Clinical trial results:
A randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response of a starting dose of 15 µg follitropin delta (REKOVELLE) to a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme.

Summary

EudraCT number	2021-001785-38
Trial protocol	ES IT FR AT
Global end of trial date	16 April 2024

Results information

Result version number	v1 (current)
This version publication date	28 March 2025
First version publication date	28 March 2025
Summary attachment (see zip file)	Trial results (Result synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	000401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05263388
WHO universal trial number (UTN)	U1111-1267-1119

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	Amager Strandvej 405, Kastrup, Denmark, 2770
Public contact	Global Clinical Compliance, Ferring Pharmaceuticals A/S, +1 8622865200, disclosure@ferring.com
Scientific contact	Global Clinical Compliance, Ferring Pharmaceuticals A/S, +1 8622865200, 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	23 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare a starting dose of 15 µg Rekovelle to a starting dose of 225 IU Gonal-f in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation. The trial consisted of a stimulation period of max 20 days, during which a GnRH antagonist was initiated on stimulation day 5 or day 6 and continued throughout the stimulation period. After stimulation, triggering of final follicular maturation was done with either human chorionic gonadotropin (hCG) or a GnRH agonist. After triggering, oocyte retrieval occurred within 36h (±2h). After fertilization, either fresh or thawed blastocysts were transferred. The end-of-trial visit took place within max 14 days after triggering.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and International Council for Harmonisation (ICH) Good Clinical Practice (2016).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2022
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	United Kingdom: 42
Country: Number of subjects enrolled	Spain: 132
Country: Number of subjects enrolled	Austria: 68
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 50
Worldwide total number of subjects	300
EEA total number of subjects	258

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	300
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 17 investigational sites in 5 countries randomised participants in the trial: 2 sites in Austria, 2 in France, 4 in Italy, 7 in Spain, 2 in United Kingdom.

Pre-assignment

Screening details:

Participants were screened within 90 days prior to randomisation, for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects were randomised in a 2:1 ratio to treatment with either REKOVELLE or GONAL-F, and stimulation was initiated.

Period 1

Period 1 title	Trial main part (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Data analyst, Assessor[2]

Blinding implementation details:

The trial was open-label but assessor-blind. The assessor-blinding ensured blinding and thereby unbiased evaluation by the investigators and other assessors such as embryologists. Similarly, sponsor staff also remained blinded to individual participant treatment allocation during the conduct of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rekovelle (follitropin delta)

Arm description:

Rekovelle administered as single daily subcutaneous injections in the abdomen.

Arm type	Experimental
Investigational medicinal product name	Rekovelle
Investigational medicinal product code	
Other name	follitropin delta, FE 999049
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Rekovelle administered as single daily subcutaneous injections in the abdomen. Daily starting dose of 15 µg, fixed for at least the first four stimulation days. Dose adjustments could be implemented on the day of starting the gonadotropin-releasing hormone antagonist (stimulation day 5 or day 6) or later, and could occur no more frequently than once every second day. At each dose adjustment, the daily Rekovelle dose could be increased or decreased by 5 µg based on the participant’s response. The minimum Rekovelle dose was 5 µg and the maximum Rekovelle dose was 20 µg. Participants could be treated for a maximum of 20 days.

Arm title	Gonal-f (follitropin alfa)

Arm description:

Gonal-f administered as single daily subcutaneous injections in the abdomen.

Arm type	Active comparator
Investigational medicinal product name	Gonal-f
Investigational medicinal product code	
Other name	follitropin alfa
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Gonal-f administered as single daily subcutaneous injections in the abdomen. Daily starting dose of 225 IU, fixed for at least the first four stimulation days. Dose adjustments could be implemented on the day

of starting the gonadotropin-releasing hormone antagonist (stimulation day 5 or day 6) or later, and could occur no more frequently than once every second day. At each dose adjustment, the daily Gonal-f dose could be adjusted by 75 IU based on the participant’s response. The minimum Gonal-f dose was 75 IU and the maximum Gonal-f dose was 300 IU. Participants could be treated for a maximum of 20 days.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The trial was single-blinded, as it was open-label but assessor-blind. The assessor-blinding ensured blinding and thereby unbiased evaluation by the investigators and other assessors such as embryologists. Similarly, sponsor staff (including 'Data Analyst') also remained blinded to individual participant treatment allocation during the conduct of the trial.

