

**Clinical trial results:****PROSPECTIVE AND RANDOMIZED STUDY FOR ASSESSMENT OF CONTROLLED OVARIAN STIMULATION WITH ALFA Corifollitropin IN PATIENTS WITH OVARIAN RESPONSE EXPECTED OR POOR IN VITRO FERTILIZATION CYCLE.****Summary**

EudraCT number	2013-002027-42
Trial protocol	ES
Global end of trial date	24 April 2019

Results information

Result version number	v1 (current)
This version publication date	13 February 2022
First version publication date	13 February 2022

Trial information**Trial identification**

Sponsor protocol code	POR-ELONVA
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Instituto de Investigación Sanitaria La Fe de Valencia
Sponsor organisation address	Avenida Fernando Abril Martorell, Torre 106 A 7planta, 46026 València, , Valencia, Spain,
Public contact	UREC, INSTITUTO DE INVESTIGACION SANITARIA LA FE, 34 961246611, investigacion_clinica@iislafe.es
Scientific contact	UREC, INSTITUTO DE INVESTIGACION SANITARIA LA FE, 34 961246611, investigacion_clinica@iislafe.es

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	03 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2019
Global end of trial reached?	Yes
Global end of trial date	24 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficiency of OVARTICA STIMULATION CONTROLLED by alpha Corifollitropin, in patients with expected or poor ovarian response undergoing IVF / ICSI.

Protection of trial subjects:

The reference study was conducted in Spain under the legal framework of Royal Decree 1090/2015. It has been performed in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study has been conducted in accordance with the protocol, good clinical practice (GCP) in accordance with the guidelines of the international conference on harmonization (ICH) and regulatory requirements for participating institutions.

An appropriately performed informed consent has been used, in compliance with GCP according to ICH guidelines and approved by the CEIm of the Hospital Universitario y Politécnico La Fe. Prior to inclusion of subjects in the study, a copy of the CEIm-approved informed consent has been reviewed with the prospective participant, signed and dated. The investigator has provided a copy of each subject's signed informed consent form and has retained a copy in the subject's study file.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2013
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	Spain: 234
Worldwide total number of subjects	234
EEA total number of subjects	234

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)	234
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment ended on 07 SEPTEMBRE 2016. A number of 234 patients were included, 221 patients completed all the study procedures and 13 patients were excluded.

Pre-assignment

Screening details:

Patients ≥ 18 years of age, who have previously signed consent to participate. patients affected by subsidiary infertility who present one of the following factors: 1. history of surgical or medical treatment as a risk factor of POR. 2. poor ovarian response in response to EOC, 3 A poor ovarian response is expected due to abnormal ovarian reserve

Pre-assignment period milestones

Number of subjects started	437 ^[1]
Number of subjects completed	234

Pre-assignment subject non-completion reasons

Reason: Number of subjects	selection errors: 203
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In the pre-assigned period, 437 patients were selected, of which 203 were unsuccessful, therefore, the number of patients who did continue in the clinical trial was 234

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The randomization will be carried out by the Pharmacy Service of the Hospital U. yP. of the Hospital U.yP. La Fe Hospital through the web page www.randomization.com. A randomization list will be generated. The block randomization method will be used in the 2 treatment arms and the treatment allocation sequence will be blinded to the investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1

Arm description:

ELONVA® (CFA) + MENOPUR® HMG

Arm type	Experimental
Investigational medicinal product name	ELONVA®.
Investigational medicinal product code	CFA
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

250µg/24h from the day a follicle > 14mm is observed.

Investigational medicinal product name	MENOPUR®
Investigational medicinal product code	HMG
Other name	
Pharmaceutical forms	Solution for injection/infusion

Routes of administration	Subcutaneous use
Dosage and administration details:	
Dose: 300 IU/24h, if needed from the 8th day of EOC, until the hCG day.	
Investigational medicinal product name	ORGALUTRAN®
Investigational medicinal product code	Ganirelix
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
250µg/24h from the day a follicle > 14mm is observed.	
Investigational medicinal product name	OVITREL LE®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
6500 UI, single dose, when follicles > 17 mm are observed.	
Investigational medicinal product name	UTROGESTAN®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Vaginal use
Dosage and administration details:	
400mg/24, from embryo transfer until the day of b hCG.	
Arm title	Arm 2
Arm description:	
MENOPUR® HMG	
Arm type	Experimental
Investigational medicinal product name	MENOPUR®
Investigational medicinal product code	HMG
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
300 IU/24h from the 2nd day of the cycle, during the whole stimulation.	
Investigational medicinal product name	ORGALUTRAN®
Investigational medicinal product code	Ganirelix
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
250µg/24h from the day a follicle > 14mm is observed.	
Investigational medicinal product name	OVITREL LE®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
6500 UI, single dose, when follicles > 17 mm are observed.	

Investigational medicinal product name	UTROGESTAN®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Vaginal use

Dosage and administration details:

400mg/24, from embryo transfer until the day of b hCG.

Number of subjects in period 1	Arm 1	Arm 2
Started	117	117
Completed	112	109
Not completed	5	8
Physician decision	5	8

Baseline characteristics

Reporting groups

Reporting group title	Arm 1
Reporting group description: ELONVA® (CFA) + MENOPUR® HMG	
Reporting group title	Arm 2
Reporting group description: MENOPUR® HMG	

Reporting group values	Arm 1	Arm 2	Total
Number of subjects	117	117	234
Age categorical			
Units: Subjects			
>18	112	109	221
Not recording	5	8	13
Gender categorical			
Taking into account the equivalence and safety profile of CFA corifollitropin alfa, the active ingredient of ELONVA ®), a systematic review and meta-analysis and a Cochrane review conclude that, appears to be an alternative to daily rFSH injections in normoresponders undergoing ovarian stimulation in IVF/ICSI treatment cycles. but more is needed research to determine if long-acting FSH is safe and effective for use in low and high responder women			
Units: Subjects			
Female	117	117	234

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description:	
ELONVA® (CFA) + MENOPUR® HMG	
Reporting group title	Arm 2
Reporting group description:	
MENOPUR® HMG	

Primary: % Ongoing pregnancy rate

End point title	% Ongoing pregnancy rate
End point description:	
End point type	Primary
End point timeframe:	
20-24 weeks	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: mean				
arithmetic mean (standard deviation)				
started cycle	15.2 (± 0.33)	20.2 (± 0.33)		
ocytes retrieval	15.7 (± 0.29)	21.4 (± 0.29)		
embryo transfer	22.4 (± 0.30)	29.7 (± 0.30)		

Statistical analyses

Statistical analysis title	Ongoing pregnancy and LBR
Comparison groups	Arm 1 v Arm 2
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Median difference (final values)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.1
upper limit	5

Variability estimate	Standard deviation
Dispersion value	0.33

Notes:

[1] - The primary outcome was ongoing pregnancy rate (20-24 weeks). Additionally, due to the long and slow process of recruiting patients, we have also been able to obtain the current birth rate.

Secondary: Stimulation characteristic

End point title	Stimulation characteristic
End point description:	
End point type	Secondary
End point timeframe:	
cycle outcome	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: mean				
arithmetic mean (standard deviation)				
Cancelled cycles before OR, n(%)	4 (± 3.6)	6 (± 5.5)		
Duration of COS (days)	10.4 (± 1.99)	9.9 (± 2.07)		
Cycles with COS > 7 days, n (%)	105 (± 93.8)	100 (± 91.7)		
Dose hp-hMG (IU) from 8 ^o Day COS	1070.8 (± 546.13)	899.3 (± 600.43)		
E2 Day hCG (pg/ml)	1320 (± 634.20)	1611 (± 765.4)		
P day hCG (ng/ml)	1 (± 0.51)	0.8 (± 0.44)		
Endometrial thickness day hCG (mm)	9.9 (± 1.7)	9.9 (± 1.65)		
Total follicles day hCG	8.2 (± 3.60)	8.5 (± 3.63)		

Statistical analyses

Statistical analysis title	Cycle outcomes
Comparison groups	Arm 1 v Arm 2
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Median difference (final values)

Notes:

[2] - There were differences in the mean duration of the days of stimulation, hp-hMG doses from the 8th day of the COS, E2 levels and progesterone levels on the day of hCG, between the study groups. No significant differences were observed in other efficacy endpoints measures.

Secondary: Results of the cycle and laboratory

End point title	Results of the cycle and laboratory
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End point description:

End point type	Secondary
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End point timeframe:

Serum hCG 15 days after follicular puncture and demonstration of the presence of intrauterine gestational sac with heartbeat, by transvaginal ultrasound, 15 days after positive determination of β hCG.

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: number				
Cycles with OR, n (%)	108	103		
Nº of aspirated follicles	6	6		
Nº of oocytes retrieved	4	5		
Nº of mature oocyte (MII)	3	4		
Fertilization rate	65	63		
Nº of embryos on D +2/3	2	2		
Nº of embryos transferred	2	2		
Top quality embryos transferred	1	1		
cycles with ET n (%)	76	74		
Ciclyes with vitrified embryos n(%)	9	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Pregnancy outcome

End point title	Pregnancy outcome
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End point description:

End point type	Secondary
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End point timeframe:

Pregnancy outcomes

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Number				
Biochemical pregnancy, n	23	27		
Clinical pregnancy, n	21	26		
Ongoing pregnancy and liver Birth, n	17	22		
Miscarriage m (%)	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulatie pregnancy

End point title	Cumulatie pregnancy
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End point description:

End point type	Secondary
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End point timeframe:

gestation > 20 week.

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Percentage				
Ongoing pregnancy and LBR/ cycle, %	15	24		
Ongoing pregnancy and LBR/ OR %	16	22		
Ongoing pregnancy and LBR/ ET %	21	23		
Miscarriage rate, n(%)	7	30		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

All events that meet the definition of an AE and occur within the period from the time the patient signs the informed consent form until 28 days after the end of treatment should be recorded.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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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: No ectopic gestations and no adverse secondary effects to ovarian stimulation were observed in any of those in either study group.

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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30428403>