Clinical trial results:
A randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 (follitropin delta) dosing, using a long GnRH agonist protocol and a GnRH antagonist protocol in women undergoing controlled ovarian stimulation

Summary

EudraCT number	2017-002783-40
Trial protocol	AT DK NO NL IT
Global end of trial date	16 February 2022

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	000304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03809429
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	International PharmaScience Center, Amager Strandvej 405, Kastrup, Denmark, 2770
Public contact	Global Clinical Compliance, Ferring Pharmaceuticals A/S, DK0-Disclosure@ferring.com
Scientific contact	Global Clinical Compliance, Ferring Pharmaceuticals A/S, DK0-Disclosure@ferring.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	Final
Date of interim/final analysis	24 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2022
Global end of trial reached?	Yes
Global end of trial date	16 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of individualised FE 999049 treatment on ovarian response in a long GnRH agonist protocol versus a GnRH antagonist protocol

Protection of trial subjects:

The trial was performed in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2019
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	Netherlands: 57
Country: Number of subjects enrolled	Norway: 231
Country: Number of subjects enrolled	Austria: 60
Country: Number of subjects enrolled	Denmark: 31
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Israel: 25
Worldwide total number of subjects	435
EEA total number of subjects	400

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)	435
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was performed at 16 investigational sites in 7 countries between May 2019 to Feb 2022.

Pre-assignment

Screening details:

In total, 532 subjects were screened of which 437 were randomized. Of the 437 subjects, 435 subjects were included in the FAS: 220 subjects to long GnRH agonist and 215 subjects to GnRH antagonist. 406 subjects were exposed to the investigational medicinal product (IMP): 202 subjects to long GnRH agonist and 204 subjects to GnRH antagonist.

Period 1

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

Blinding implementation details:

Open Label

Arms

Are arms mutually exclusive?	Yes
Arm title	FE 999049 + GnRH agonist (GONAPEPTYL)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	FE 999049 + GnRH agonist
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Injection

Dosage and administration details:

FE 999049 in solution for subcutaneous injection; 72 µg follitropin delta in 2.16 mL pre-filled injection pen

Arm title	FE 999049 + GnRH Antagonist (CETROTIDE)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	FE 999049 + GnRH Antagonist (CETROTIDE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Injection

Dosage and administration details:

CETROTIDE (cetrorelix acetate) is provided as powder and solvent for solution for injection. After reconstitution, 1 mL solvent contains 0.25 mg cetrorelix acetate.

Number of subjects in period 1	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)
Started	220	215
Completed	192	195
Not completed	28	20
Consent withdrawn by subject	7	3
Physician decision	12	7
Adverse event, non-fatal	6	9
COVID-19	3	1

Baseline characteristics

Reporting groups	
Reporting group title	FE 999049 + GnRH agonist (GONAPEPTYL)
Reporting group description: -	
Reporting group title	FE 999049 + GnRH Antagonist (CETROTIDE)
Reporting group description: -	

Reporting group values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)	Total
Number of subjects	220	215	435
Age categorical Units: Subjects			
<35 years	143	141	284
35-37 years	47	48	95
38-40 years	30	26	56
Age continuous Units: years			
arithmetic mean	32.3	32.4	
standard deviation	± 4.4	± 4.2	-
Gender categorical Units: Subjects			
Female	220	215	435
Male	0	0	0
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	24.36	24.39	
standard deviation	± 3.50	± 3.55	-

End points

End points reporting groups	
Reporting group title	FE 999049 + GnRH agonist (GONAPEPTYL)
Reporting group description: -	
Reporting group title	FE 999049 + GnRH Antagonist (CETROTIDE)
Reporting group description: -	

Primary: Number of Oocytes Retrieved	
End point title	Number of Oocytes Retrieved
End point description: The number of oocytes retrieved was recorded at the oocyte retrieval visit.	
End point type	Primary
End point timeframe: On day of oocyte retrieval (up to 22 days after start of stimulation)	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Oocytes				
arithmetic mean (standard deviation)	11.1 (± 5.9)	9.6 (± 5.5)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0185 [2]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	2.4

Notes:

[1] - Subjects in this analysis: 435

[2] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Secondary: Proportion of Subjects With Cycle Cancellation Due to Poor Ovarian Response or Excessive Ovarian Response

End point title	Proportion of Subjects With Cycle Cancellation Due to Poor Ovarian Response or Excessive Ovarian Response

End point description:

For each subject, the reason for cycle cancellation was recorded.

End point type	Secondary

End point timeframe:

At end-of-stimulation (up to 20 days)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
Excessive response	2	3		
Poor response	1	3		
Other reason	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Blastocyst Transfer Cancellation After Oocyte Retrieval Due to (Risk of) Ovarian Hyperstimulation Syndrome (OHSS)

End point title	Proportion of Subjects With Blastocyst Transfer Cancellation After Oocyte Retrieval Due to (Risk of) Ovarian Hyperstimulation Syndrome (OHSS)

End point description:

For each subject, the reason for blastocyst transfer cancellation was recorded.

End point type	Secondary

End point timeframe:

At end of transfer (up to 4 weeks)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
Transfer cancellation	27	30		
No transfer cancellation	171	167		
N/A	4	7		
Reason for transfer cancellation: Adverse Event	5	8		
Reason for transfer cancellation: Risk of OHSS	1	1		
Reason for transfer cancellation: No blastocyst	13	18		
Reason for transfer cancellation: COVID-19	3	1		
Reason for transfer cancellation: Other reason	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Follicles

End point title	Number of Follicles
End point description:	
The total number of follicles and the number of follicles per size category will be reported	
End point type	Secondary
End point timeframe:	
On stimulation day 6 and at end-of-stimulation (up to 20 days)	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Follicles				
arithmetic mean (standard deviation)				
Total number of follicles at Stimulation Day 6	15.2 (± 6.3)	14.9 (± 6.3)		
Follicles >= 10 mm at Stimulation Day 6	4.6 (± 4.3)	7.1 (± 3.6)		
Follicles >= 12 mm at Stimulation Day 6	1.6 (± 2.7)	3.8 (± 2.9)		
Total number of follicles at End-of-stimulation	18.3 (± 7.1)	17.1 (± 8.0)		

Follicles >= 10 mm at End-of-stimulation visit	14.8 (± 6.4)	13.3 (± 6.1)		
Follicles >= 12 mm at End-of-stimulation visit	12.2 (± 5.3)	10.9 (± 5.1)		
Follicles >= 15 mm at End-of-stimulation visit	7.9 (± 3.7)	7.2 (± 3.3)		
Follicles >= 17 mm at End-of-stimulation visit	4.8 (± 2.1)	4.6 (± 2.0)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description:	
>=8 mm at end-of-stimulation	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1095 [3]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	2.02

Notes:

[3] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description:	
>=10 mm at end-of-stimulation	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0281 [4]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	2.15

Notes:

[4] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description:	
>=12 mm at end-of-stimulation	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0258 [5]
Method	Negative-binomial regression
Parameter estimate	Difference
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.86

Notes:

[5] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description:	
>=15 mm at end-of-stimulation	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0672 [6]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	1.2

Notes:

[6] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description:	
>=17 mm at end-of-stimulation	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.339 [7]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.63

Notes:

[7] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Secondary: Proportion of Subjects With <4, 4-7, 8-14, 15-19 and ≥20 Oocytes Retrieved

End point title	Proportion of Subjects With <4, 4-7, 8-14, 15-19 and ≥20 Oocytes Retrieved

End point description:

Grouped according to number of oocytes

End point type	Secondary

End point timeframe:

On day of oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
<4	13	26		
4-7	47	56		
8-14	84	82		
15-19	42	29		
>=20	16	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Metaphase II Oocytes

End point title	Number of Metaphase II Oocytes

End point description:

Only applicable for those inseminated using ICSI

End point type	Secondary

End point timeframe:

