Clinical trial results:
RIOT C: REDUCING THE IMPACT OF OVARIAN STIMULATION. NOVEL APPROACHES TO LUTEAL SUPPORT IN IVF. STUDY 2.

Summary

EudraCT number	2017-004433-93
Trial protocol	DK
Global end of trial date	30 November 2020

Results information

Result version number	v1 (current)
This version publication date	22 December 2021
First version publication date	22 December 2021

Trial information

Trial identification

Sponsor protocol code	RIOTCSTUDY22017

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Nicholas Stephan Macklon, Region Zealand Fertility Clinic
Sponsor organisation address	Lykkebækvej 14, Køge, Denmark, 4600
Public contact	Unit of Reproductive Medicine, Nichohlas Stephen Macklon, Professor, MD, PhD. Unit of Reproductive Medicine, 45 53621645, nick.macklon@londonwomensclinic.com
Scientific contact	Unit of Reproductive Medicine, Nichohlas Stephen Macklon, Professor, MD, PhD. Unit of Reproductive Medicine, 45 47324007, nism@regionsjaelland.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	01 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The goal of the trial is to determine wheather co-treatment with aromatase inhibitor in ovarian stimulation in egg donors normalize the duartion of the unsupported luteal phase, reduce the endometrium thickness, positively modulate endocrine markers of luteal phase quality and endometrial markers of receptivity.

Protection of trial subjects:

Participants were withdrawn from the study if they suffered from serious adverse events or reactions during OS including severe allergy to study drug or withdraw consent. In case of severe degree of hot flushes, severe degree of nausea/vomiting, severe diarrhea or severe degree of muscle and joint pain the participant were also excluded.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2018
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	Denmark: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	25
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Egg donors were invited to participate in this study at their first visit in the Fertility clinic or at the day of starting up ovarian stimulation. Before inclusion the paticipant received verbal and written information about the study and signed a consent form.

Pre-assignment

Screening details:

The inclusion criteria included acceptance as an oocyte donor according to local criteria, age ≤35 years and regular ovulatory cycle of 26-32 days. Exclusion criteria were polycystic ovary syndrome, known allergy to letrozole or an intrauterine device (within the last three months from inclusion).

Pre-assignment period milestones

Number of subjects started	25
Number of subjects completed	25

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Letrozole group

Arm description:

Adjuvant letrozole 5,0 mg/day from stimulation day 1 and throughout ovarian stimulation with a flexible dose of rFSH i an antagonist protocol

Arm type	Letrozole group
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg per day from ovarian stimulation day 1 and throughout stimulation

Arm title	Control group

Arm description:

Standard ovarian stimulation with a flexible dose of rFSH in an antagonist protocol

Arm type	Control group

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Letrozole group	Control group
Started	11	14
Completed	10	12
Not completed	1	2
Consent withdrawn by subject	-	1
Cycle cancellation	1	-
Lack of compliance	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Letrozole group
Reporting group description:	
Adjuvant letrozole 5,0 mg/day from stimulation day 1 and throughout ovarian stimulation with a flexible dose of rFSH i an antagonist protocol	
Reporting group title	Control group
Reporting group description:	
Standard ovarian stimulation with a flexible dose of rFSH in an antagonist protocol	

Reporting group values	Letrozole group	Control group	Total
Number of subjects	11	14	25
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)	11	14	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	29.0	30.5	
inter-quartile range (Q1-Q3)	25.3 to 31.0	25.0 to 31.0	-
Gender categorical			
Units: Subjects			
Female	11	14	25
Male	0	0	0
AMH			
Anti-Müllerian hormone			
Units: pmol/L			
median	19.5	18.0	
inter-quartile range (Q1-Q3)	16.0 to 40.9	8.5 to 34.1	-
Cycle duration			
Days of menstrual cycle			
Units: Days			
median	28.0	28.0	
inter-quartile range (Q1-Q3)	28.0 to 29.25	28.0 to 29.8	-
BMI			
Body Mass Index			
Units: kg/m2			
median	25.3	25.2	
inter-quartile range (Q1-Q3)	22.0 to 27.9	22.3 to 29.4	-

End points

End points reporting groups

Reporting group title	Letrozole group
Reporting group description:	
Adjuvant letrozole 5,0 mg/day from stimulation day 1 and throughout ovarian stimulation with a flexible dose of rFSH i an antagonist protocol	
Reporting group title	Control group
Reporting group description:	
Standard ovarian stimulation with a flexible dose of rFSH in an antagonist protocol	

Primary: Duration of luteal phase

End point title	Duration of luteal phase
End point description:	

End point type	Primary
End point timeframe:	
From oocyte aspiration and 14 days ahead.	

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[1]	12[2]		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Increase of duration of luteal phase	8.0 (6.8 to 11.5)	5.0 (5.0 to 6.8)		

Notes:

[1] - One participant was excluded

[2] - Two participants were excluded

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Secondary: Estradiol OPU

End point title	Estradiol OPU

End point description:

End point type	Secondary
End point timeframe:	
At oocyte pick up (OPU)	

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))				
Reduction in estradiol	0.9 (0.2 to 1.2)	2.8 (1.3 to 3.4)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)

Secondary: Progesterone OPU

End point title	Progesterone OPU
End point description:	

End point type	Secondary
End point timeframe:	
At oocyte retrieval	

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	25.9 (15.2 to 39.2)	21.6 (12.8 to 36.2)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.628
Method	Wilcoxon (Mann-Whitney)

Secondary: LH OPU

End point title	LH OPU

End point description:

End point type	Secondary

End point timeframe:

At oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	6.4 (6.4 to 10.8)	3.0 (2.6 to 5.1)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Secondary: FSH OPU

End point title	FSH OPU

End point description:

End point type	Secondary

End point timeframe:
At oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	9.4 (8.1 to 11.7)	8.1 (6.7 to 9.9)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.203
Method	Wilcoxon (Mann-Whitney)

Secondary: Endometrial thickness OPU

End point title	Endometrial thickness OPU

End point description:

End point type	Secondary

End point timeframe:
At oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: mm				
median (inter-quartile range (Q1-Q3))	9.9 (6.7 to 11.3)	9.7 (8.1 to 13.1)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	Wilcoxon (Mann-Whitney)

Secondary: Estradiol OPU+2

End point title	Estradiol OPU+2

End point description:

End point type	Secondary

End point timeframe:

Two days after Oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	0.2 (0.1 to 0.3)	1.6 (1.1 to 3.2)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Endometrial thickness OPU+5

End point title	Endometrial thickness OPU+5

End point description:

End point type	Secondary

End point timeframe:

Five days after ovarian stimulation

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	6.0 (4.3 to 8.1)	5.7 (4.0 to 7.7)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Control group v Letrozole group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Wilcoxon (Mann-Whitney)

Secondary: Estradiol OPU+5

End point title	Estradiol OPU+5

End point description:

End point type	Secondary

End point timeframe:

Five days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	0.2 (0.2 to 0.2)	0.3 (0.2 to 0.4)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Wilcoxon (Mann-Whitney)

Secondary: Estradiol OPU+14

End point title	Estradiol OPU+14

End point description:

End point type	Secondary

End point timeframe:

14 days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.2)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.436
Method	Wilcoxon (Mann-Whitney)

Secondary: Progesterone OPU+2

End point title	Progesterone OPU+2

End point description:

End point type	Secondary

End point timeframe:

Two days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	76.1 (57.0 to 126.3)	32.9 (17.4 to 52.8)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Progesterone OPU+5

End point title	Progesterone OPU+5

End point description:

End point type	Secondary

End point timeframe:

Five days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	67.1 (15.7 to 101.8)	2.3 (1.1 to 10.7)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Progesterone OPU+14

End point title	Progesterone OPU+14

End point description:

End point type	Secondary

End point timeframe:

14 days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	0.8 (0.3 to 2.1)	0.3 (0.3 to 0.4)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Control group v Letrozole group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Wilcoxon (Mann-Whitney)

Secondary: LH OPU+2

End point title	LH OPU+2

End point description:

End point type	Secondary

End point timeframe:

Two days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	1.8 (1.4 to 2.4)	1.2 (0.5 to 1.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Secondary: LH OPU+5

End point title	LH OPU+5

End point description:

End point type	Secondary

End point timeframe:

Five days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	1.6 (1.3 to 3.0)	1.8 (1.2 to 2.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Control group v Letrozole group
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.654
Method	Wilcoxon (Mann-Whitney)

Secondary: LH OPU+14

End point title	LH OPU+14

End point description:

End point type	Secondary

End point timeframe:

14 days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	4.9 (3.4 to 6.0)	5.8 (3.3 to 8.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	Wilcoxon (Mann-Whitney)

Secondary: FSH OPU+2

End point title	FSH OPU+2

End point description:

End point type	Secondary

End point timeframe:

Two days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	4.1 (3.4 to 5.7)	3.9 (2.4 to 4.8)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.456
Method	Wilcoxon (Mann-Whitney)

Secondary: FSH OPU+5

End point title	FSH OPU+5

End point description:

End point type	Secondary

End point timeframe:

Five days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	3.9 (1.8 to 4.8)	2.0 (0.5 to 3.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	Wilcoxon (Mann-Whitney)

Secondary: FSH OPU+14

End point title	FSH OPU+14

End point description:

End point type	Secondary

End point timeframe:

14 days after oocyte retrieval

End point values	Letrozole group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	6.4 (6.0 to 7.9)	6.2 (4.5 to 8.7)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Letrozole group v Control group
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.739
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From start of stimulation to 14 days after oocyte aspiration

Adverse event reporting additional description:

Only serious adverse events OR rections as well as NOT KNOWN reactions/events were reported

Assessment type	Non-systematic

Dictionary used

Dictionary name	No
Dictionary version	0

Reporting groups

Reporting group title	All adverse events

Reporting group description:

All adverse events

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: In this study ONLY Serious adverse events/reactions OR not known events/reactions were recorded.

Serious adverse events	All adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Abdominal pain	Additional description: One participant in the control group was admitted to the hospital overnight for observation because of abdominal pain after oocyte aspiration		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2019	1. Co-investigator added 2. Extension of study, changed to November 30th 2020 3. Inclusion criteria: Duration of menstruation cycle changed to 26 to 32 days from 26 to 28 days. 4. Flexible dose of FSH in stead of fixed dose 5. Endometrial fluid aspiration removed from protocol 6. Ultrasound examination two days after oocyte retrieval removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 March 2020	Due to the Covid-19 pandemic the Fertility clinics were closed down in this period of time	04 May 2020

Notes:

Limitations and caveats

None reported