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

Justification: The trial was single-blinded, as it was open-label but assessor-blind. The assessor-blinding ensured blinding and thereby unbiased evaluation by the investigators and other assessors such as embryologists. Similarly, sponsor staff (including 'Data Analyst') also remained blinded to individual participant treatment allocation during the conduct of the trial.

Number of subjects in period 1	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)
Started	200	100
Completed	196	94
Not completed	4	6
No end-of-trial visit but performed follow-up	1	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2
Cycle cancellation due to poor ovarian response	-	1
Started 2nd ovarian stimulation in luteal phase	1	-
Participant withdrew from trial	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rekovelle (follitropin delta)
Reporting group description:	
Rekovelle administered as single daily subcutaneous injections in the abdomen.	
Reporting group title	Gonal-f (follitropin alfa)
Reporting group description:	
Gonal-f administered as single daily subcutaneous injections in the abdomen.	

Reporting group values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)	Total
Number of subjects	200	100	300
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	200	100	300
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.5	34.5	
standard deviation	± 3.8	± 3.4	-
Gender categorical Units: Subjects			
Female	200	100	300
Male	0	0	0

End points

End points reporting groups	
Reporting group title	Rekovelle (follitropin delta)
Reporting group description:	
Rekovelle administered as single daily subcutaneous injections in the abdomen.	
Reporting group title	Gonal-f (follitropin alfa)
Reporting group description:	
Gonal-f administered as single daily subcutaneous injections in the abdomen.	

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	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: oocytes				
median (inter-quartile range (Q1-Q3))	9.0 (6.0 to 13.5)	9.0 (6.5 to 13.0)		

Statistical analyses

Statistical analysis title	Primary analysis of primary endpoint
Comparison groups	Rekovelle (follitropin delta) v Gonal-f (follitropin alfa)
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.2

Secondary: Number of follicles (total) at end-of-stimulation

End point title	Number of follicles (total) at end-of-stimulation

End point description:

Counted by ultrasound for the right and left ovary for each participant.

End point type	Secondary

End point timeframe:

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

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: follicles				
median (inter-quartile range (Q1-Q3))	12.0 (9.0 to 16.0)	12.0 (9.0 to 16.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Size of the follicles at end-of-stimulation

End point title	Size of the follicles at end-of-stimulation

End point description:

Measured by ultrasound for the right and left ovary for each subject.

End point type	Secondary

End point timeframe:

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

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	99		
Units: mm				
median (inter-quartile range (Q1-Q3))	15.7 (14.7 to 16.8)	16.0 (15.1 to 16.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of estradiol at end-of-stimulation

End point title	Serum concentrations of estradiol at end-of-stimulation

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	96		
Units: pmol/L				
median (inter-quartile range (Q1-Q3))	6085.0 (3516.0 to 8602.0)	5853.5 (4053.5 to 9742.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of progesterone at end-of-stimulation

End point title	Serum concentrations of progesterone at end-of-stimulation

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	96		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	2.9 (1.9 to 3.8)	2.5 (1.6 to 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of fertilized oocytes

End point title	Number of fertilized oocytes

End point description:

The number of pronuclei were counted after insemination. Fertilized oocytes with 2 pronuclei (2PN) 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	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: fertilized oocytes				
median (inter-quartile range (Q1-Q3))	5.0 (3.0 to 8.0)	5.0 (3.0 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fertilization rate

End point title	Fertilization rate

End point description:

The fertilization rate was defined as the number of oocytes with 2 pronuclei (2PN) divided by the number of oocytes retrieved.

End point type	Secondary

End point timeframe:

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

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	96		
Units: fertilized oocytes (%)				
median (inter-quartile range (Q1-Q3))	54.5 (40.0 to 71.4)	57.7 (40.0 to 71.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Blastocysts and Number of Good Quality Blastocysts

End point title	Number of Blastocysts and Number of Good Quality Blastocysts

End point description:

The quality evaluation of blastocysts consisted of assessment of three parameters, as per the Gardner & Schoolcraft system: blastocyst expansion and hatching status (graded: 1-6), inner cell mass (graded: A-D) and trophectoderm (graded: A-D). A good-quality blastocyst was defined as a blastocyst of grade 3BB or higher.

End point type	Secondary

End point timeframe:

On Day 5 or Day 6 (as applicable) after oocyte retrieval (up to 27 or 28 days after start of stimulation).

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: blastocysts				
median (inter-quartile range (Q1-Q3))				
Blastocytes in total	2.0 (1.0 to 5.0)	3.0 (1.0 to 4.5)		
Good-quality blastocyts	2.0 (1.0 to 4.0)	2.0 (0.0 to 3.0)		

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 (IMP).

End point type	Secondary

End point timeframe:

Up to 20 stimulation days.

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: microgram				
median (inter-quartile range (Q1-Q3))	135.0 (120.0 to 160.0)	148.5 (137.5 to 165.0)		

Statistical analyses

No statistical analyses for this end point

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 stimulation days.

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: days				
median (inter-quartile range (Q1-Q3))	9.0 (8.0 to 10.0)	9.0 (8.0 to 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with early ovarian hyperstimulation syndrome (OHSS) (overall and by grade) and/or preventive interventions for early OHSS

End point title	Proportion of subjects with early ovarian hyperstimulation syndrome (OHSS) (overall and by grade) and/or preventive interventions for early OHSS

End point description:

Early ovarian hyperstimulation syndrome (OHSS) was defined as OHSS with onset ≤9 days after triggering of final follicular maturation. Classification of grade was according to Golan's classification system, and all OHSS cases were graded as mild, moderate or severe. Unit: %.

End point type	Secondary

End point timeframe:

Time Frame: Up to 9 days after triggering of final follicular maturation.

End point values	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	100		
Units: Proportion of subjects (%)				
number (not applicable)				
Early OHSS (any grade)	2.5	3.0		

Early OHSS (moderate/severe)	0.5	1.0		
Early OHSS (any grade) and/or preventive interv.	16.5	17.0		
Early OHSS (mod/sev) and/or preventive interv.	15.0	16.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events with onset after start of IMP administration and up to and including the end-of-trial visit.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	Rekovelle (follitropin delta)
Reporting group description: -	
Reporting group title	Gonal-f (follitropin alfa)
Reporting group description: -	

Serious adverse events	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 200 (0.00%)	2 / 100 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Haemoperitoneum			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 200 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rekovelle (follitropin delta)	Gonal-f (follitropin alfa)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 200 (12.00%)	11 / 100 (11.00%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 200 (11.50%)	8 / 100 (8.00%)	
occurrences (all)	27	12	
Reproductive system and breast			

disorders Pelvic pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 200 (0.50%) 1	 5 / 100 (5.00%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2022	The main protocol updates introduced with amendment were the addition of exclusion criteria, addition of specific trial stopping criteria, collection of late OHSS data, and changes related to switching EDC system (including a switch to performing randomisation through the IRT system). In addition, the amendment introduced the possibility to use different formulations of a non-investigational medicinal product (OVITRELLE). Finally, it introduced a change to the duration of culturing blastocysts (removal of day 3 as option for last day of culture; all blastocysts cultured to day 5 or 6), and the possibility of triggering with GnRH agonist in case the participant was at risk of developing OHSS, to align with other clinical trial protocols in development for follitropin delta (REKOVELLE) at the same time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported