CLINICAL TRIAL REPORT
Synopsis

TITLE OF TRIAL

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

Sponsor Trial Code: 000401 **Universal Trial Number:** U1111-1267-1119 **Pediatric status:** Not applicable	**ClinicalTrials.gov identifier:** NCT05263388 **EudraCT number:** 2021-001785-38

NAME OF ACTIVE SUBSTANCE

FE 999049 (follitropin delta)

NAME OF SPONSOR

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SIGNATORY INVESTIGATOR

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TRIAL SITES

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

PUBLICATION

Not applicable

TRIAL PERIOD	**CLINICAL PHASE**
Initiation date (first patient first visit): 01-Aug-2022 Global completion date (last patient last visit): 16-Apr-2024 Database lock (of the main part of the trial): 08-May-2024 Database lock (of the pregnancy follow-up): 23-Aug-2024	Phase 3b

DATA CUT-OFF DATE

The report reflects the data in the clinical database as of 23-Aug-2024

RATIONALE FOR THE TRIAL

Follitropin delta (REKOVELLE) is a human recombinant follicle-stimulating hormone (rFSH) under development by Ferring Pharmaceuticals. The indication is: “Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle”.

The posology for REKOVELLE is individualised for each patient based on her body weight and anti-Müllerian hormone (AMH). It is a fixed-dose regimen, with the daily dose maintained throughout the stimulation period. The maximum daily dose of REKOVELLE is 12 µg in the first treatment cycle and 24 µg in subsequent treatment cycles.

Other rFSH preparations, such as follitropin alfa (GONAL-F) and follitropin beta (PUREGON / FOLLISTIM), apply a conventional dosing approach with a starting dose of 150-225 IU, fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments, with a maximum daily dose of 450 IU.

The present trial explored the use of REKOVELLE in a conventional dosing approach; i.e. a standard starting dose fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments.

Previous clinical trial data suggested that a daily dose of 10.0 µg [95% confidence interval 9.2 to 10.8] REKOVELLE provides an ovarian response equal to that obtained with 150 IU GONAL-F. Applying this dose equivalence factor, it was extrapolated that 15 µg/day REKOVELLE would provide an ovarian response comparable to that obtained with 225 IU/day GONAL-F.

Measures of protection of subjects included approval of the trial protocol by independent ethics committees and health authorities, monitoring of the trial conduct to ensure compliance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, and provisions to protect the privacy of subjects after trial participation.

OBJECTIVES

Primary Objective

- 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

Secondary Objectives

- To compare the follicular development, endocrine profile and embryo development associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the treatment efficiency associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the safety profile associated with conventional dosing of REKOVELLE and GONAL-F

ENDPOINTS

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of follicles (total and by size category) at end-of-stimulation
- Serum concentrations of estradiol and progesterone at end-of-stimulation
- Number of fertilised oocytes and fertilisation rate
- Number of blastocysts (total and by quality)
- Total gonadotropin dose and number of stimulation days
- Early OHSS (overall and by grade) and/or preventive interventions for early OHSS

Exploratory Assessment

- Blood sample on stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response (requires additional, optional consent)

Follow-up Assessments

- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer) in the first transfer cycle

- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred) in the first transfer cycle

Note: the first transfer cycle covers cycles with transfer occurring within 3 months after start of stimulation

METHODOLOGY

This was a randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial that compared the ovarian response associated with a starting dose of 15 µg follitropin delta (REKOVELLE) and a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens. The primary endpoint was the number of oocytes retrieved, and secondary endpoints included pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. Treatment efficiency in terms of gonadotropin use and duration of stimulation was also evaluated. The assessor-blind design ensured that the investigators and other assessors such as embryologists were blinded to individual treatment allocation. A trial medication delegate was responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject.

Subjects 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. Subjects randomised to REKOVELLE received a daily starting dose of 15 µg, which was fixed for at least the first four stimulation days. Dose adjustments could be implemented on the day of starting the gonadotropin-releasing hormone (GnRH) 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 subject's response. The minimum REKOVELLE dose was 5 µg and the maximum REKOVELLE dose was 20 µg. Subjects randomised to GONAL-F received a daily starting dose of 225 IU which was fixed for at least the first four stimulation days. Dose adjustments could be implemented on the day of starting the GnRH 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 subject's response. The minimum GONAL-F dose was 75 IU and the maximum GONAL-F dose was 300 IU. Subjects could be treated with rFSH for a maximum of 20 days, and coasting was not allowed.

To prevent a premature luteinising hormone surge, a GnRH antagonist (ganirelix acetate, FYREMADEL, SUN Pharma) was initiated on stimulation day 5 or day 6 at a daily dose of 0.25 mg and was continued throughout the stimulation period. Triggering of final follicular maturation was done as soon as ≥3 follicles with a diameter ≥17 mm were observed (i.e. on the day or the day after). Triggering could also be done in case 1 or 2 follicles with a diameter ≥17 mm were observed and the investigator judged that ≥3 follicles with a diameter ≥17 mm could not be reached, and that triggering was preferred instead of cycle cancellation. The triggering drug was either human chorionic gonadotropin (hCG) or GnRH agonist, depending on the extent of ovarian response and whether transfer in the fresh cycle or in a subsequent frozen

cycle (including a freeze-all approach) was intended. If transfer in the fresh cycle was intended, 250 µg hCG (choriogonadotropin alfa, OVITRELLE, Merck) was administered. If there were ≥25 follicles with a diameter ≥12 mm or the serum estradiol was ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or a freeze-all approach was intended, 0.2 mg GnRH agonist (triptorelin acetate, GONAPEPTYL, Ferring) was administered. Moreover, if these criteria for triggering with GnRH agonist were not met, but the investigator judged that the subject was at risk of developing ovarian hyperstimulation syndrome (OHSS) and that triggering with hCG was not advisable, the subject could undergo triggering with GnRH agonist. In case of poor ovarian response, defined as the investigator judging that the triggering criterion could not be reached by day 20, the cycle was to be cancelled. In case of excessive ovarian response, defined as the investigator judging that triggering of final follicular maturation was not advisable due to safety concerns, the cycle was to be cancelled. The number and size of follicles at the end-of-stimulation was recorded.

Oocyte retrieval took place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm had to be retrieved. The oocytes could be inseminated by IVF and/or ICSI. Fertilisation was assessed on day 1 after oocyte retrieval. The number and quality of blastocysts was assessed at the last day of culture, i.e. day 5 or day 6 (as applicable) after oocyte retrieval. The day 5 / day 6 blastocyst quality assessment was based on the Gardner & Schoolcraft blastocyst scoring system. Blastocysts that were not transferred in the fresh cycle were cryopreserved in accordance with local guidelines and/or regulations.

Blood samples were collected at stimulation day 1 for measurement of AMH, estradiol and progesterone as well as at end-of-stimulation for measurement of estradiol and progesterone. For subjects who had provided additional, optional consent, blood samples were collected at stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response.

For subjects who underwent triggering of final follicular maturation, the end-of-trial visit had to take place 9-14 days after triggering to cover the assessment of early OHSS (onset ≤9 days after triggering). For subjects who did not undergo triggering of final follicular maturation, the end-of-trial assessments had to be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit).

If trial procedures and/or assessments were to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments could be postponed to the upcoming weekday (maximum one day after original visit schedule).

Follow-up Period – First Transfer Cycle

Follow-up information was collected from the subject's first transfer cycle, irrespective of whether the first transfer took place in a fresh or frozen cycle. This follow-up covered cycles with the transfer procedure occurring within 3 months after start of stimulation.

Depending on blastocyst availability, it was expected that subjects who had undergone triggering of final follicular maturation with hCG would undergo transfer on day 5 after oocyte retrieval and

that subjects who had undergone triggering of final follicular maturation with GnRH agonist would undergo transfer in a frozen cycle using blastocysts cryopreserved on day 5 or day 6 after oocyte retrieval. The number of transferred blastocyst(s) in the first fresh or frozen cycle was based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations. The number and quality of transferred blastocyst(s) was recorded. Luteal phase support in fresh and frozen cycles as well as potential other medicinal products for programming of frozen cycles was in accordance with the site's clinical practice.

Clinical pregnancy in the first transfer cycle was assessed by transvaginal ultrasound 5-6 weeks (35-48 days) after transfer, and the number of gestational sacs was recorded. For subjects who underwent transfer in the fresh cycle, assessment of late OHSS (onset >9 days after triggering) took place during the follow-up period.

PROTOCOL AMENDMENTS

There was 1 protocol amendment (Protocol Amendment 01, non-substantial, dated 21 January 2022) issued during the conduct of the trial. Changes introduced with Amendment 01 were included in the consolidated protocol version 2.0, dated 21 January 2022. The amendment was issued before FPFV.

NUMBER OF SUBJECTS

A total of 337 subjects were screened in the trial. Of these, 37 subjects (11.0%) were screening failures, and 300 subjects (89.0%) were randomised. All 300 randomised subjects were exposed to investigational medicinal product (IMP): 200 subjects in the REKOVELLE group and 100 in the GONAL-F group. A total of 290 subjects completed the trial (196 in the REKOVELLE group and 94 in the GONAL-F group).

The full analysis set (FAS) comprised 300 subjects randomised and exposed to IMP: 200 subjects in the REKOVELLE group and 100 in the GONAL-F group. The per-protocol (PP) analysis set comprised 290 subjects: 193 subjects in the REKOVELLE group and 97 in the GONAL-F group. The safety analysis set was identical to the FAS.

MAIN CRITERIA FOR INCLUSION AND EXCLUSION

This trial included women aged 18-40 years who had been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II, or had partners diagnosed with male factor infertility, and who were considered eligible for IVF or ICSI. They were allowed to have undergone previous infertility treatment.

The women had regular menstrual cycles of 21-35 days (both inclusive), presumed to be ovulatory. Early follicular phase serum levels of FSH were between 1 and 15 IU/L. Presence and adequate visualisation of ovaries, without evidence of significant abnormalities, was to be documented.

The exclusion criteria incorporated the contraindications for the use of gonadotropins.

MEDICINAL PRODUCTS

Investigational Medicinal Products

Subjects were randomised in a 2:1 ratio to treatment with either REKOVELLE or GONAL-F.

Controlled ovarian stimulation with REKOVELLE or GONAL-F was initiated on day 2-3 of the menstrual cycle. The IMP was administered as a daily subcutaneous injection in the abdomen.

The first injection took place at the clinic and was performed by either the trial medication delegate or the subject under supervision of the trial medication delegate. Subsequent injections could be done at home or at the clinic. The trial medication delegate gave the subject instructions on how to administer the IMP.

IMP	Drug type	Active ingredient; pharmaceutical dosage form; concentration	Daily dose	Batch number, expiry date (month, year)
REKOVELLE	rFSH	Follitropin delta, solution for subcutaneous injection, 72 µg FSH in 2.16 mL	Daily starting dose of 15 µg fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg.	NS0048A (Sep-2022)[a)] NS0048F (Sep-2022) NT0078C (Apr-2024) NU0025A (Sep-2024)[a)]
GONAL-F	rFSH	Follitropin alfa, solution for subcutaneous injection, 900 IU FSH in 1.5 mL	Daily starting dose of 225 IU fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU.	AU031303 (Jul-2022)[a)] AU032252 (Aug-2022)[a)] AU032324 (Oct-2022) AU034011 (Jun-2023) AU036136 (Apr-2024) AU036223 (Apr-2024) AU035867 (Feb-2024) AU036967 (May-2024) AU039567 (Jan-2025)[a)] AU042567 (Jun-2025)[a)]

a) Batch released but not used by any subject in the trial

GnRH: gonadotropin-releasing hormone; IMP: investigational medicinal product; rFSH: recombinant follicle-stimulating hormone;

Concomitant Fertility Medication / Non-investigational Medicinal Products (NIMPs)

NIMP	Drug type	Active ingredient; route of administration	Dose	Batch number, expiry date (month, year)
FYREMADEL[a)]	GnRH antagonist	Ganirelix acetate, solution for injection	0.25 mg subcutaneous injection once daily starting on stimulation day 5 or day 6 and continued throughout the stimulation period. FYREMADEL and REKOVELLE / GONAL-F should be administered approximately at the same time. However, the preparations should not be mixed and different injection sites are to be used.	JKX2487A (May-2022)[b)] HAC0216A (Dec-2022) HAD0573B (Jan-2024) HAD1792A (May-2024) HAE1207A (May-2025)[b)]
OVITRELLE	hCG	Choriogonadotropin alfa, solution for injection	A single 250 µg subcutaneous injection as soon as reaching the criterion for triggering of final follicular maturation with hCG (≥3 follicles with a diameter of ≥17 mm and intended transfer in the fresh cycle. Note: triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation).	BA070516 (Jun-2022)[b)] BA076341 (Jun-2023) BA082566 (Apr-2024) BA089042 (Feb-2025)
GONAPEPTYL[c)]	GnRH agonist	Triptorelin acetate, solution for injection	Two consecutive subcutaneous injections of 0.1 mg, i.e. a total of 0.2 mg, as soon as reaching the additional criteria for triggering of final follicular maturation with GnRH agonist (≥25 follicles with a diameter of ≥12 mm or serum estradiol concentration ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or intended freeze-all approach). Note: the subject can undergo triggering with GnRH agonist if the investigator judges that the subject is at risk of developing early OHSS.	S10110F (Jan-2023) S16430E (Sep-2023) T17844H (Nov-2024) U15616E (Oct-2025)[b)]

a) Other tradenames in Europe include FYREMADEL GE.
b) Batch released but not used by any subject in the trial.
c) Other tradenames in Europe include FERTIPEPTIL and DECAPEPTYL.
GnRH: gonadotropin-releasing hormone; hCG:human chorionic gonadotropin; NIMP: non-investigational medicinal product; OHSS: ovarian hyperstimulation syndrome

DURATION OF TREATMENT

The maximum period of exposure to FE 999049 or GONAL-F was 20 days.

STATISTICAL METHODS

Sample size

It was planned to randomise 300 subjects in a 2:1 ratio to REKOVELLE and GONAL-F. Assuming a standard deviation for the number of oocytes retrieved of 6.0 based on pervious trial data, this sample size would result in a 2-sided 95% confidence interval ranging from -1.44 to +1.44 oocytes from the observed difference in oocytes retrieved.

Primary Endpoint

The primary endpoint, number of oocytes retrieved, was analysed using the FAS and was compared between REKOVELLE and GONAL-F using a negative binominal model with treatment and AMH level at stimulation day 1 (AMH<15 pmol/L, AMH≥15 pmol/L, or missing) as factors. The absolute treatment difference in number of oocytes retrieved, the associated 95% confidence interval, and the p-value for no treatment difference were derived from the model estimates using the delta method. The treatment difference was also investigated for AMH sub-groups, using the same methods as described above. The distribution of the number of oocytes was summarised.

As a supplementary analysis, the analysis of the primary endpoint was repeated using the PP analysis set.

No formal hypothesis testing was conducted using these methods.

DEMOGRAPHY OF TRIAL POPULATION

The demographic characteristics were comparable between treatment groups. Overall, the mean age was 34.5±3.7 years, with 42.0% being <35 years, 37.7% being 35-37 years, and 20.3% being 38-40 years. Concerning race, the vast majority of the trial population were white (96.3%), followed by 2.3% Asian, 0.7% Black or African American and 0.7% American Indian or Alaska Native. Regarding ethnicity, 15.7% of the trial population were Hispanic or Latino.

EFFICACY RESULTS

For the FAS, the number of oocytes retrieved was similar for REKOVELLE and GONAL-F, with an adjusted mean of 9.9 oocytes retrieved in each treatment group. The estimated treatment difference was 0.0 oocytes, with a 95% confidence interval of -1.3 to 1.2. The mean number of oocytes retrieved was also comparable between treatment groups in each AMH subgroup (AMH<15 pmol/L and AMH≥15 pmol/L). The supplementary PP analysis supported the results of the primary endpoint analysis with the FAS.

Secondary endpoints related to ovarian response were in line with the results of the primary endpoint analysis: The number and size of follicles at end-of-stimulation was similar in both treatment groups, with an estimated treatment difference of 0.2 follicles (≥10 mm) and a corresponding 95% CI of -1.0 to 1.5. Serum levels of both estradiol and progesterone at end-of-stimulation were comparable between treatment groups, with a REKOVELLE to GONAL-F

treatment ratio of 0.9 for estradiol (95% CI for the ratio 0.8 to 1.0) and 1.1 for progesterone (95% CI for the ratio 0.9 to 1.2).

Secondary endpoints related to oocyte development such as the number of fertilised oocytes, fertilisation rate, or number and quality of blastocysts on day 5 or 6 all were similar between treatment groups as well.

The duration of stimulation was similar in both treatment groups with approximately 9 days. The total gonadotropin dose measured in µg was numerically lower in the REKOVELLE group than in the GONAL-F group.

SAFETY RESULTS

The overall frequency of subjects reporting adverse events was similar in the two treatment groups, with 36.5% in the REKOVELLE group and 40.0% in the GONAL-F group.

The most commonly reported adverse events (≥2.0% of subjects) were as follows in the REKOVELLE and GONAL-F group: headache (11.5% and 8.0%), pelvic discomfort (3.5% and 4.0%), fatigue (4.0% and 2.0%), procedural pain (3.0% and 4.0%), ovarian hyperstimulation (3.5% and 3.0%), breast tenderness (1.5% and 4.0%), diarrhoea (2.5% and 1%), and pelvic pain (0.5% and 5.0%).

Adverse drug reactions were reported at a frequency of 19.5% in the REKOVELLE group and 22.0% in the GONAL-F group. The most commonly reported adverse drug reactions (≥2.0% of subjects) were headache (5.5% and 4.0%), OHSS (3.5% and 3.0%), fatigue (4.0% and 1.0%), and pelvic discomfort (2.5% and 3.0%).

No deaths occurred during the trial. There were no serious adverse events reported in the REKOVELLE group and 2 serious adverse events (2%) reported in the GONAL-F group. The serious adverse events were 2 cases of haemoperitoneum, one of moderate and one of severe intensity, and were judged by the investigator as having no reasonable possibility of being caused by IMP.

Adverse events leading to discontinuation from the trial were recorded for 1 subject (1%) in the GONAL-F group.

Early OHSS occurred in 2.5% (5/200) of subjects in the REKOVELLE group and 3% (3/100) of subjects in the GONAL-F group. Early moderate/severe OHSS occurred in 0.5% (1/200) and 1% (1/100) of subjects, respectively. Preventive interventions for early OHSS were implemented in 15% of subjects in each treatment group. 1% of subjects in each treatment group had both a preventive intervention and early OHSS.

Late OHSS occurred in 1% (2/200) of subjects in the REKOVELLE group and 0% (0/100) in the GONAL-F group during the main trial. Both cases were late moderate/severe OHSS. No additional cases of late OHSS were recorded during the trial follow-up period.

In total, OHSS occurred in 3.5% (7/200) of subjects in the REKOVELLE group and 3% (3/100) of subjects in the GONAL-F group. The total moderate/severe OHSS frequency was 1.5% (3/200) and 1% (1/100) in the REKOVELLE and GONAL-F group, respectively.

Clinically significant changes in physical examination results or in gynaecological examination results were recorded for few subjects in the trial.

FOLLOW-UP INFORMATION

Among the subjects who started controlled ovarian stimulation, the clinical pregnancy rate was similar between the two treatment groups, with 31.6% in the REKOVELLE group and 31.0% in the GONAL-F group, in subjects' first fresh or frozen transfer cycle within 3 months after start of stimulation.

The implantation rate was similar between the two treatment groups, with 39.0% in the REKOVELLE group and 36.2% in the GONAL-F group.

No late OHSS cases were recorded during the trial follow-up.

CONCLUSIONS

- Treatment with REKOVELLE in a conventional dosing regimen with starting dose 15 µg resulted in a similar number of oocytes retrieved compared to 225 IU GONAL-F and in a comparable ovarian response in terms of follicular development and endocrine profile, as well as comparable blastocyst development parameters.
- The total gonadotropin dose measured in µg was numerically lower in the REKOVELLE group than in the GONAL-F group and the duration of stimulation was similar.
- The safety profile for REKOVELLE in a conventional dosing regimen was similar to GONAL-F and as expected for gonadotropin preparations.
- Clinical pregnancy rate and implantation rate were similar for REKOVELLE in a conventional dosing regimen compared to GONAL-F.

Ferring Pharmaceuticals A/S hereby confirms the accuracy of the information provided in this synopsis.