Ovarian stimulation with follitropin delta is safe and effective: results from the RITA randomized, double-blind, placebo-controlled trials

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Objective: To demonstrate the efficacy and safety of follitropin delta (recombinant follicle-stimulating hormone produced from the human cell line PER.C6) for ovarian stimulation in patients aged 18–34 and 35–42 years undergoing in vitro fertilization or intracytoplasmic sperm injection treatment in the United States.
Design: Two randomized, double-blind, placebo-controlled, parallel-group, multicenter trials (RITA-1 and RITA-2).
Subjects: A total of 1,165 patients (578 women aged 18–34 years in RITA-1 and 587 women aged 35–42 years in RITA-2), randomized 10:1 to follitropin delta or placebo.
Intervention: Ovarian stimulation with follitropin delta at a fixed starting dose (12 μg/d for patients aged $<$35 years and 15 μg/d for patients aged $\geq$35 years) for the first 4 stimulation days and subsequent dose adjustments as needed, or placebo as a reference group, in a gonadotropin-releasing hormone antagonist cycle.
Main Outcome Measures: Cumulative ongoing pregnancy rate after fresh and cryopreserved cycles initiated within 12 months from start of ovarian stimulation.
Results: The cumulative ongoing pregnancy rates with follitropin delta were 64.0% in patients aged $<$35 years (RITA-1) and 43.9% in patients aged $\geq$35 years (RITA-2) vs. 0 with placebo, thus establishing superiority of follitropin delta to placebo (RITA-1, difference, 64.0% [95% confidence interval, 56.9%–68.1%]; RITA-2, difference, 43.9% [95% confidence interval, 37.0%–48.2%]). The cumulative live birth rates with follitropin delta were 62.5% in patients aged $<$35 years and 42.4% in patients aged $\geq$35 years. In the fresh transfer cycle, the ongoing pregnancy rates with follitropin delta were 49.5% in patients aged $<$35 years and 34.8% in patients aged $\geq$35 years, and the live birth rates were 48.2% and 33.9%, respectively. In cryopreserved transfer cycles, the ongoing pregnancy rates with follitropin delta were 44.2% in patients aged $<$35 years and 31.2% in patients aged $\geq$35 years, and the live birth rates were 42.8% and 29.9%, respectively. The incidence rates of ovarian hyperstimulation syndrome in the fresh cycle were 3.8% in patients aged $<$35 years and 2.4% in patients aged $\geq$35 years after treatment with follitropin delta.
Conclusion: Follitropin delta, dosed on the basis of maternal age, is an effective and safe therapeutic for ovarian stimulation in in vitro fertilization/intracytoplasmic sperm injection patients.

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Supported by Ferring Pharmaceuticals, Inc. USA Parsippany, NJ. Sponsor trial codes: 000001 (RITA-1) and 000001 (RITA-2). The trials were designed by the sponsor in collaboration with the academic investigators. Data collection and trial sites were monitored by the sponsor. The data were collected by the sponsor and analyzed as per prespecified statistical analysis plan.
Portions of these data were presented at the Annual Meeting of the American Society for Reproductive Medicine, 14–18 October 2023, New Orleans, Louisiana, USA; and European Society of Human Reproduction and Embryology, 7–10 July 2024, Amsterdam, the Netherlands. The CONSORT checklist was followed for the manuscript development.
Data sharing statements: Ferring will provide access to individual deidentified participant data on request via a secure portal, to researchers whose proposals meet the research criteria and other conditions. To gain access, data requestors must enter into a data access agreement with Ferring.
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Trial Registration: For RITA-1, NCT03740737 (ClinicalTrials.gov), registered on October 24, 2018, first subject enrolled on October 26, 2018. For RITA-2, NCT03738618 (ClinicalTrials.gov), registered on October 24, 2018, first subject enrolled on October 29, 2018. (Fertil Steril® 2026;125:54–63. ©2025 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Cumulative live birth rate, follitropin delta, cryopreserved cycles, ovarian stimulation, Rekovelle

Controlled ovarian stimulation with exogenous gonadotropins is critical for achieving pregnancy and live birth outcomes in assisted reproductive technology (ART) protocols. Selection of gonadotropin dosages are guided by individual patient characteristics and clinician experience (1). The recombinant follicle-stimulating hormone (rFSH) follitropin delta was developed in the human cell line PER.C6, selected for its established use in biopharmaceutical manufacturing and capacity for posttranslational protein glycosylation that mimics that of native human follicle-stimulating hormone (FSH); conversely, existing rFSH alfa and beta are produced in rodent Chinese Hamster Ovary cells. Phase 1 analyses of equivalent international unit (IU) dosing of follitropin delta revealed distinct pharmacokinetic and pharmacodynamic properties compared with follitropin alfa, with higher FSH serum levels and slower clearance, as well as a significantly higher number of follicles and estradiol levels when stimulated by follitropin delta (2).

The greater potency of follitropin delta indicated that traditional rFSH dosing in IUs, which is based on bioactivity measured in rodents, does not accurately reflect follitropin delta bioactivity in humans. Therefore, microgram (μg) dosing was selected for follitropin delta using an individualized dosing algorithm on the basis of body weight and serum anti-Müllerian hormone (AMH) level (3–5). Follitropin delta dose per body weight-response curves across baseline AMH level were calculated to achieve a target number of 8–14 oocytes retrieved, a range suggested to maximize efficacy while maintaining safety after fresh transfer (3). Women with a baseline AMH level of $<$2.1 ng/mL receive a fixed dose of 12-μg/d follitropin delta, whereas those with an AMH level of $\geq$2.1 ng/mL received a fixed daily dose on the basis of AMH and body weight (6). The efficacy and safety of this individualized follitropin delta regimen were established in a global program inclusive of phase 3 trials (ESTHER-1 and GRAPE, both using conventionally dosed follitropin alfa as the comparator; STORK, using conventionally dosed follitropin beta as the comparator) resulting in approval in 75 countries (6–9). A meta-analysis of randomized controlled trials indicated that follitropin delta dosed by algorithm was associated with higher live birth rates and improved safety outcomes than conventional dosing of follitropin alfa or beta for women with increased AMH levels (9).

Regulatory considerations related to the use of a companion diagnostic (AMH) to set starting dose made US development with the algorithm impractical. Instead, a flexible treatment regimen was employed, with dosages selected using data from the global program, considering mitigation of ovarian hyperstimulation syndrome (OHSS) risk, and was based on subject age (12 μg and 15 μg starting doses for women aged $<$35 and 35–42 years, respectively) with 3 μg dose adjustments on the basis of ovarian response. Because US-marketed rFSH gonadotropin preparations are delivered in proprietary branded pen devices, it is not possible to develop a dummy comparator to meet strict US regulatory requirements for double-blind design. Moreover, chemical structure, pharmacokinetic, and pharmacodynamic differences in follitropin delta relative to follitropin alpha/beta meant that it was classified as a new molecular entity and not a biosimilar. Therefore, a placebo control, the gold standard for registration of new drugs, was selected as an appropriate comparator after extensive discussions with the Food and Drug Administration (FDA).

The RITA trials are the first to use a cumulative pregnancy primary endpoint to more completely capture the biologic potential of a single stimulation cycle for gonadotropin registration establishing a new paradigm. Here, we describe the efficacy and safety of follitropin delta for ovarian stimulation in women aged 18–34 years (RITA-1 trial) and $\geq$35 years (RITA-2 trial) undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment in the United States.

MATERIALS AND METHODS

Trial design

RITA-1 (Trial 000001) and RITA-2 (Trial 000002) were randomized, placebo-controlled, double-blind, parallel-group, multicenter phase 3 trials assessing the efficacy and safety of follitropin delta compared with placebo in patients undergoing ovarian stimulation for IVF/ICSI after a gonadotropin-releasing hormone (GnRH) antagonist protocol. Patients aged 18–34 and 35–42 years were enrolled in RITA-1 and RITA-2, respectively. The trials were conducted at 23 (RITA-1) and 24 (RITA-2) investigational sites in the United States between October 2018 and November 2020, with subsequent pregnancy outcome follow-up. All patients, clinical trial site staff, central laboratory personnel, and sponsor staff were blinded to treatment allocation throughout the trials. The trials were approved by Institutional Review Boards and performed in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Guidelines for Good Clinical Practice, and applicable US laws and regulatory requirements. All patients provided written informed consent.

Trial population

Eligible participants included women who were candidates for IVF/ICSI treatment and were diagnosed with tubal infertility, unexplained infertility, or infertility related to endometriosis stage I/II or with partners diagnosed with male

factor infertility. Supplemental Tables 1 and 2 (available online) show the full inclusion/exclusion criteria.

Treatment regimen

On days 2–3 of the menstrual cycle, patients in each trial were randomized 10:1 to follitropin delta or an indistinguishable placebo for ovarian stimulation. Randomization was performed centrally through an electronic case report form in blocks of 11 according to a randomization list prepared by an independent statistician. Patients randomized to follitropin delta (FE 999049/Rekovelle, 72 μg/2.16 mL; Ferring Pharmaceuticals, Saint-Prex, Switzerland; prefilled injection pen for subcutaneous injection) received a starting dose of 12 μg/d (patients aged <35 years) or 15 μg/d (patients aged ≥35 years) that was fixed for the first 4 stimulation days. On the basis of ovarian response, the assigned follitropin delta/placebo dose could be adjusted in 3-μg steps, increases up to once every 2 days, and decreases implemented per investigator judgment. The minimum and maximum daily doses were 6 and 24 μg, respectively.

On stimulation day 5 for patients with ≥3 follicles of ≥10-mm diameter, 250 μg GnRH antagonist (ganirelix acetate, Ganirelix; Merck Sharp & Dohme, a subsidiary of Merck & co., Inc., Whitehouse Station, NJ) was initiated and maintained throughout stimulation. Patients who did not meet GnRH antagonist criterion on stimulation day 5 were monitored at least every second day, and GnRH antagonist was initiated if criterion was met. When ≥2 follicles with a diameter of ≥17 mm and <20 follicles with a diameter of ≥12 mm were observed, final follicular maturation was triggered with 10,000 IU of human chorionic gonadotropin (hCG, Novarel; Ferring Pharmaceuticals). If there were ≥20 follicles of ≥12 mm or if the serum estradiol level was ≥3,000 pg/mL, 4.0 mg of GnRH agonist (leuprolide acetate; Sandoz Inc., Princeton, NJ) was administered, and fresh blastocyst transfer was cancelled. If after 8 days of stimulation, the investigator judged that triggering criterion was not likely to be reached by day 20 or if triggering criterion was not met by day 20, the cycle was canceled.

Oocytes were retrieved 36 hours (± 2 hours) after triggering final follicular maturation and inseminated by IVF or ICSI 4 hours (± 1 hour) after retrieval. For patients with <20 oocytes retrieved after triggering with hCG, transfer was performed on day 5 after oocyte retrieval.

For patients with ≥20 oocytes retrieved or who underwent GnRH agonist triggering, no fresh transfer was performed, and blastocysts were cryopreserved. Luteal phase support in fresh transfers was standardized, and programmed or natural cycles could be selected for any cryopreserved transfer cycle (Supplemental Materials, available online).

Patients aged 18–34 years (RITA-1) had transfer of one blastocyst of the highest quality available. Patients aged 35–42 years (RITA-2) had transfer of one good-quality blastocyst (i.e., grade 3BB or above (10)) or one or two blastocysts if no good-quality blastocyst was available. Blastocyst biopsy, assisted hatching, and preimplantation genetic diagnosis or screening were not allowed. Patients who failed to reach triggering criterion due to poor ovarian response, or who had ≤3 oocytes retrieved, were offered medication and financial support for an ART cycle with an approved gonadotropin preparation outside of the trial.

Trial endpoints and trial assessments

The primary endpoint was cumulative ongoing pregnancy rate (≥1 intrauterine viable fetus at 8–9 weeks after transfer, confirmed by abdominal or transvaginal ultrasound) after fresh or cryopreserved cycles initiated within 12 months of start of ovarian stimulation, capturing the clinical efficacy of a single ovarian stimulation cycle in a more complete manner (Supplemental Materials).

The secondary endpoints included cumulative live birth rate occurring from transfer cycles initiated within 12 months from the start of controlled ovarian stimulation, pregnancy outcomes and live birth rate for fresh cycle and cryopreserved cycles, follicular development, endocrine profile, number of oocytes retrieved, number of fertilized oocytes, embryo development (embryo biopsy was prohibited), and mean gonadotropin dose and duration of stimulation.

A serum βhCG test was performed 10–14 days after transfer, and clinical and vital pregnancy was assessed by transvaginal ultrasound 5–6 weeks after transfer. Blood samples were collected during the trial for analysis of AMH, FSH, luteinizing hormone, estradiol, progesterone, inhibin A, and inhibin B at a central laboratory (Covance Central Laboratory Services L.P., Indianapolis, IN; Supplemental Table 3). To prevent accidental unblinding, central laboratory results were not reported to the sites or Ferring during the trial, and trial sites were not allowed to assess FSH.

Adverse events in the fresh cycle were recorded from when the patient signed informed consent through the end of the cycle, that is, the ongoing pregnancy visit or earlier in case of no pregnancy. All cases of OHSS were recorded as adverse events and categorized according to the Golan classification system (11). Ovarian hyperstimulation syndrome was defined as early if onset was ≤9 days and late if it was >9 days after triggering final follicular maturation. Local tolerability after subcutaneous administration of the study drug was assessed by the patient thrice daily: immediately; 30 minutes; and 24 hours after each injection. The injection site reactions (redness, pain, itching, swelling, and bruising) were rated as "none," "mild," "moderate," or "severe."

Sample size and statistical analysis

For each trial, RITA-1 and RITA-2, a sample size of 550 patients (follitropin delta-to-placebo, 500:50) was determined to provide an adequate safety data set on the basis of the anticipated frequency of adverse events. This sample size provided 99% power for the primary efficacy comparison.

Analysis of the primary endpoint and secondary efficacy endpoints was based on the modified intention-to-treat analysis set, that is, all randomized and exposed patients according to planned treatment. Endpoints were analyzed on the basis of the per-protocol analysis set, that is, all patients

in the modified intention-to-treat analysis set except those who were excluded for major protocol deviations.

The primary endpoint, cumulative ongoing pregnancy rate, was tested for superiority of follitropin delta against placebo using a one-sided Fisher's exact test and providing two-sided Agresti-Min exact confidence intervals. The status of ongoing pregnancy was determined as soon as either of the following was met: the patient achieved an ongoing pregnancy, or all cryopreserved blastocysts had been exhausted or after assessment of ongoing pregnancy status in cryopreserved cycles initiated within 12 months from start of controlled stimulation. Missing observations for the primary endpoint of cumulative ongoing pregnancy rate were imputed as "negative" irrespective of the reason why data were not recorded.

The key secondary endpoint, cumulative live birth rate, was compared between treatment groups using a one-sided Fisher's exact test and providing two-sided Agresti-Min exact confidence intervals. A hierarchical testing procedure was used to ensure strict type I error control across the tests for the primary and key secondary endpoint. Treatment effects on log-transformed endocrine parameters were

TABLE 1

Demographics and baseline characteristics, modified intention-to-treat populations.

	Treatment group			
	RITA-1		RITA-2	
Characteristic	Follitropin delta (N = 525)	Placebo (N = 53)	Follitropin delta (N = 533)	Placebo (N = 54)
Age, y				
All patients, mean ± SD	30.7 ± 2.7	30.9 ± 2.9	37.7 ± 2.1	37.9 ± 2.1
<35, n (%)	525 (100)	53 (100)	0	0
35–37, n (%)	0	0	286 (53.7)	25 (46.3)
38–40, n (%)	0	0	185 (34.7)	21 (38.9)
41–42, n (%)	0	0	62 (11.6)	8 (14.8)
Race, n (%)				
American Indian or Alaska Native	1 (0.2)	0	2 (0.4)	0
Asian	33 (6.3)	6 (11.3)	57 (10.7)	5 (9.3)
Black or African American	49 (9.3)	2 (3.8)	70 (13.1)	4 (7.4)
Native Hawaiian or other Pacific Islander	5 (1.0)	0	5 (0.9)	0
White	437 (83.2)	45 (84.9)	398 (74.7)	45 (83.3)
Body weight, kg; mean ± SD	71.4 ± 15.2	70.7 ± 12.6	73.1 ± 15.0	76.0 ± 15.8
BMI, kg/m^2				
All patients, mean ± SD	26.5 ± 5.1	26.5 ± 4.8	27.0 ± 5.1	27.9 ± 5.1
<18.5, n (%)	9 (1.7)	0	2 (0.4)	0
18.5 to <25.0, n (%)	228 (43.4)	22 (41.5)	219 (41.1)	15 (27.8)
≥25.0 to <30.0, n (%)	165 (31.4)	17 (32.1)	163 (30.6)	20 (37.0)
≥30.0, n (%)	123 (23.4)	14 (26.4)	149 (28.0)	19 (35.2)
Infertility history				
Duration of infertility, mo; mean ± SD	36.5 ± 25.4	38.2 ± 18.3	42.7 ± 37.6	45.9 ± 43.2
Primary infertility, n (%)	318 (60.6)	29 (54.7)	226 (42.4)	26 (48.1)
Primary reason for infertility, n (%)				
Unexplained infertility	234 (44.6)	22 (41.5)	251 (47.1)	28 (51.9)
Tubal infertility	83 (15.8)	6 (11.3)	120 (22.5)	7 (13.0)
Male factor	184 (35.0)	20 (37.7)	139 (26.1)	17 (31.5)
Endometriosis stage I/II	24 (4.6)	5 (9.4)	20 (3.8)	2 (3.7)
Other[a]	0	0	3 (0.6)	0
Endometrial thickness, mm; mean ± SD	5.0 ± 1.8	4.7 ± 1.7	5.1 ± 1.8	5.2 ± 2.0
Antral follicle count, n; mean ± SD[b]	17.2 ± 8.9	16.3 ± 7.2	13.3 ± 7.6	12.1 ± 6.8
Endocrine profile, median (IQR)[c]				
AMH, pmol/L[d]	20.7 (12.9–31.3)	18.5 (13.9–26.7)	13.2 (7.2–20.9)	11.3 (6.7–18.3)
FSH, IU/L	8.3 (7.1–9.7)	8.5 (7.6–10.3)	8.7 (7.4–10.6)	8.9 (7.4–10.5)
LH, IU/L	5.1 (3.8–6.6)	4.7 (3.9–5.5)	4.8 (3.7–6.3)	5.0 (3.6–6.6)
Estradiol, pmol/L	145 (120–179)	138 (116–186)	151 (124–193)	148 (125–179)
Progesterone, nmol/L	1.7 (0.8–2.4)	1.6 (0.8–2.2)	1.7 (0.8–2.3)	1.7 (0.8–2.3)
Inhibin A, pg/mL	4.3 (2.8–6.0)	4.3 (3.4–5.0)	5.3 (3.8–7.0)	5.8 (4.3–7.0)
Inhibin B, pg/mL	82 (61–104)	80 (59–105)	75 (52–99)	79 (51–99)

Note: Data are for all patients unless stated otherwise. AMH = anti-mullerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; IQR = interquartile range; LH = luteinizing hormone; n = number of patients with observation; N = total number of patients.

[a] The category "other" includes one patient with "cervical factor," 1 patient with "mild ovulatory dysfunction," and one patient with endometriosis stage III/IV as primary reason for infertility. Endometriosis stage III/IV was an exclusion criterion per clinical trial protocol; however, one patient with endometriosis stage III/IV was randomized in RITA-2; this was recorded as a protocol deviation.

[b] This measurement reports the total number of antral follicles with a diameter of 2–10 mm for both ovaries combined, assessed by transvaginal ultrasound on the day of starting ovarian stimulation.

[c] Samples taken on stimulation day 1 before start of stimulation.

[d] The serum level of AMH was assessed by a central laboratory using the Elecsys AMH assay from Roche Diagnostics.

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compared using a multiplicative analysis of covariance model, with the change from baseline in each log-transformed endocrine parameter as the dependent variable and the baseline log-transformed endocrine parameter and treatment group as covariates. Follicular development, number of oocytes retrieved, number of fertilized oocytes, and embryo development were compared between treatment groups using the Wilcoxon rank sum test.

RESULTS

Baseline characteristics

In the RITA trials, a total of 1,165 patients (578 women aged <35 years in RITA-1 and 587 women aged ≥35 years in RITA-2) were randomized and exposed to study drug, of whom 1,058 (525 in RITA-1 and 533 in RITA-2) were treated with follitropin delta and 107 (53 in RITA-1 and 54 in RITA-2) were treated with placebo (Supplemental Figs. 1 and 2, available online). Within each trial, demographics and baseline characteristics were balanced between treatment groups (Table 1).

The mean (SD) treatment durations with follitropin delta were 8.1 (1.4) days for patients aged <35 years (RITA-1) and 8.2 (1.4) days for patients aged ≥35 years (RITA-2). The mean (SD) daily doses were 12.8 (1.4) μg for patients aged <35 years and 16.0 (1.4) μg for patients aged ≥35 years, accumulating to a total follitropin delta dose of 104.2 (25.3) μg and 131.2 (30.8) μg, respectively. Most patients exposed to follitropin delta (55.8% of patients aged <35 years and 50.7% of patients aged ≥35 years) maintained the starting daily dose on stimulation day 5, whereas a dose increase was requested for 37.9% and 43.2% of patients aged <35 and ≥35 years, respectively, and a dose decrease was requested for 6.3% and 6.2%, respectively.

Cumulative ongoing pregnancy and cumulative live birth

Superiority of follitropin delta to placebo regarding cumulative ongoing pregnancy was demonstrated for both patients aged <35 years (RITA-1) and patients aged ≥35 years (RITA-2) (both $P<.001$; Table 2). The cumulative ongoing pregnancy rates were 64.0% for patients aged <35 years and 43.9% for patients aged ≥35 years for those who started follitropin delta treatment, whereas no patient in the placebo groups achieved an ongoing pregnancy. The cumulative live birth rates were 62.5% for patients aged <35 years and 42.4% for patients aged ≥35 years for follitropin delta group. Similar results regarding cumulative ongoing pregnancy and cumulative live birth were obtained in the per-protocol analysis set (Table 2) and in additional data analyses for 12 calendar months, in which lost transfer cycles due to the coronavirus disease 2019 temporary trial hold were not compensated for (Supplemental Table 4). Two embryos were transferred in eight fresh and one cryopreserved cycle, respectively. Of the eight fresh cycle double embryo transfers, two resulted in twin pregnancies and, later, the live birth of twins. The one cryopreserved cycle double embryo transfer also resulted in a twin pregnancy. However, one twin was lost to miscarriage, whereas the other was a successful live birth.

Pregnancy outcomes in the fresh and cryopreserved cycles

For patients in the follitropin delta group who underwent blastocyst transfer in the fresh cycle, the ongoing pregnancy rates were 49.5% for patients aged <35 years (RITA-1) and 34.8% for patients aged ≥35 years (RITA-2; Table 3). The corresponding live birth rates were 48.2% and 33.9%, respectively. After blastocyst transfer in cryopreserved cycles (416

TABLE 2

Cumulative ongoing pregnancy rate and cumulative live birth rate.

Outcome variable	Treatment group: Follitropin delta	Placebo	Difference (95% CI)[a]	*P* value[b]
Cumulative ongoing pregnancy rate in 12 mo, % (n/N)				
RITA-1 (patients aged <35 y)				
mITT analysis set[c]	64.0 (336/525)	0 (0/53)	64.0 (56.9–68.1)	<.001
PP analysis set[d]	65.3 (329/504)	0 (0/50)	65.3 (57.7–69.3)	<.001
RITA-2 (patients aged ≥35 y)				
mITT analysis set[c]	43.9 (234/533)	0 (0/54)	43.9 (37.0–48.2)	<.001
PP analysis set[d]	46.2 (224/485)	0 (0/53)	46.2 (39.1–50.7)	<.001
Cumulative live birth rate in 12 mo, % (n/N)				
RITA-1 (patients aged <35 y)				
mITT analysis set[c]	62.5 (328/525)	0 (0/53)	62.5 (55.2–66.6)	<.001
PP analysis set[d]	63.7 (321/504)	0 (0/50)	63.7 (56.3–67.8)	<.001
RITA-2 (patients aged ≥35 y)				
mITT analysis set[c]	42.4 (226/533)	0 (0/54)	42.4 (35.6–46.7)	<.001
PP analysis set[d]	44.5 (216/485)	0 (0/53)	44.5 (37.5–49.0)	<.001

Note: CI = confidence interval; mITT = modified intention-to-treat; n = number of patients with observations; N = total number of patients; PP = per-protocol.
[a] Two-sided 95% exact confidence intervals (Agresti-Min).
[b] *P* value from the 1-sided Fisher's exact test.
[c] The mITT analysis set comprised all randomized and exposed patients.
[d] The PP analysis set comprised all mITT patients except those who were excluded for major protocol deviations.

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cycles with transfer in RITA-1 and 375 in RITA-2), the ongoing pregnancy rates were 44.2% for patients aged <35 years (RITA-1) and 31.2% for patients aged ≥35 years (RITA-2). The corresponding live birth rates were 42.8% and 29.9%, respectively. Only 12.4% of patients aged <35 years and 11.4% of patients aged ≥35 years who had blastocysts still available and had not yet achieved a pregnancy did not initiate cryopreserved transfer cycles (Supplemental Figs. 3 and 4).

Notably, the observed pregnancy outcomes in fresh and cryopreserved cycles stem predominantly from single blastocyst transfer (all transfers in patients aged <35 years, and 91.7% of fresh and 97.1% of cryopreserved transfers in patients aged ≥35 years), corresponding to ongoing implantation rates in the fresh cycle of 49.5% and 32.7% for patients aged <35 and ≥35 years, respectively, and 44.2% and 30.6% in cryopreserved cycles. In the placebo groups, no patients underwent blastocyst transfer in fresh or cryopreserved cycles.

Ovarian response, embryology, and safety

Triggering final follicular maturation after ovarian stimulation with follitropin delta occurred in 98.5% (517/525) of patients aged <35 years and 94.6% (504/533) of patients aged ≥35 years and in 1.9% (1/53 and 1/54) of both age groups receiving placebo. Human chorionic gonadotropin was used in 77.0% (404/525) and 79.5% (424/533) of the follitropin delta cycles in patients aged <35 and ≥35 years, respectively, whereas the strict GnRH agonist triggering criteria of ≥20 follicles with a diameter of ≥12 mm or serum estradiol level of ≥3,000 pg/mL led to cancellation of transfer in the fresh cycle of 21.5% (113/525) and 15.0% (80/533), respectively (all cycle cancellations are shown in Supplemental Figs. 1 and 2). After follitropin delta treatment, approximately 98% (515/525) of patients aged <35 years and 93% (497/533) of patients aged ≥35 years had at least one oocyte retrieved. In the placebo groups, no patient aged <35 years had any oocyte retrieved, and one patient aged ≥35 years had one oocyte retrieved.

On average, after follitropin delta treatment, patients aged <35 years (RITA-1) had a mean (SD) of 15.1 (10.4) oocytes retrieved, and patients aged ≥35 years (RITA-2) had 11.3 (8.9) oocytes retrieved (Table 4). This resulted in means (SDs) of 4.6 (4.1) and 3.3 (3.8) good-quality blastocysts for patients aged <35 and ≥35 years, respectively. The blastocyst survival rate after cryopreservation and subsequent warming was high in both trials, with 98.8% (416/421) for patients aged <35 years and 98.5% (388/394) for patients aged ≥35 years.

Early OHSS (any grade) with follitropin delta occurred in 2.9% (15/525) of patients aged <35 years and 1.5% (8/533) of patients aged ≥35 years; early OHSS classified as moderate/severe occurred in 1.9% (10/525) and 0.8% (4/533) of patients treated with follitropin delta, respectively. Late OHSS (any grade) with follitropin delta occurred in 1.0% (5/525) of patients aged <35 years and 0.9% (5/533) of patients aged ≥35 years; in each trial, late OHSS classified as moderate/severe occurred in 0.8% (4/525 and 4/533) of patients treated with follitropin delta. No patient in the placebo groups experienced OHSS.

The pooled frequency of injection site reactions after administration of follitropin delta was 4.2% (2,661/63,601 and 2,697/64,939 in RITA-1 and RITA-2, respectively), similar to 4.9% (374/6,545 and 274/6,805) with placebo, on the basis of all assessments made at any time point. Most injection site reactions were mild, and only 0.1% (61/63,601

TABLE 3

Pregnancy outcomes in the fresh cycle and in cryopreserved cycles with transfer.

	RITA-1 (patients aged < 35 y)	RITA-2 (patients aged ≥35 y)
Outcome variable[a]	**Follitropin delta**	**Follitropin delta**
Pregnancy outcomes,[b] % (n/N) of cycles with transfer		
Positive βhCG rate		
Fresh cycle	58.8 (184/313)	50.9 (171/336)
Cryopreserved cycles	57.9 (241/416)	49.3 (185/375)
Clinical pregnancy rate		
Fresh cycle	53.4 (167/313)	42.6 (143/336)
Cryopreserved cycles	51.7 (215/416)	41.1 (154/375)
Vital pregnancy rate		
Fresh cycle	51.1 (160/313)	37.2 (125/336)
Cryopreserved cycles	45.7 (190/416)	33.1 (124/375)
Ongoing pregnancy rate		
Fresh cycle	49.5 (155/313)	34.8 (117/336)
Cryopreserved cycles	44.2 (184/416)	31.2 (117/375)
Live birth rate		
Fresh cycle	48.2 (151/313)	33.9 (114/336)
Cryopreserved cycles	42.8 (178/416)	29.9 (112/375)

Note: hCG = human chorionic gonadotropin; n = number of cycles with observations; N = total number of cycles.
[a] Presented for modified intention-to-treat analysis set that comprised all randomized and exposed patients.
[b] Cryopreserved cycles initiated within 12 months from the start of ovarian stimulation.

Scheiber. Follitropin delta in ovarian stimulation. Fertil Steril 2026.

TABLE 4

Ovarian response and embryology, modified intention-to-treat population.

	RITA-1 (patients aged <35 y)			RITA-2 (patients aged ≥35 y)		
Outcome variable	Follitropin delta (N = 525)	Placebo (N = 53)	*P* value	Follitropin delta (N = 533)	Placebo (N = 54)	*P* value
End of stimulation						
Follicles, n; mean ± SD	23.0 ± 11.8	15.6 ± 7.6	<.001[a]	17.4 ± 10.0	13.6 ± 9.5	<.001[a]
Follicles ≥12 mm, n; mean ± SD	13.0 ± 7.3	0.7 ± 0.5	<.001[a]	10.1 ± 6.3	0.8 ± 0.7	<.001[a]
Follicles ≥17 mm, n; mean ± SD	4.4 ± 2.5	0.3 ± 0.5	<.001[a]	3.6 ± 2.3	0.4 ± 0.5	<.001[a]
FSH, IU/L; median (IQR)	20.8 (16.5–25.1)	6.7 (5.2–8.4)	<.001[b]	24.8 (20.2–30.3)	7.1 (6.2–9.6)	<.001[b]
LH, IU/L; median (IQR)	1.9 (1.1–3.1)	7.7 (6.0–10.6)	<.001[b]	2.0 (1.3–3.3)	8.8 (6.5–14.7)	<.001[b]
Estradiol, pmol/L; median (IQR)	6,780 (4,119–10,020)	387 (214–601)	<.001[b]	5,400 (3,271–8,416)	402 (191–641)	<.001[b]
Progesterone, nmol/L; median (IQR)	3.5 (2.5–4.8)	1.6 (1.0–1.9)	<.001[b]	3.5 (2.2–4.8)	1.0 (1.0–1.9)	<.001[b]
Inhibin A, pg/mL; median (IQR)	329.8 (226.9–480.4)	12.4 (7.7–22.6)	<.001[b]	258.7 (159.6–379.8)	19.8 (8.0–35.4)	<.001[b]
Inhibin B, pg/mL; median (IQR)	1,106 (665–1,640)	80 (59–112)	<.001[b]	671 (356–1,039)	65 (51–97)	<.001[b]
Oocytes retrieved, n; mean ± SD	15.1 ± 10.4	0	<.001[a]	11.3 ± 8.9	0.0 ± 0.1	<.001[a]
Metaphase II oocytes,[c] n; mean ± SD	10.9 ± 7.6	0	—[d]	8.8 ± 6.7	1.0	—[d]
Fertilized oocytes, n; mean ± SD	8.4 ± 6.3	0	<.001[a]	6.4 ± 5.7	0.0 ± 0.1	<.001[a]
Blastocysts,[e] n; mean ± SD	5.7 ± 4.6	0	<.001[a]	4.3 ± 4.4	0.0 ± 0.0	<.001[a]
Good-quality blastocysts,[e] n; mean ± SD	4.6 ± 4.1	0	<.001[a]	3.3 ± 3.8	0.0 ± 0.0	<.001[a]

Note: FSH = follicle-stimulating hormone; IQR = interquartile range; LH = luteinizing hormone; n = number of oocytes retrieved, number of metaphase II oocytes, number of fertilized oocytes, or number of blastocysts, respectively.

[a] *P* values were from the Wilcoxon rank sum test.

[b] *P* values corresponded to the F-test of treatment effect. Comparison was based on multiplicative analysis of covariance model with treatment as fixed factor and adjusted for the log-transformed baseline value. Values below lower limit of quantification were set to lower limit of quantification/2. Values above upper limit of quantification were set to upper limit of quantification.

[c] Data were based on patients with all oocytes inseminated by intracytoplasmic sperm injection.

[d] No *P* value was provided because numbers refer to a subset of patients in the modified intent-to-treat analysis set (patients with all oocytes inseminated by intracytoplasmic sperm injection).

[e] Number of blastocysts or good-quality blastocysts on day 5 or 6.

Scheiber. Follitropin delta in ovarian stimulation. Fertil Steril 2026.

and 3/6,545; 88/64,939 and 10/6,805) were rated as moderate/severe with either follitropin delta in RITA-1 or RITA-2, respectively, or placebo. The most common injection site reactions were redness and pain, both immediately after and 30 minutes after administration of follitropin delta or placebo, whereas bruising was most common after 24 hours.

The pooled incidence of adverse drug reactions with follitropin delta was 12.0% (73/525 and 54/533 in RITA-1 and RITA-2, respectively) compared with 3.7% (2/53 and 2/54) with placebo. The most frequently reported adverse drug reactions with follitropin delta, in RITA-1 and RITA-2, respectively, were pelvic discomfort (4.7% [29/525 and 21/533]), OHSS (3.0% [19/525 and 13/533]), pelvic pain (1.5% [10/525 and 6/533]), nausea (1.5% [6/525 and 10/533]), headache (1.4% [8/525 and 7/533]), and fatigue (1.2% [8/525 and 5/533]).

DISCUSSION

RITA-1 and RITA-2, the first placebo-controlled trials in women undergoing ovarian stimulation for ART treatment, demonstrated superiority of follitropin delta to placebo for the primary endpoint of cumulative ongoing pregnancy rate after fresh or cryopreserved cycles initiated within 12 months of ovarian stimulation. The observed cumulative ongoing pregnancy rates and cumulative live birth rates after follitropin delta treatment compared favorably with data reported in the literature that was used to estimate potential efficacy in the protocols and regulatory interactions before the RITA trials. In previous phase 3 clinical trials of follitropin beta, the cumulative ongoing pregnancy rates were reported to be 51.9% in North American women aged ≤36 years (12) and 30.1% in US women aged 35–42 years (13), 12.1 and 12.8 percentage points lower than the cumulative ongoing pregnancy rates observed for follitropin delta in the RITA trials. The cumulative live birth rates with follitropin delta were also higher than those reported in the Society for Assisted Reproductive Technology registry, which indicates a cumulative live birth rate of approximately 55% for women aged <35 years from 2017 to 2021 (14), 7.5 percentage points lower than that observed in RITA-1. Importantly, the high cumulative ongoing pregnancy rates and cumulative live birth rates in the RITA trials were achieved almost exclusively via single blastocyst transfer, which was performed in 100% of transfer cycles in women aged <35 years (RITA-1) and 94.5% of transfer cycles in women aged ≥35 years (RITA-2). In contrast, single embryo transfer accounted for only up to 11% of patients with transfer in the follitropin beta group in previous clinical trials (12, 13). Demonstrating superiority of follitropin delta in this study vs. placebo, although necessary to meet regulatory requirements for double-blind design, is not as clinically relevant as showing efficacy relative to FDA-approved gonadotropins. However, it is not possible to conduct a double-blind, controlled clinical trial (as required by the US FDA for registrational trials) using an FDA-approved gonadotropin delivered via prefilled proprietary device as the comparator.

In both fresh and cryopreserved cycles, all pregnancy parameters further support the efficacy of follitropin delta for controlled ovarian stimulation. In the follitropin delta group

for patients who underwent fresh blastocyst transfer, the ongoing pregnancy rates in RITA were slightly higher than numbers reported in the literature for comparable age groups in previous clinical trials with follitropin beta (48.4% in North American women aged ≤36 years (12) and 25.8% in US women aged 35–42 years (13)).

Because follitropin delta is manufactured in a human cell line, it is classified as a new molecular entity, which carries a strict regulatory requirement for double-blind, placebo-controlled registrational trial design. Importantly, use of GnRH antagonist in both trials was based on follicular development and not fixed to a specific stimulation day, with a goal of limiting its use to those patients at risk of premature luteinizing hormone surge, thereby avoiding an iatrogenic barrier to placebo response. To address ethical concerns of a placebo-controlled trial in this population, patients who exhibited poor response (≤3 oocytes retrieved) were offered medication and financial support for an ART cycle with an approved gonadotropin outside of the trial. The RITA trials are the first to demonstrate that any placebo response (i.e., multifollicular development) in this population is minimal.

Stimulation with follitropin delta led to excellent outcomes despite the absence of preimplantation genetic testing for aneuploidy and with short treatment durations (8.1 [1.4] days in RITA-1 and 8.2 [1.4] days in RITA-2), the latter likely due to the trigger criterion selected for placebo-controlled design (≥2 follicles with a diameter of ≥17 mm; higher numbers of follicles were deemed implausible in the placebo group).

The numbers of oocytes retrieved after follitropin delta treatment were 15.1 for women aged <35 years (RITA-1) and 11.3 for women aged ≥35 years (RITA-2), within the range shown to provide an optimal balance of efficacy and safety in controlled ovarian stimulation (15,16). The follitropin delta dosing regimen evaluated in the RITA trials, therefore, demonstrated an alternative approach to its well-validated algorithmic dosing that could also be used depending on clinical context and patient characteristics. Indeed, the incidence of OHSS was low in both RITA trials and similar to that observed in other follitropin delta phase 3 trials that used more conservative dosing via the algorithm (6). This is likely due to a more stringent criteria for GnRH agonist trigger and fresh transfer cancellation in the RITA trials.

Study strengths include a large, double-blind, multicenter design; wide geographic distribution of study sites; broad eligibility criteria; and a diverse study population, all increasing the generalizability of findings. As described earlier, the study conclusions are limited with the use of placebo rather than an active comparator, and outcomes may not be generalizable to women with a body mass index of >38 kg/m^2 who were excluded from the trial.

CONCLUSION

In summary, the RITA trials established the efficacy and safety of follitropin delta, dosed on the basis of maternal age, for controlled ovarian stimulation in patients with infertility for both fresh and frozen cycles. The RITA trials are also the first to use a cumulative pregnancy endpoint, including fresh and frozen cycle outcomes, with standardized criteria for trial procedures and assessments that allow a full understanding of the contribution of controlled ovarian stimulation with follitropin delta on clinical endpoints.

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CRediT Authorship Contribution Statement

Michael D. Scheiber: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Kevin J. Doody:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Eric D. Foster:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Sarah A. Grover:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Patrick W. Heiser:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Interests

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SUPPLEMENTAL MATERIAL

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La estimulación ovárica con folitropina delta es segura y eficaz: resultados de los ensayos RITA aleatorizados, doble ciego y controlados con placebo.

Objetivo: Demostrar la eficacia y seguridad de la folitropina delta (hormona folículo estimulante recombinante producida a partir de la línea celular humana PER.C6) para la estimulación ovárica en pacientes de 18 a 34 y de 35 a 42 años sometidas a fertilización in vitro o inyección intracitoplasmática de espermatozoides en Estados Unidos.

Diseño: Dos ensayos aleatorizados, doble ciego, controlados con placebo, de grupos paralelos y multicéntricos (RITA-1 y RITA-2).

Sujetos: Un total de 1165 pacientes (578 mujeres de 18 a 34 años en el RITA-1 y 587 mujeres de 35 a 42 años en el RITA-2), aleatorizadas en una proporción de 10:1 a folitropina delta o placebo.

Intervención: Estimulación ovárica con folitropina delta a una dosis inicial fija (12 μg/día para pacientes $<$35 años y 15 μg/día para pacientes $\geq$35 años) durante los primeros 4 días de estimulación y ajustes de dosis posteriores según sea necesario, o placebo como grupo de referencia, en un ciclo con antagonista de la hormona liberadora de gonadotropina.

Principales medidas de resultado: Tasa acumulada de embarazo en curso tras ciclos en fresco y criopreservados iniciados dentro de los 12 meses posteriores al inicio de la estimulación ovárica.

Resultados: Las tasas acumuladas de embarazo en curso con folitropina delta fueron del 64.0 % en pacientes $<$35 años (RITA-1) y del 43,9 % en pacientes $\geq$35 años (RITA-2) frente a 0 con placebo, lo que demuestra la superioridad de la folitropina delta sobre el placebo (RITA-1, diferencia, 64.0 % [intervalo de confianza del 95 %, 56.9 %–68.1 %]; RITA-2, diferencia, 43.9 % [intervalo de confianza del 95 %, 37.0 %–48.2 %]). Las tasas acumuladas de nacidos vivos con folitropina delta fueron del 62.5 % en pacientes $<$35 años y del 42.4 % en pacientes $\geq$35 años. En el ciclo de transferencia en fresco, las tasas de embarazo en curso con folitropina delta fueron del 49.5 % en pacientes $<$35 años y del 34.8 % en pacientes $\geq$35 años, y las tasas de nacidos vivos fueron del 48.2 % y el 33.9 %, respectivamente. En los ciclos de transferencia criopreservada, las tasas de embarazo en curso con folitropina delta fueron del 44.2 % en pacientes $<$35 años y del 31.2 % en pacientes $\geq$35 años, y las tasas de nacidos vivos fueron del 42.8 % y el 29.9 %, respectivamente. Las tasas de incidencia del síndrome de hiperestimulación ovárica en el ciclo en fresco fueron del 3.8 % en pacientes $<$35 años y del 2.4 % en pacientes $\geq$35 años tras el tratamiento con folitropina delta.

Conclusión: La folitropina delta, dosificada en función de la edad materna, es un tratamiento eficaz y seguro para la estimulación ovárica en pacientes sometidas a fertilización in vitro/inyección intracitoplasmática de espermatozoides.