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

Summary

EudraCT number	2014-000447-32
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	Agonist5

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, ATT. Fertilitetsklinikken, Skive, Denmark, 7800
Public contact	Peter humaidan, Skive fertility clinic, +45 78445773, peter.humaidan@midt.rm.dk
Scientific contact	Peter humaidan, Skive 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 support after GnRHa trigger in a population of IVF patients without imminent risk of OHSS development compared with a control group who will receive hCG.
The primary end-point will be the reproductive outcome defined as the ongoing pregnancy rate per patient at 10th week of gestation.

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: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

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)	130
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	GnRHa trigger

Arm description:

Ovulation trigger with a bolus of 0.5 mg Buserelin (Suprefact®, Sanofi A/S, Copenhagen, Denmark), followed by a bolus of 1500 IU hCG (Pregnyl®, MSD, Skovlunde, Denmark) after OR and an additional bolus of 1000 IU hCG (Pregnyl®) on OR + 4 days.

Arm type	Experimental
Investigational medicinal product name	Buserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	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), followed by a bolus of 1500 IU hCG (Pregnyl®, MSD, Skovlunde, Denmark) after OR and an additional bolus of 1000 IU hCG (Pregnyl®) on OR + 4 days.

Arm title	hCG trigger

Arm description:

trigger with 6500 IU hCG (Ovitrelle®) followed by 100 mg vaginal progesterone (Lutinus®, Ferring, Copenhagen, Denmark) 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	Subcutaneous use

Dosage and administration details:

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

Number of subjects in period 1	GnRHa trigger	hCG trigger
Started	65	65
Completed	50	54
Not completed	15	11
Protocol deviation	15	11

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	130	130	
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	29.5		
standard deviation	± 4.0	-	
Gender categorical			
All females			
Units: Subjects			
Female	130	130	
Male	0	0	

End points

End points reporting groups

Reporting group title	GnRHa trigger
Reporting group description:	
Ovulation trigger with a bolus of 0.5 mg Buserelin (Suprefact®, Sanofi A/S, Copenhagen, Denmark), followed by a bolus of 1500 IU hCG (Pregnyl®, MSD, Skovlunde, Denmark) after OR and an additional bolus of 1000 IU hCG (Pregnyl®) on OR + 4 days.	
Reporting group title	hCG trigger
Reporting group description:	
trigger with 6500 IU hCG (Ovitrelle®) followed by 100 mg vaginal progesterone (Lutinus®, Ferring, Copenhagen, Denmark) three times daily until the pregnancy test (14 days after OR), after which LPS was stopped.	
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.	

Primary: Ongoing pregnancy

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

End point values	GnRHa trigger	hCG trigger	modified intention to treat analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	54	104	
Units: fetal heartbeat at scan	50	54	104	

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	GnRHa trigger v hCG trigger v modified intention to treat analysis

Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Risk ratio (RR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.45

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
14 weeks	
Adverse event reporting additional description:	
We did not collect adverse events systematically	
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 systematically collect adverse events. Ovarian hyperstimulation syndrome will be reported in the publication already submitted to an international journal

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 and no blinding.

Notes: