Clinical trial results:
The exogenous progesterone free luteal phase after GnRHa trigger – a randomized controlled pilot study in high-responder IVF patients

Summary

EudraCT number	2014-000448-13
Trial protocol	DK
Global end of trial date	15 October 2019

Results information

Result version number	v1 (current)
This version publication date	17 December 2020
First version publication date	17 December 2020
Summary attachment (see zip file)	Summary of outcomes (Tables_Eudract_upload.docx)

Trial information

Trial identification

Sponsor protocol code	Agonist6

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The Fertility Clinic Skive
Sponsor organisation address	Resenvej 25, Skive, Denmark, 7800
Public contact	Peter Humaidan, The Fertility Clinic, +45 78445773, peter.humaidan@midt.rm.dk
Scientific contact	Peter Humaidan, The Fertility Clinic, 78445760 78445773, 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 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2019
Global end of trial reached?	Yes
Global end of trial date	15 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this pilot RCT is to explore the exogenous progesterone free luteal phase after GnRHa trigger in a population of IVF patients at risk of OHSS development, characterized by the development of 14-25 follicles ≥11 mm on the day of triggering of final follicular maturation.

Protection of trial subjects:

The study was approved by the scientific Ethics Committee of the Central Denmark Region – Project number: M201337713.
Written informed consent was obtained from all participants prior to inclusion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 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: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled in November 2014 and the last patient was enrolled in August 2019. All patients were from The fertility clinic, Skive Regional Hospital, Denmark.

Pre-assignment

Screening details:

A total of 275 IVF patients were assessed for eligibility and 250 patients were subsequently recruited for two studies, 2014-000448-13 and 2014-000447-32. 120 patients were randomized in 2014-000448-13 and 130 patients were randomized in 2014-000447-32. No patient was lost to follow-up.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	hCG trigger

Arm description:

Ovulation trigger with 6500 IU hCG (Ovitrelle®), followed by 100 mg vaginal progesterone (Lutinus®) three times daily until the pregnancy test (14 days after OR), after which LPS was stopped.

Arm type	Active comparator
Investigational medicinal product name	Ovitrelle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Ovulation trigger with 6500 IU hCG (Ovitrelle®)

Arm title	GnRHa trigger

Arm description:

Ovulation trigger with a bolus of 0.5 mg Buserelin (Suprefact®), followed by a bolus of 1000 IU hCG (Pregnyl®) after OR and an additional bolus of 500 IU hCG (Pregnyl®) on OR + 4

Arm type	Experimental
Investigational medicinal product name	Buserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for cutaneous solution, Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

trigger with a bolus of 0.5 mg Buserelin (Suprefact®, Sanofi A/S, Copenhagen, Denmark)

Number of subjects in period 1	hCG trigger	GnRHa trigger
Started	60	60
Completed	52	46
Not completed	8	14
Protocol deviation	8	14

Baseline characteristics

Reporting groups

Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	120	120	
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			
We adjusted for female age as continous parameter			
Units: years			
arithmetic mean	28.9		
standard deviation	± 3.9	-	
Gender categorical			
All were women			
Units: Subjects			
Female	120	120	
Male	0	0	

Subject analysis sets

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

Subject analysis set description:

The primary analysis was the modified intention to treat analysis (White et al., 2011) of all randomized patients having an embryo transfer under the assumption that missing outcome data (patients not having an embryo transfer) was missing conditionally at random.

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Strict intention to treat for all patients randomized

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Per prootocol defined by those meeting all the eligibility criteria as well as complying with the protocol

Reporting group values	modified intention to treat analysis	Intention to treat	Per protocol
Number of subjects	101	120	98
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
We adjusted for female age as continous parameter			
Units: years			
arithmetic mean	28.9	28.9	28.9
standard deviation	± 3.9	± 3.9	± 3.9
Gender categorical			
All were women			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	hCG trigger
Reporting group description:	
Ovulation trigger with 6500 IU hCG (Ovitrelle®), followed by 100 mg vaginal progesterone (Lutinus®) three times daily until the pregnancy test (14 days after OR), after which LPS was stopped.	
Reporting group title	GnRHa trigger
Reporting group description:	
Ovulation trigger with a bolus of 0.5 mg Buserelin (Suprefact®), followed by a bolus of 1000 IU hCG (Pregnyl®) after OR and an additional bolus of 500 IU hCG (Pregnyl®) on OR + 4	
Subject analysis set title	modified intention to treat analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The primary analysis was the modified intention to treat analysis (White et al., 2011) of all randomized patients having an embryo transfer under the assumption that missing outcome data (patients not having an embryo transfer) was missing conditionally at random.	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Strict intention to treat for all patients randomized	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Per prootocol defined by those meeting all the eligibility criteria as well as complying with the protocol	

Primary: Ongoing pregnancy week 12

End point title	Ongoing pregnancy week 12
End point description:	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	hCG trigger	GnRHa trigger	modified intention to treat analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	49	101	
Units: Fetal heartbeat at scan	52	49	101	

Statistical analyses

Statistical analysis title	Binary regression

Statistical analysis description:

A binary regression model was used to calculate the crude relative risks and relative differences (cRR, cRD) and adjusted relative risks and relative differences (aRR, aRD) for the primary outcome.

Comparison groups	hCG trigger v GnRHa trigger v modified intention to treat analysis
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
Method	Regression, Linear
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.22

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Approximately 14 weeks.	
Adverse event reporting additional description:	
We did not investigate adverse events other than OHSS.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

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

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: We did not observe any adverse events. OHSS rates will be reported in the publication.

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Sample size, lack of blinding.

Full manuscript has been submitted for publication.

Notes: