



## Clinical trial results:

### A phase III assessor-blinded randomised parallel group multi-centre study to compare efficacy and safety of two r-hFSH formulations (AFOLIA and Gonal-f®) in women for assisted reproductive treatment Summary

EudraCT number	2010-019287-37
Trial protocol	DE AT ES GB DK
Global end of trial date	31 December 2012

#### Results information

Result version number	v1
This version publication date	04 March 2016
First version publication date	04 March 2016

#### Trial information

##### Trial identification

Sponsor protocol code	FIN3001
-----------------------	---------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01121666
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Finox AG
Sponsor organisation address	Technikumstrasse 2, Burgdorf, Switzerland, 3401
Public contact	Julian Jenkins, Finox AG, +41 34 426 11 11, info@finoxbiotech.com
Scientific contact	Julian Jenkins, Finox AG, +41 34 426 11 11, info@finoxbiotech.com

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	Interim
Date of interim/final analysis	28 September 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2012
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to show equivalence between AFOLIA and Gonal-f® with regard to the number of oocytes retrieved in women for assisted reproductive treatment

Protection of trial subjects:

Study Design:

This was a multi-centre, assessor-blind, comparative Phase 3 study with central patient randomization. After obtaining informed consent, patients were screened for eligibility for the study. The endogenous FSH production of eligible patients was down-regulated with a GnRH-agonist. After down-regulation of endogenous FSH, patients were randomised 2:1 to receive either AFOLIA or Gonal f daily. FSH in both groups was administered s.c. A starting dose of 150 IU/day was administered in both groups. Ovarian response was assessed by vaginal ultrasound on day 1, 6, 8, and on the day of hCG application, 16 days after start of treatment with r-hFSH at the latest. For patients' safety serum E2 concentration was measured as well. After day 8 assessment, follicular development was monitored by vaginal ultrasound at 2-3 days interval. Patients received daily r-hFSH until at least 1 follicle reached a diameter of  $\geq 18$  mm and 2 additional follicles reached a diameter of  $\geq 16$  mm, but no longer than 16 days. At this time, hCG was given to trigger ovulation. Oocytes were removed and ICSI or IVF was done according to standard techniques. A maximum of two embryos were transferred 2 to 5 days after oocyte retrieval. Pregnancy rate was determined biochemically and clinically.

Criteria for Safety Evaluation:

- Adverse events
- Local and systemic adverse event pattern (incl. ovarian hyper stimulation syndrome (OHSS))
- Time to first Onset of OHSS
- Time to first Dose Reduction due to imminent OHSS
- Percentage of patients with dose reduction due to imminent OHSS
- Clinical laboratory tests
- Vital signs
- Physical examination / Health status

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2010
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: 52
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Austria: 131
Country: Number of subjects enrolled	Denmark: 112

Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Switzerland: 11
Worldwide total number of subjects	372
EEA total number of subjects	361

Notes:

<b>Subjects enrolled per age group</b>	
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)	372
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were screened and enrolled at 15 centers in six European countries from July 2010 until April 2012

### Pre-assignment

Screening details:

Of 460 participants in this trial 88 were reported as screening failures prior the group assignment

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor <sup>[1]</sup>

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	AFOLIA-150 (Follitropin Alfa)

Arm description:

Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days

Arm type	Experimental
Investigational medicinal product name	AFOLIA-150 (Follitropin alfa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

150IU per day subcutaneously for a maximum of 16 days

<b>Arm title</b>	Gonal-f® (Follitropin Alfa)
------------------	-----------------------------

Arm description:

Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days.

Arm type	Active comparator
Investigational medicinal product name	Gonal-f® (Follitropin alfa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

150IU per day subcutaneously for a maximum of 16 days

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding (masking) indicates that knowledge of the intervention assignments is hidden from participants, trial investigators, or assessors. The terminology single blind usually means that one of the three categories of individuals remains unaware of intervention assignments throughout the trial. A single-blind trial might also, confusingly, mean that the participant and investigator both know the intervention, but that the assessor remains unaware of it.

<b>Number of subjects in period 1</b>	<b>AFOLIA-150 (Follitropin Alfa)</b>	<b>Gonal-f® (Follitropin Alfa)</b>
Started	249	123
Completed	220	113
Not completed	29	10
Protocol deviation	29	10

## Baseline characteristics

### Reporting groups

Reporting group title	AFOLIA-150 (Follitropin Alfa)
Reporting group description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days	
Reporting group title	Gonal-f® (Follitropin Alfa)
Reporting group description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days.	

Reporting group values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)	Total
Number of subjects	249	123	372
Age categorical Units: Subjects			
Adults (18-64 years)	249	123	372
Age continuous Units: years			
arithmetic mean	31.8	32.1	-
standard deviation	± 4.02	± 3.76	-
Gender categorical Units: Subjects			
Female	249	123	372
Male	0	0	0
FSH baseline concentration			
The FSH concentration was measured at baseline in IU/L.			
Units: IU/L			
arithmetic mean	6.9	6.9	-
standard deviation	± 1.51	± 1.56	-
Antral follicle count Units: Antral follicle count			
arithmetic mean	15.1	15.3	-
standard deviation	± 3.77	± 3.83	-
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	22.7	22.4	-
standard deviation	± 2.9	± 2.56	-
GnRH-agonist duration Units: days			
arithmetic mean	23.5	22.7	-
standard deviation	± 7.89	± 7.46	-

### Subject analysis sets

Subject analysis set title	AFOLIA-150 (Follitropin Alfa) (Per Protocol Population)
Subject analysis set type	Per protocol
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Per Protocol Population	
Subject analysis set title	Gonal-f® (Follitropin Alfa) (Per Protocol Population)

Subject analysis set type	Per protocol
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Per Protocol Population	
Subject analysis set title	AFOLIA-150 (Follitropin Alfa) (2nd treatment cycle)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Population with a second treatment cycle	
Subject analysis set title	Gonal-f® (Follitropin Alfa) (2nd treatment cycle)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Population with a second treatment cycle	

Reporting group values	AFOLIA-150 (Follitropin Alfa) (Per Protocol Population)	Gonal-f® (Follitropin Alfa) (Per Protocol Population)	AFOLIA-150 (Follitropin Alfa) (2nd treatment cycle)
Number of subjects	220	113	72
Age categorical Units: Subjects			
Adults (18-64 years)	220	113	72
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
FSH baseline concentration			
The FSH concentration was measured at baseline in IU/L.			
Units: IU/L arithmetic mean standard deviation	±	±	±
Antral follicle count Units: Antral follicle count arithmetic mean standard deviation	±	±	±
Body Mass Index Units: kilogram(s)/square meter arithmetic mean standard deviation	±	±	±
GnRH-agonist duration Units: days arithmetic mean standard deviation	±	±	±
Reporting group values	Gonal-f® (Follitropin Alfa) (2nd treatment cycle)		
Number of subjects	38		

Age categorical			
Units: Subjects			
Adults (18-64 years)	38		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			
FSH baseline concentration			
The FSH concentration was measured at baseline in IU/L.			
Units: IU/L			
arithmetic mean			
standard deviation	±		
Antral follicle count			
Units: Antral follicle count			
arithmetic mean			
standard deviation	±		
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean			
standard deviation	±		
GnRH-agonist duration			
Units: days			
arithmetic mean			
standard deviation	±		



## End points

### End points reporting groups

Reporting group title	AFOLIA-150 (Follitropin Alfa)
Reporting group description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days	
Reporting group title	Gonal-f® (Follitropin Alfa)
Reporting group description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days.	
Subject analysis set title	AFOLIA-150 (Follitropin Alfa) (Per Protocol Population)
Subject analysis set type	Per protocol
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Per Protocol Population	
Subject analysis set title	Gonal-f® (Follitropin Alfa) (Per Protocol Population)
Subject analysis set type	Per protocol
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Per Protocol Population	
Subject analysis set title	AFOLIA-150 (Follitropin Alfa) (2nd treatment cycle)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Population with a second treatment cycle	
Subject analysis set title	Gonal-f® (Follitropin Alfa) (2nd treatment cycle)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days; Population with a second treatment cycle	

### Primary: Number of Oocytes Retrieved (Per Protocol Population)

End point title	Number of Oocytes Retrieved (Per Protocol Population)
End point description:	
As soon as ovulation criteria were reached, HCG was given to trigger ovulation and 34-36 hours later, oocytes were retrieved. If criteria for ovulation triggering could not be reached by FSH stimulation on day 16, treatment was to be stopped.	
The equivalence in the number of retrieved oocytes was tested using a pre-determined clinical equivalence margin of +/- 2.9 oocytes	
End point type	Primary
End point timeframe:	
34-36 hours after hCG administration and after maximum 16 days of r-hFSH treatment	

End point values	AFOLIA-150 (Follitropin Alfa) (Per Protocol Population)	Gonal-f® (Follitropin Alfa) (Per Protocol Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	220	113		
Units: Number of retrieved oocytes				
arithmetic mean (standard deviation)	10.8 (± 5.11)	10.6 (± 6.06)		

## Statistical analyses

<b>Statistical analysis title</b>	Number of Oocytes Retrieved (Per Protocol Pop.)
Statistical analysis description: This study was powered to test equivalence using a two one-sided test (TOST) of the number of oocytes retrieved.	
Comparison groups	AFOLIA-150 (Follitropin Alfa) (Per Protocol Population) v Gonal-f® (Follitropin Alfa) (Per Protocol Population)
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
P-value	= 0.0003 <sup>[2]</sup>
Method	Shuirmann's TOST

Notes:

[1] - This study was powered to test equivalence using a two one-sided test (TOST) of the number of oocytes retrieved with a power of 90%, an alpha error of 2.5% and a pre-determined clinical equivalence margin of +/-2.9 oocytes for the relevant population.

[2] - This study was powered to test equivalence using a two one-sided test (TOST) with a power of 90%, an alpha error of 2.5% and a pre-determined clinical equivalence margin of +/-2.9 oocytes for the relevant population.

## Primary: Number of Oocytes Retrieved (Intention-to-treat Population)

End point title	Number of Oocytes Retrieved (Intention-to-treat Population)
End point description: As soon as ovulation criteria were reached, HCG was given to trigger ovulation and 34-36 hours later, oocytes were retrieved. If criteria for ovulation triggering could not be reached by FSH stimulation on day 16, treatment was to be stopped. The equivalence in the number of retrieved oocytes was tested using a pre-determined clinical equivalence margin of +/- 2.9 oocytes	
End point type	Primary
End point timeframe: 34-36 hours after hCG administration and after maximum 16 days of r-hFSH treatment	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Number of retrieved oocytes				
arithmetic mean (standard deviation)	10.7 (± 5.62)	10.4 (± 6.14)		

## Statistical analyses

<b>Statistical analysis title</b>	Number of Oocytes Retrieved (Intention to treat)
Comparison groups	AFOLIA-150 (Follitropin Alfa) v Gonal-f® (Follitropin Alfa)
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[3]</sup>
P-value	= 0.0003
Method	Shuirmann's TOST

Notes:

[3] - This study was powered to test equivalence using a two one-sided test (TOST) of the number of oocytes retrieved with a power of 90%, an alpha error of 2.5% and a pre-determined clinical equivalence margin of +/-2.9 oocytes for the relevant population.

## Secondary: Number and Size of Follicles ≥ 12 mm at Day 8 of Stimulation

End point title	Number and Size of Follicles ≥ 12 mm at Day 8 of Stimulation
End point description:	
The number and size of follicles 12 mm or over in diameter at day 8 of stimulation were evaluated as secondary end-point.	
End point type	Secondary
End point timeframe:	
Day 8 of stimulation	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Number of follicles				
arithmetic mean (standard deviation)				
≥ 12 mm	11.8 (± 4.73)	11.1 (± 4.23)		
≥ 15 mm	8.3 (± 3.81)	7.7 (± 3.6)		
≥ 17 mm	4.9 (± 3.29)	4.5 (± 2.71)		

## Statistical analyses

<b>Statistical analysis title</b>	Number/Size of Follicles ≥ 12 mm day 8 of stimul.
Comparison groups	AFOLIA-150 (Follitropin Alfa) v Gonal-f® (Follitropin Alfa)
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2357 <sup>[4]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Follicles of 12 mm

<b>Statistical analysis title</b>	Number/Size of Follicles ≥ 12 mm day 8 of stimul.
Comparison groups	AFOLIA-150 (Follitropin Alfa) v Gonal-f® (Follitropin Alfa)

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1395 <sup>[5]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Follicles of 15 mm

<b>Statistical analysis title</b>	Number/Size of Follicles $\geq$ 12 mm day 8 of stimul.
Comparison groups	AFOLIA-150 (Follitropin Alfa) v Gonal-f® (Follitropin Alfa)
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3992 <sup>[6]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Follicles of 17 mm

### Secondary: E2 Concentration at Day 8 and at Day of hCG Administration

End point title	E2 Concentration at Day 8 and at Day of hCG Administration
End point description: The serum concentration of oestradiol was assessed at day 8 and the day of hCG administration.	
End point type	Secondary
End point timeframe: Day 8 of stimulation and at the day of hCG administration (after max. 16 days of r-FSH treatment)	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: pmol/L				
arithmetic mean (standard deviation)				
Day of hCG administration	8982.3 ( $\pm$ 6535.3)	7704.2 ( $\pm$ 5345.8)		
Day 8	3958.9 ( $\pm$ 3699.4)	3234 ( $\pm$ 2428.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Dose of r-hFSH Administered

End point title	Total Dose of r-hFSH Administered
End point description: Total dose of r-hFSH required was assessed.	

End point type	Secondary
End point timeframe:	
Day of hCG administration (after maximum 16 days of r-hFSH treatment)	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Mean total dose of r-hFSH (IU)				
arithmetic mean (standard deviation)	1555.7 (± 293)	1569.2 (± 259.2)		

### Statistical analyses

Statistical analysis title	Total Dose of r-hFSH Administered
Comparison groups	AFOLIA-150 (Follitropin Alfa) v Gonal-f® (Follitropin Alfa)
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9638
Method	Wilcoxon (Mann-Whitney)

### Secondary: Quality of Oocytes Retrieved

End point title	Quality of Oocytes Retrieved
End point description:	
Number of patients with ovum pick-up	
End point type	Secondary
End point timeframe:	
34-36 hours after hCG administration	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Participants				
Day 2	82	36		
Day 3	53	28		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Fertilisation Rate of Oocytes

End point title	Fertilisation Rate of Oocytes
-----------------	-------------------------------

End point description:

Fertilisation rate was assessed

End point type	Secondary
----------------	-----------

End point timeframe:

1 day after ovum pick-up

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Participants				
arithmetic mean (standard deviation)	66.1 (± 24.84)	64 (± 24.76)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Embryo Quality: Mean Number of Blastomeres

End point title	Embryo Quality: Mean Number of Blastomeres
-----------------	--

End point description:

Main embryo quality parameter "mean number of blastomeres"

End point type	Secondary
----------------	-----------

End point timeframe:

Day 2 of OPU/fertilisation

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Number of blastomeres at day 3				
arithmetic mean (standard deviation)	6.6 (± 2.41)	6.4 (± 2.49)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Cryopreserved 2PNs, Embryos/Blastocysts

End point title Number of Cryopreserved 2PNs, Embryos/Blastocysts

End point description:

End point type Secondary

End point timeframe:

Day 1, 2, 3 and 5 of OPU/fertilisation

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Patients with cryopreservation	103	55		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Days of r-hFSH Stimulation

End point title Number of Days of r-hFSH Stimulation

End point description:

Mean duration of stimulation was assessed.

End point type Secondary

End point timeframe:

At the day of hCG administration

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Duration of FSH medication (days)				
arithmetic mean (standard deviation)	10.6 (± 1.91)	10.7 (± 1.72)		

### Statistical analyses

Statistical analysis title Number of Days of r-hFSH Stimulation

Comparison groups AFOLIA-150 (Follitropin Alfa) v Gonal-f® (Follitropin Alfa)

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8926
Method	Wilcoxon (Mann-Whitney)

### Secondary: Number of Patients With Cycle Cancellation

End point title	Number of Patients With Cycle Cancellation
End point description:	Number of patients with cycle cancellation was assessed.
End point type	Secondary
End point timeframe:	At the end of the study

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Cycle cancellations	13	5		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Patients With Good Response

End point title	Number of Patients With Good Response
End point description:	Good response was defined as "patients with an oocyte retrieval of four or more oocytes"
End point type	Secondary
End point timeframe:	At the end of the study

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Participants	217	107		



## Statistical analyses

No statistical analyses for this end point

## Secondary: Local and Systemic Adverse Events

End point title	Local and Systemic Adverse Events
-----------------	-----------------------------------

End point description:

Assessment of patients with Ovarian hyperstimulation syndrome (OHSS), patients with OHSS and Anti-Müllerian Hormone (AMH)  $\geq 24$  pmol/L, patients with dose reduction due to risk of hyperstimulation, patients with coasting due to risk of hyperstimulation and patients with hCG withdrawal due to risk of hyperstimulation.

End point type	Secondary
----------------	-----------

End point timeframe:

During the study

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Number of patients				
Ovarian hyperstimulation syndrome (OHSS)	14	4		
Patients with OHSS and AMH $\geq 24$ pmol/L	8	1		
Patients with dose reduction	38	16		
Patients with coasting	3	3		
Patients with hCG withdrawal	5	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Implantation Rate

End point title	Implantation Rate
-----------------	-------------------

End point description:

Defined as fetal sac per embryo transferred.

End point type	Secondary
----------------	-----------

End point timeframe:

Five to six weeks after oocyte retrieval

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Percentage of implantations				
number (not applicable)	31.8	36.7		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Pregnancy Rate

End point title	Clinical Pregnancy Rate
End point description:	Presence of at least one intrauterine gestational sac.
End point type	Secondary
End point timeframe:	Five to six weeks after oocyte retrieval

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Clinical pregnancies	90	55		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ongoing Pregnancy

End point title	Ongoing Pregnancy
End point description:	Ongoing pregnancy per embryo transfer. Presence of at least one viable fetus 10 weeks after embryo transfer.
End point type	Secondary
End point timeframe:	Ten weeks after embryo transfer

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Ongoing pregnancies	84	51		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Live Birth Rate

End point title	Live Birth Rate
End point description:	
Patients with liveborn children	
End point type	Secondary
End point timeframe:	
After childbirth with questionnaire	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Patients with liveborn children	80	51		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Embryo Quality: Absence of Multinucleation

End point title	Embryo Quality: Absence of Multinucleation
End point description:	
Main embryo quality parameter "absence of multinucleation" observed.	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Percentage of absent multinucleation				
number (not applicable)	93.6	93.9		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Oocytes Retrieved

End point title	Quality of Oocytes Retrieved
End point description:	
Number of patients with transferred blastocysts	
End point type	Secondary
End point timeframe:	
At day 4 and 5	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Participants				
Day 4	10	2		
Day 5	76	46		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Oocytes Retrieved

End point title	Quality of Oocytes Retrieved
End point description:	
Number of embryos per blastocysts transferred	
End point type	Secondary
End point timeframe:	
Day of transfer	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Embryos per blastocysts transferred				
arithmetic mean (standard deviation)	1.5 (± 0.52)	1.6 (± 0.53)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Pregnancy Rate (Second Treatment Cycle)

End point title	Clinical Pregnancy Rate (Second Treatment Cycle)
End point description:	Presence of at least one intrauterine gestational sac.
End point type	Secondary
End point timeframe:	Five to six weeks after oocyte retrieval

End point values	AFOLIA-150 (Follitropin Alfa) (2nd treatment cycle)	Gonal-f® (Follitropin Alfa) (2nd treatment cycle)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	38		
Units: Clinical pregnancies	25	10		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ongoing Pregnancy (Second Treatment Cycle)

