Clinical trial results:
A Randomised Study Comparing Two Different Regimens of Ovarian Stimulation Using Pergoveris and Cetrorelix for Controlled Ovarian Superovulation in Assisted Conception Treatment.

Summary

EudraCT number	2009-012847-40
Trial protocol	GB
Global end of trial date	05 November 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2020
First version publication date	29 July 2020
Summary attachment (see zip file)	Summary (Pergoveris.pdf)

Trial information

Trial identification

Sponsor protocol code	Pergoveris_Cetrorelix_1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh/NHS Lothian
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
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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	16 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2014
Global end of trial reached?	Yes
Global end of trial date	05 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to investigate whether controlled ovarian stimulation using Pergoveris with early administration of Cetrorelix (from day 2 of period, i.e. day 1 of gonadotrophin stimulation) versus administration of cetrorelix starting on day 6 of stimulation will result in more top quality embryos.

Protection of trial subjects:

nclusion criteria:
Healthy females aged 21-38 years old, regular menses 24-35 days, less than 3 failed IVF/ICSI cycles, both ovaries present (no previous surgery), able to understand protocol and no ovarian cysts of more than 20mm

Exclusion criteria:
PCOS, severe endmetriosis, AMH,6pmol, known history of poor ovarian response during assisted conception treatment, allergic to investigational compounds, lactation, use of depot hormonal contraceptive within 6 months or use of oral contraceptive within 8 weeks of starting treatment, hypertension (systolic.150mmHg; diastolic.90mmHG, history of alcohol/drug abuse, abnormal biochemistry/haematology at screening, administration of investigational drugs within 20 days of screening and ovarian cysts of more than 20mm.

Background therapy:

This was a randomised pilot trial comparing two regimens of controlled ovarian stimulation. Pergoveris 150IU was used for ovarian stimulation which was started on day 2 of menstrual cycle. Cetrorelix 0.25mg was started on day 2 of menses versus day 7 of menstrual cycle (day 6 of ovarian stimulation).

The dose of Pergoveris was increased if the patient had poor response (less than 4 follicles or serum oestradiol less than 500 pmol/l) on day 6 of Pergoveris administration (cycle day 7) to 225IU. If there is clinical evidence of ovarian hyperstimulation (excessive follicular response), the dose of Pergoveris was reduced to 112.5IU to reduce the risk of ovarian hyperstimulation syndrome.

Evidence for comparator:

Patients were randomised to each of the study arms after recruitment.

Actual start date of recruitment	19 October 2010
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	United Kingdom: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	80
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who were undergoing IVF treatment in the Assisted Conception Unit and satisfy the inclusion criteria were approached and recruited to the study. recruitment was carried out between 19 October 2010 to 4 September 2014.
80 women were recruited.

Pre-assignment

Screening details:

I: healthy women;21-38 yrs;regular menses 24-35 ds;<3 failed IVF/ICSI cycles;both ovaries present;understand protocol.
E: PCOS;severe endometriosis;AMH < 6pmol/l;POR during IUI/IVF;allergic to IMPs; prior to COS;hypertension;alcohol/drug abuse;abnormal biochem/haematology results;IMP used in prior 20 ds, use of hormonal contraception within 2 mths

Pre-assignment period milestones

Number of subjects started	80
Number of subjects completed	80

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cetrorelix day 2 of menses

Arm description:

Patients were randomised to receive Cetrorelix 0.25mg on day 2 (early administration/EA) of menses. Pergoveris rFSH/75IUrLH was used ofr ovarian stimulation and started on day 2 of menses

Arm type	Experimental
Investigational medicinal product name	Pergoveris
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously. Pergoveris 150IU FSH and 75IU LH starting day 2 of menses

Investigational medicinal product name	Cetrotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously. Cetrotide 0.25mg daily starting on day 2 of menses

Investigational medicinal product name	Ovitrelle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Ovitrelle 0.25mg 35h before oocyte retrieval

Arm title	Cetrorelix day 7

Arm description:

Patients were randomised to receive Cetrorelix 0.25mg on day 7 (late administration/LA) on day 7 of menses. Pergoveris rFSH/75IUrLH was used for ovarian stimulation and started on day 2 of menses

Arm type	Active comparator
Investigational medicinal product name	Pergoveris
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously. Pergoveris 150IU FSH and 75IU LH starting day 2 of menses

Investigational medicinal product name	Cetrotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Cetrotide 0.25mg daily starting day 6 of Pergoveris stimulation (cycle day 7)

Investigational medicinal product name	Ovitrelle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Ovitrelle 0.25mg 35h before oocyte retrieval

Number of subjects in period 1	Cetrorelix day 2 of menses	Cetrorelix day 7
Started	40	40
Completed	40	40

Baseline characteristics

Reporting groups	
Reporting group title	Cetrorelix day 2 of menses
Reporting group description:	
Patients were randomised to receive Cetrorelix 0.25mg on day 2 (early administration/EA) of menses. Pergoveris rFSH/75IUrLH was used ofr ovarian stimulation and started on day 2 of menses	
Reporting group title	Cetrorelix day 7
Reporting group description:	
Patients were randomised to receive Cetrorelix 0.25mg on day 7 (late administration/LA) on day 7 of menses. Pergoveris rFSH/75IUrLH was used for ovarian stimulation and started on day 2 of menses	

Reporting group values	Cetrorelix day 2 of menses	Cetrorelix day 7	Total
Number of subjects	40	40	80
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)	40	40	80
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	32	33	
standard deviation	± 3.6	± 3	-
Gender categorical			
Units: Subjects			
Female	40	40	80
Male	0	0	0

End points

End points reporting groups

Reporting group title	Cetrorelix day 2 of menses
Reporting group description:	
Patients were randomised to receive Cetrorelix 0.25mg on day 2 (early administration/EA) of menses. Pergoveris rFSH/75IUrLH was used ofr ovarian stimulation and started on day 2 of menses	
Reporting group title	Cetrorelix day 7
Reporting group description:	
Patients were randomised to receive Cetrorelix 0.25mg on day 7 (late administration/LA) on day 7 of menses. Pergoveris rFSH/75IUrLH was used for ovarian stimulation and started on day 2 of menses	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients allocated to the treatment arm to which they were randomised.	

Primary: Number of top quality embryos

End point title	Number of top quality embryos
End point description:	

End point type	Primary
End point timeframe:	
Completion of treatment.	

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Number of embryos	40	40		

Statistical analyses

Statistical analysis title	Number of top quality embryos
Comparison groups	Cetrorelix day 2 of menses v Cetrorelix day 7
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.3
Variability estimate	Standard deviation

Primary: Number and size of follicles on day of hCG

End point title	Number and size of follicles on day of hCG

End point description:

End point type	Primary

End point timeframe:

35 hours before oocyte retrieval.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: mm				
median (inter-quartile range (Q1-Q3))				
6-10mm	3 (2 to 5)	2 (1 to 4)		
10-14mm	6 (4 to 8)	5 (3.5 to 7.5)		
15-16mm	3 (2 to 5)	3.5 (1.5 to 5)		
17mm or larger	5 (4 to 8)	5 (3.5 to 6)		

Statistical analyses

Statistical analysis title	Number and size of follicles on day of hCG
Comparison groups	Cetrorelix day 2 of menses v Cetrorelix day 7
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Number and quality of oocytes and transferable embyos

End point title	Number and quality of oocytes and transferable embyos

End point description:

End point type	Primary

End point timeframe:

Day of operation and embryo transfers.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Number and embyo quality	40	40		

Statistical analyses

Statistical analysis title	Number and quality of oocytes and transferable emb
Comparison groups	Cetrorelix day 2 of menses v Cetrorelix day 7
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.7
Variability estimate	Standard deviation

Primary: Endocrine profiles on day of hCG (LH)

End point title	Endocrine profiles on day of hCG (LH)

End point description:

End point type	Primary

End point timeframe:

On day of ovulation trigger.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: IU/L				
median (inter-quartile range (Q1-Q3))	1.6 (1.4 to 2.2)	1.5 (1.3 to 2.6)		

Statistical analyses

Statistical analysis title	Endocrine profiles on day of hCG (LH)
Comparison groups	Cetrorelix day 2 of menses v Cetrorelix day 7

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Endocrine profiles on day of hCG (E2)

End point title	Endocrine profiles on day of hCG (E2)

End point description:

End point type	Primary

End point timeframe:

On day of ovulation trigger.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: pmol/L				
median (inter-quartile range (Q1-Q3))	8092 (6257 to 10290)	8586 (6766 to 10546)		

Statistical analyses

Statistical analysis title	Endocrine profiles on day of hCG (E2)
Comparison groups	Cetrorelix day 7 v Cetrorelix day 2 of menses
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-929
upper limit	1796
Variability estimate	Standard deviation

Primary: Endocrine profiles on day of hCG (Progesterone)

End point title	Endocrine profiles on day of hCG (Progesterone)

End point description:

End point type	Primary
End point timeframe: On day of ovulation trigger.	

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	3.3 (3.1 to 4.6)	3.8 (3.3 to 4.5)		

Statistical analyses

Statistical analysis title	Endocrine profiles on day of hCG (Progesterone)
Comparison groups	Cetrorelix day 7 v Cetrorelix day 2 of menses
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.6
Variability estimate	Standard deviation

Secondary: Prevention of premature LH surge

End point title	Prevention of premature LH surge
End point description:	

End point type	Secondary
End point timeframe: Between randomisation and day 2 of treatment until ovulation trigger.	

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Number of patients	40	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose of r-FSH (Pergoveris)

End point title	Dose of r-FSH (Pergoveris)

End point description:

End point type	Secondary

End point timeframe:

From start of treatment to ovulation trigger.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: IU				
number (not applicable)	40	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days of administration of Pergoveris

End point title	Number of days of administration of Pergoveris

End point description:

End point type	Secondary

End point timeframe:

Starting day 2 of menses (cycle day 2), provided no ovarian cysts greater than or equal to 2 cm, up to day when three follicles are greater than or equal to 17 mm diameter.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Days	40	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Ovarian cyst formation

End point title	Ovarian cyst formation

End point description:

End point type	Secondary

End point timeframe:

From time of first administration to ovulation trigger.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Number of subjects	40	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Outcome of treatment cycle and pregnancy rate

End point title	Outcome of treatment cycle and pregnancy rate

End point description:

End point type	Secondary

End point timeframe:

Completion of treatment cycle. Clinical pregnancy rate after confirmation of heart beat at 7 weeks gestation.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Number of pregnancies	40	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of poor ovarian response

End point title	Rate of poor ovarian response

End point description:

End point type	Secondary

End point timeframe:

Defined as four or less eggs retrieved at operation.

End point values	Cetrorelix day 2 of menses	Cetrorelix day 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Number of subjects	40	40		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events refers to the study period.

Adverse event reporting additional description:

One patient had OHSS and admitted to hospital. The patient conceived from treatment and had late OHSS. The pregnancy hormone, hCG produced endogenously, stimulates the ovaries further and late OHSS is a recognised complication of IVF treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 80 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 80 (1.25%)		
Pregnancy, puerperium and perinatal conditions			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		

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