Clinical trial results:
Clinical effect of follicular preparation with testosterone in poor ovarian response: a randomized controlled clinical trial (TESTOPRIM)

Summary

EudraCT number	2016-004302-33
Trial protocol	ES
Global end of trial date	11 February 2019

Results information

Result version number	v1 (current)
This version publication date	16 February 2022
First version publication date	16 February 2022

Trial information

Trial identification

Sponsor protocol code	TESTOPRIM

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, 0034 961246711, investigacion_clinica@iislafe.es
Scientific contact	UREC, INSTITUTO DE INVESTIGACION SANITARIA LA FE, 0034 961246711, 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	11 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2019
Global end of trial reached?	Yes
Global end of trial date	11 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determining whether a Follicular preparation with transdermal testosterone increases the number of mature oocytes retrieved in patients diagnosed with Poor Ovarian Response and which testosterone administration regimen is more effective for this purpose.

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 August 2017
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: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	63
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Previous episode of POR defined by 3 or less oocytes retrieved with a conventional stimulation protocol. Advanced maternal age (40 years old or more) or any other factor for POR such as ovarian endometriomas, previous ovarian surgery and previous exposure to known gonadotoxic agents. At least one abnormal ovarian reserve test (AFC < 7 or AMH < 7.9

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	63
Number of subjects completed	49

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 14

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 long Testosterone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Testim®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Transdermal use

Dosage and administration details:

The dose calculated to be received by the intervention groups was 12.5 mg a day. This was equivalent to 1.25 g of the gel (10 mg per gram). Patients were instructed by the research nurse to fill an empty 2.5 ml syringe to 1.50 ml which according to the calculations performed by our pharmacy unit was the volume of gel containing 12.5 mg of testosterone. This finding was reproducible with several experiments by the pharmacy unit.

Arm title	Group 2 Short Testosterone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Testim®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Transdermal use

Dosage and administration details:

The dose calculated to be received by the intervention groups was 12.5 mg a day. This was equivalent to 1.25 g of the gel (10 mg per gram). Patients were instructed by the research nurse to fill an empty

2.5 ml syringe to 1.50 ml which according to the calculations performed by our pharmacy unit was the volume of gel containing 12.5 mg of testosterone. This finding was reproducible with several experiments by the pharmacy unit.

Arm title	Group 3 Control
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1[1]	Group 1 long Testosterone	Group 2 Short Testosterone	Group 3 Control
Started	17	16	16
Completed	17	16	16

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The globally number enrolled are all patients who have been pre-screened, under "pre-screening" all those who were not part of the clinical trial have been removed.

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 long Testosterone
Reporting group description: -	
Reporting group title	Group 2 Short Testosterone
Reporting group description: -	
Reporting group title	Group 3 Control
Reporting group description: -	

Reporting group values	Group 1 long Testosterone	Group 2 Short Testosterone	Group 3 Control
Number of subjects	17	16	16
Age categorical Units: Subjects			
>18 years	17	16	16
Gender categorical Units: Subjects			
Female	17	16	16

Reporting group values	Total		
Number of subjects	49		
Age categorical Units: Subjects			
>18 years	49		
Gender categorical Units: Subjects			
Female	49		

End points

End points reporting groups	
Reporting group title	Group 1 long Testosterone
Reporting group description: -	
Reporting group title	Group 2 Short Testosterone
Reporting group description: -	
Reporting group title	Group 3 Control
Reporting group description: -	

Primary: MII oocytes	
End point title	MII oocytes
End point description:	
End point type	Primary
End point timeframe:	
72 days	

End point values	Group 1 long Testosterone	Group 2 Short Testosterone	Group 3 Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	16	16	
Units: number				
arithmetic mean (standard deviation)				
MII oocytes	2.16 (± 2.65)	2.71 (± 2.95)	2.91 (± 2.43)	

Statistical analyses

Statistical analysis title	Poisson
Comparison groups	Group 1 long Testosterone v Group 2 Short Testosterone v Group 3 Control
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
Method	POISSON
Parameter estimate	Median difference (final values)
Point estimate	0.719
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.719
Variability estimate	Standard deviation
Dispersion value	0.71

Secondary: Testosterone Hormone

End point title	Testosterone Hormone

End point description:

End point type	Secondary

End point timeframe:

the first day of the cycle at the time of inclusion in the study, the day of initiation of controlled ovarian stimulation and the day of ovulation induction will be analyzed.

End point values	Group 1 long Testosterone	Group 2 Short Testosterone	Group 3 Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	16	16	
Units: ng/ml				
arithmetic mean (standard deviation)				
Testosterone start COS	1.67 (± 1.38)	3.03 (± 2.39)	0.14 (± 0.11)	
Testosterone HCG day	0.34 (± 0.13)	0.34 (± 0.29)	0.21 (± 0.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Androstendione Hormone

End point title	Androstendione Hormone

End point description:

End point type	Secondary

End point timeframe:

the first day of the cycle at the time of inclusion in the study, the day of initiation of controlled ovarian stimulation and the day of ovulation induction will be analyzed.

End point values	Group 1 long Testosterone	Group 2 Short Testosterone	Group 3 Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	16	16	
Units: ng/ml				
arithmetic mean (standard deviation)				
Androstendione start COS	1.46 (± 1.05)	1.85 (± 0.89)	1.27 (± 0.97)	
Androstendione HCG day	1.95 (± 0.61)	2.04 (± 0.95)	1.50 (± 0.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: s-DHEA hormone

End point title	s-DHEA hormone

End point description:

End point type	Secondary

End point timeframe:

the first day of the cycle at the time of inclusion in the study, the day of initiation of controlled ovarian stimulation and the day of ovulation induction will be analyzed.

End point values	Group 1 long Testosterone	Group 2 Short Testosterone	Group 3 Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	16	16	
Units: ng/ml				
arithmetic mean (standard deviation)				
s-DHEA start COS (ng/ml)	1899.87 (± 896.08)	2338 (± 2077.57)	1490.15 (± 675.01)	
s-DHEA HCG day (ng/ml)	1815.86 (± 532.24)	1750.75 (± 914.50)	1442.45 (± 579.10)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The investigator will report all SAEs immediately (within 24 hours) after becoming aware of the event. The report has to be communicated to the promoter. The initial report will be immediately followed by detailed written reports and reflected in the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

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 adverse side effects were reported on any of the groups, apart from one natural pregnancy during follicular
preparation in one patient allocated to Group 1 (long-testosterone). The patient discontinued the use of testosterone as soon as the pregnancy was confirmed and the pregnancy was followed-up with no complications
reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2017	Protocol changes
24 November 2017	Protocol y HIPyCI changes

Notes:

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/34312088