End point title	Ongoing Pregnancy (Second Treatment Cycle)
End point description:	Ongoing pregnancy per embryo transfer. Presence of at least one viable fetus 10 weeks after embryo transfer.
End point type	Secondary
End point timeframe:	10 weeks after embryo transfer

End point values	AFOLIA-150 (Follitropin Alfa) (2nd treatment cycle)	Gonal-f® (Follitropin Alfa) (2nd treatment cycle)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	38		
Units: Ongoing pregnancies	22	9		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Oocytes Retrieved

End point title	Quality of Oocytes Retrieved
End point description: The maturity of the cumulus oophorus was assessed.	
End point type	Secondary
End point timeframe: After oocyte retrieval	

End point values	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Percentage of cumulus oophori number (not applicable)				
very mature	9.1	9.4		
mature	75.7	75.3		
immature	14.2	14.2		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Oocytes Retrieved

End point title	Quality of Oocytes Retrieved
End point description: The nuclear maturity was assessed (Germinal vesicle, Metaphase I, Metaphase II).	
End point type	Secondary
End point timeframe: After oocyte retrieval	

<b>End point values</b>	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	123		
Units: Percentage of cells				
number (not applicable)				
Germinal vesicle	9.5	9.1		
Metaphase I	7.2	7.7		
Metaphase II	83.4	83.3		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Study period plus 30 days

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.1
--------------------	------

### Reporting groups

Reporting group title	AFOLIA-150 (Follitropin Alfa)
-----------------------	-------------------------------

Reporting group description:

Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days

Reporting group title	Gonal-f® (Follitropin Alfa)
-----------------------	-----------------------------

Reporting group description:

Follitropin alfa: 150IU per day subcutaneously for a maximum of 16 days.

Serious adverse events	AFOLIA-150 (Follitropin Alfa)	Gonal-f® (Follitropin Alfa)	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 249 (4.82%)	3 / 123 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 249 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	7 / 249 (2.81%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian haemorrhage			



subjects affected / exposed	1 / 249 (0.40%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Abdominal pain			
subjects affected / exposed	2 / 249 (0.80%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Biliary colic			
subjects affected / exposed	1 / 249 (0.40%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	<b>AFOLIA-150 (Follitropin Alfa)</b>	<b>Gonal-f® (Follitropin Alfa)</b>	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 249 (73.09%)	83 / 123 (67.48%)	
<b>Nervous system disorders</b>			
Headache			
subjects affected / exposed	55 / 249 (22.09%)	25 / 123 (20.33%)	
occurrences (all)	55	25	
<b>General disorders and administration site conditions</b>			
Injection site erythema			
subjects affected / exposed	68 / 249 (27.31%)	44 / 123 (35.77%)	
occurrences (all)	68	44	
Injection site haematoma			
subjects affected / exposed	60 / 249 (24.10%)	19 / 123 (15.45%)	
occurrences (all)	60	19	
Injection site pain			
subjects affected / exposed	39 / 249 (15.66%)	21 / 123 (17.07%)	
occurrences (all)	39	21	
Injection site swelling			

subjects affected / exposed	15 / 249 (6.02%)	10 / 123 (8.13%)	
occurrences (all)	15	10	
Fatigue			
subjects affected / exposed	13 / 249 (5.22%)	4 / 123 (3.25%)	
occurrences (all)	13	4	
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	55 / 249 (22.09%)	16 / 123 (13.01%)	
occurrences (all)	55	16	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	23 / 249 (9.24%)	6 / 123 (4.88%)	
occurrences (all)	23	6	
Abdominal distension			
subjects affected / exposed	14 / 249 (5.62%)	6 / 123 (4.88%)	
occurrences (all)	14	6	
Abdominal pain			
subjects affected / exposed	13 / 249 (5.22%)	6 / 123 (4.88%)	
occurrences (all)	13	6	
Abdominal pain upper			
subjects affected / exposed	7 / 249 (2.81%)	7 / 123 (5.69%)	
occurrences (all)	7	7	

## 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/25735918>