On day of oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	99		
Units: MII oocytes				
arithmetic mean (standard deviation)	9.2 (± 4.8)	7.9 (± 4.7)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0962 [8]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	2.41

Notes:

[8] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Secondary: Fertilization Rate

End point title	Fertilization Rate

End point description:

Measured by the number of pronuclei. Fertilized oocytes with 2 pronuclei were regarded as correctly fertilized

End point type	Secondary

End point timeframe:

On day 1 after oocyte retrieval (up to 23 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	197		
Units: Percentage of fertilized oocytes				
arithmetic mean (standard deviation)	53.8 (± 24.1)	54.4 (± 26.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Embryos

End point title	Number of Embryos

End point description:

The number of embryos (total and good-quality) was reported. Embryo quality is determined by combined assessment of cleavage stage (number of blastomeres/compaction status) and embryo morphology parameters

End point type	Secondary

End point timeframe:

On day 3 after oocyte retrieval (up to 25 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Embryos				
arithmetic mean (standard deviation)				
Total number of embryos	5.7 (± 3.9)	5.0 (± 3.9)		
Number of good-quality embryos	4.0 (± 3.2)	3.9 (± 3.3)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist

Statistical analysis description:

Number of embryos

Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.1894 [10]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	1.27

Notes:

[9] - Subjects in this analysis: 435

[10] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist

Statistical analysis description:

Number of Good-quality embryos

Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.9361 [12]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.63

Notes:

[11] - Subjects in this analysis: 435

[12] - Negative binomial regression model with treatment, age strata, and AMH group as factors

Secondary: Number of Blastocysts

End point title	Number of Blastocysts

End point description:

The number of blastocysts (total and good-quality) was reported. Blastocyst quality is assessed by blastocyst expansion and hatching status, blastocyst inner cell mass grading, and trophectoderm grading. The scoring is based on the classification system by Gardner and Schoolcraft, with additional categories for inner cell mass (degenerative or no inner cell mass) and trophectoderm (degenerative or very large cells)

End point type	Secondary

End point timeframe:

On day 5 after oocyte retrieval (up to 27 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Blastocysts				
arithmetic mean (standard deviation)				
Total number of blastocysts	3.8 (± 3.1)	3.3 (± 2.9)		
Number of good-quality blastocysts	2.3 (± 2.3)	2.1 (± 2.2)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description: Total number of blastocysts	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.2025 [14]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.94

Notes:

[13] - Subjects in this analysis: 435

[14] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Statistical analysis description: Number of good-quality blastocysts	
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.5946 [16]
Method	Negative binomial regression
Parameter estimate	Difference
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.54

Notes:

[15] - Subjects in this analysis: 435

[16] - Negative binomial regression model with treatment, age strata, and AMH group as factors.

Secondary: Circulating Concentrations of Follicle-stimulating Hormone (FSH)

End point title	Circulating Concentrations of Follicle-stimulating Hormone (FSH)

End point description:

Blood samples for analysis of circulating concentrations of FSH were drawn.

FE 999049 + GnRH agonist (GONAPEPTYL): Stimulation Day 6 (n=198), End-of-stimulation (n=199), Oocyte retrieval (n=196)
FE 999049 + GnRH Antagonist (CETROTIDE): Stimulation Day 6 (n=198), End-of-stimulation (n=200), Oocyte retrieval (n=195)

End point type	Secondary

End point timeframe:

On stimulation day 6, at end-of-stimulation (up to 20 days after start of stimulation) and at oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	200		
Units: IU/L				
arithmetic mean (standard deviation)				
Stimulation Day 6	15.5 (± 4.3)	16.7 (± 4.5)		
End-of-stimulation	16.2 (± 4.4)	15.8 (± 4.0)		
Oocyte retrieval	9.4 (± 2.8)	9.8 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Concentrations of Luteinizing Hormone (LH)

End point title	Circulating Concentrations of Luteinizing Hormone (LH)

End point description:

Blood samples for analysis of circulating concentrations of LH were drawn

FE 999049 + GnRH agonist (GONAPEPTYL): Stimulation Day 6 (n=199), End-of-stimulation (n=199), Oocyte retrieval (n=196)
FE 999049 + GnRH Antagonist (CETROTIDE): Stimulation Day 6 (n=198), End-of-stimulation (n=200), Oocyte retrieval (n=195)

End point type	Secondary

End point timeframe:

On stimulation day 6, at end-of-stimulation (up to 20 days after start of stimulation) and at oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	200		
Units: IU/L				
arithmetic mean (standard deviation)				
Stimulation Day 6	1.5 (± 0.9)	5.6 (± 6.0)		
End-of-stimulation	1.8 (± 0.9)	1.8 (± 1.5)		
Oocyte retrieval	0.2 (± 0.2)	2.0 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Concentrations of Estradiol

End point title	Circulating Concentrations of Estradiol

End point description:

Blood samples for analysis of circulating concentrations of estradiol were drawn

FE 999049 + GnRH agonist (GONAPEPTYL): Stimulation Day 6 (n=198), End-of-stimulation (n=199), Oocyte retrieval (n=196)
FE 999049 + GnRH Antagonist (CETROTIDE): Stimulation Day 6 (n=200), End-of-stimulation (n=201), Oocyte retrieval (n=195)

End point type	Secondary

End point timeframe:

On stimulation day 6, at end-of-stimulation (up to 20 days after start of stimulation) and at oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: pmol/L				
arithmetic mean (standard deviation)				
Stimulation Day 6	1190.1 (± 1101.2)	2675.8 (± 1544.3)		
End-of-stimulation	7542.7 (± 4106.8)	6487.7 (± 3960.2)		
Oocyte retrieval	3485.1 (± 2129.0)	3163.5 (± 1865.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Concentrations of Progesterone

End point title	Circulating Concentrations of Progesterone

End point description:

Blood samples for analysis of circulating concentrations of progesterone were drawn

FE 999049 + GnRH agonist (GONAPEPTYL): Stimulation Day 6 (n=198), End-of-stimulation (n=200), Oocyte retrieval (n=195)
FE 999049 + GnRH Antagonist (CETROTIDE): Stimulation Day 6 (n=198), End-of-stimulation (n=200), Oocyte retrieval (n=195)

End point type	Secondary

End point timeframe:

On stimulation day 6, at end-of-stimulation (up to 20 days after start of stimulation) and at oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: nmol/L				
arithmetic mean (standard deviation)				
Stimulation Day 6	1.8 (± 1.0)	2.6 (± 1.5)		
End-of-stimulation	3.1 (± 1.4)	3.5 (± 2.0)		
Oocyte retrieval	25.9 (± 12.9)	26.0 (± 13.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Concentrations of Inhibin B

End point title	Circulating Concentrations of Inhibin B

End point description:

Blood samples for analysis of circulating concentrations of Inhibin B were drawn

FE 999049 + GnRH agonist (GONAPEPTYL): Stimulation Day 6 (n=195), End-of-stimulation (n=196), Oocyte retrieval (n=192)
FE 999049 + GnRH Antagonist (CETROTIDE): Stimulation Day 6 (n=198), End-of-stimulation (n=197), Oocyte retrieval (n=191)

End point type	Secondary

End point timeframe:

On stimulation day 6, at end-of-stimulation (up to 20 days after start of stimulation) and at oocyte retrieval (up to 22 days after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	198		
Units: pg/mL				
arithmetic mean (standard deviation)				
Stimulation Day 6	690.4 (± 419.1)	808.2 (± 428.5)		
End-of-stimulation	1032.6 (± 605.2)	938.1 (± 570.0)		
Oocyte retrieval	416.6 (± 253.9)	389.0 (± 226.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Gonadotropin Dose

End point title	Total Gonadotropin Dose

End point description:

Calculated by start dates, end dates and daily dose of investigational medicinal product

End point type	Secondary

End point timeframe:

Up to 20 days

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: ug				
arithmetic mean (standard deviation)	112.2 (± 28.9)	96.5 (± 26.0)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [17]
Method	ANOVA
Parameter estimate	Difference
Point estimate	16.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.13
upper limit	21.74

Notes:

[17] - ANOVA model with treatment, age strata, and AMH group as factors.

Secondary: Number of Stimulation Days	
End point title	Number of Stimulation Days
End point description:	
Calculated by start dates and end dates	
End point type	Secondary
End point timeframe:	
Up to 20 days	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Days				
arithmetic mean (standard deviation)	10.4 (± 1.9)	8.8 (± 1.8)		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [18]
Method	ANOVA
Parameter estimate	Difference
Point estimate	1.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.92

Notes:

[18] - ANOVA model with treatment, age strata, and AMH group as factors.

Secondary: Positive Beta Human Chorionic Gonadotropin (βhCG) Rate

End point title	Positive Beta Human Chorionic Gonadotropin (βhCG) Rate
End point description:	
Defined as positive serum βhCG test	
End point type	Secondary
End point timeframe:	
13-15 days after transfer (up to approximately 1.5 months after start of stimulation)	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
Positive βhCG test	91	79		
Negative βhCG test	111	125		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.1579 [20]
Method	Regression, Logistic
Parameter estimate	Difference
Point estimate	6.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	16.7

Notes:

[19] - Subjects in this analysis: 431

[20] - Logistic regression model with treatment, age strata, and AMH group as factors.

Secondary: Implantation Rate

End point title	Implantation Rate
End point description:	
Defined as the number of gestational sacs after transfer divided by number of blastocysts transferred	
End point type	Secondary
End point timeframe:	
5-6 weeks after transfer (up to approximately 2.5 months after start of stimulation)	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	167		
Units: Embryos				
number (not applicable)	82	68		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Pregnancy Rate

End point title	Clinical Pregnancy Rate
End point description:	
Defined as at least one gestational sac	
End point type	Secondary
End point timeframe:	
5-6 weeks after transfer (up to approximately 2.5 months after start of stimulation)	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
Positive	81	68		
Negative	121	136		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.1134 [22]
Method	Regression, Logistic
Parameter estimate	Difference
Point estimate	7.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	17.14

Notes:

[21] - Subjects in this analysis: 431

[22] - Logistic regression model with treatment, age strata, and AMH group as factors.

Secondary: Vital Pregnancy Rate

End point title	Vital Pregnancy Rate

End point description:

Defined as at least one intrauterine gestational sac with fetal heart beat

End point type	Secondary

End point timeframe:

5-6 weeks after transfer (up to approximately 2.5 months after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
Positive	77	62		
Negative	125	142		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.0642 [24]
Method	Regression, Logistic
Parameter estimate	Difference
Point estimate	8.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	18.14

Notes:

[23] - Subjects in this analysis: 431

[24] - Logistic regression model with treatment, age strata, and AMH group as factors.

Secondary: Ongoing Pregnancy Rate

End point title	Ongoing Pregnancy Rate

End point description:

At least one intrauterine viable fetus

End point type	Secondary

End point timeframe:

10-11 weeks after transfer (up to approximately 4 months after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)				
Positive	73	60		
Negative	129	144		

Statistical analyses

Statistical analysis title	FE 999049 GnRH Agonist, FE 999049 GnRH Antagonist
Comparison groups	FE 999049 + GnRH agonist (GONAPEPTYL) v FE 999049 + GnRH Antagonist (CETROTIDE)

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.1002 [26]
Method	Regression, Logistic
Parameter estimate	Difference
Point estimate	7.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	16.97

Notes:

[25] - Subjects in this analysis: 431

[26] - Logistic regression model with treatment, age strata, and AMH group as factors.

Secondary: Ongoing Implantation Rate

End point title	Ongoing Implantation Rate

End point description:

Defined as number of intrauterine viable fetuses divided by the number of blastocysts transferred

End point type	Secondary

End point timeframe:

10-11 weeks after transfer (up to approximately 4 months after start of stimulation)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	167		
Units: Embryos				
number (not applicable)	74	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Early OHSS (Including OHSS of Moderate/Severe Grade)

End point title	Proportion of Subjects With Early OHSS (Including OHSS of Moderate/Severe Grade)

End point description:

Measured as mild, moderate or severe

End point type	Secondary

End point timeframe:

Up to 9 days after triggering of final follicular maturation

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Late OHSS (Including OHSS of Moderate/Severe Grade)

End point title	Proportion of Subjects With Late OHSS (Including OHSS of Moderate/Severe Grade)
End point description:	
Measured as mild, moderate or severe	
End point type	Secondary
End point timeframe:	
>9 days after triggering of final follicular maturation	

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Adverse Events

End point title	Frequency of Adverse Events
End point description:	
Any untoward medical occurrence	
End point type	Secondary

End point timeframe:

From time of signing informed consent until the end-of-trial (approximately 7 months)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)	112	109		

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of Adverse Events

End point title	Intensity of Adverse Events

End point description:

Categorized as mild, moderate or severe

End point type	Secondary

End point timeframe:

From time of signing informed consent until the end-of-trial (approximately 7 months)

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Percentage of subjects				
number (not applicable)				
Mild adverse events	42.6	41.7		
Moderate adverse events	18.8	16.7		
Severe adverse events	4.0	3.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Technical Malfunctions of the Pre-filled Injection Pen

End point title	Technical Malfunctions of the Pre-filled Injection Pen

End point description:

Incidences of technical malfunctions of the pre-filled injection pen were recorded

End point type	Secondary

End point timeframe:

Up to 20 days

End point values	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Subjects				
number (not applicable)	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were recorded from signing of the informed consent until end-of-trial.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	FE 999049 + GnRH agonist (GONAPEPTYL)
Reporting group description: -	
Reporting group title	FE 999049 + GnRH Antagonist (CETROTIDE)
Reporting group description: -	

Serious adverse events	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 202 (1.98%)	6 / 204 (2.94%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	0 / 202 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 202 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian hyperstimulation syndrome			
subjects affected / exposed	2 / 202 (0.99%)	4 / 204 (1.96%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 202 (0.50%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial abdominal infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	FE 999049 + GnRH agonist (GONAPEPTYL)	FE 999049 + GnRH Antagonist (CETROTIDE)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 202 (33.66%)	69 / 204 (33.82%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	20 / 202 (9.90%)	12 / 204 (5.88%)	
occurrences (all)	20	12	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 202 (13.37%)	29 / 204 (14.22%)	
occurrences (all)	31	30	
Pregnancy, puerperium and perinatal conditions			
Biochemical pregnancy			
subjects affected / exposed	10 / 202 (4.95%)	11 / 204 (5.39%)	
occurrences (all)	10	11	
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	12 / 202 (5.94%)	11 / 204 (5.39%)	
occurrences (all)	12	11	
Pelvic pain			
subjects affected / exposed	14 / 202 (6.93%)	11 / 204 (5.39%)	
occurrences (all)	15	12	

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? Yes

Date	Interruption	Restart date
20 March 2020	A clinical trial application amendment was issued as an urgent safety measure due to the COVID-19 pandemic to protect subjects against immediate hazard to their health and safety. This amendment described a temporary halt of recruitment, i.e. a pause of screening and randomisation in the trial, and provided guidance for continued trial conduct and management of subjects included in the trial. All actively recruiting sites were informed about the temporary halt of recruitment on 20 March 2020. Sites in Israel were also informed about the temporary halt of recruitment, although they were not yet actively recruiting at the time of the COVID-19 pandemic trial hold. Trial activities were allowed to be resumed as per protocol in June 2020 in Austria, Denmark, Italy, the Netherlands, Norway and Switzerland, when it was judged that the situation allowed for this.	-

Notes:

Limitations and caveats

None reported