changed to Crinone. It was not possible to have Prolutex for all the patients. It didn´t affect the study outcome.
11 September 2017	extension of the inclusion periode

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported