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ARTICLE

# Follitropin delta in repeated ovarian stimulation for IVF: a controlled, assessor-blind Phase 3 safety trial

## BIOGRAPHY

Ernesto Bosch was born in Philadelphia, USA, in 1968. He graduated in Medicine in 1992, and became a specialist in obstetrics and gynaecology in 1997. He obtained his PhD in 1999, and since 2000 has worked at the Instituto Valenciano de Infertilidad in Valencia, becoming Medical Director in 2010.

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## KEY MESSAGE

Follitropin delta can be safely used for repeated ovarian stimulation, shown by its low immunogenicity potential and sustained safety in an expanded dose range. The trial also confirms the appropriateness of the follitropin delta dosing regimen in repeated cycles, with documented efficacy in terms of ovarian response, pregnancy and live birth rates.

## ABSTRACT

**Research question:** To evaluate the immunogenicity of follitropin delta in repeated ovarian stimulation.

**Design:** Controlled, assessor-blind trial in IVF/intracytoplasmic sperm injection patients undergoing repeated cycles of ovarian stimulation (cycles 2 and 3), following initial stimulation with follitropin delta or follitropin alfa (cycle 1) in a preceding randomized trial. In cycles 2 and 3, 513 and 188 women, respectively, were treated as randomized in cycle 1, with dosing based on ovarian response in the previous cycle.

**Results:** The incidence of treatment-induced anti-FSH antibodies with follitropin delta was 0.8% and 1.1% in cycles 2 and 3, respectively, which was similar to the incidence in cycle 1 (1.1%). No antibodies were of neutralizing capacity. Women with pre-existing anti-FSH antibodies were safely treated with follitropin delta without boosting an immune response. Treatment with follitropin delta and follitropin alfa gave similar outcomes for mean number of oocytes retrieved (9.2 versus 8.6 [cycle 2]; 8.3 versus 8.9 [cycle 3]), ongoing pregnancy (27.8% versus 25.7%; 27.4% versus 28.0%) and live birth rates (27.4% versus 25.3%; 26.3% versus 26.9%). The presence of anti-FSH antibodies did not affect the ovarian response.

**Conclusions:** The trial demonstrated the low immunogenicity potential of follitropin delta in repeated ovarian stimulation, and confirmed the appropriateness of the follitropin delta dosing regimen in repeated cycles, with documented efficacy and safety.

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## KEYWORDS

Follitropin delta
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Safety


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Declaration: E Bosch has received fees from Ferring Pharmaceuticals, Merck Serono, MSD and Roche Diagnostics, and fees and grant support from Finox. J Havelock has received grant support from Ferring Pharmaceuticals. BB Rasmussen, BM Klein, B Mannaerts and J-C Arce are employees of Ferring Pharmaceuticals. J-C Arce has patents pending and issued for follitropin delta. F Sanchez Martin reports no competing interests.

## INTRODUCTION

Current clinical practice of infertility treatment is moving from standardized to individualized FSH dosing, as new FSH preparations integrate individualized dosing as part of the clinical development (*La Marca and Sunkara, 2014*). Follitropin delta is a recombinant FSH (rFSH) derived from a human fetal retinal cell line, intended for ovarian stimulation for IVF. The dosing algorithm for follitropin delta directs a dose individualized to each woman based on her serum level of anti-Müllerian hormone (AMH) and her body weight (*Arce et al., 2016*). Serum concentration of AMH has been established as the preferred predictor of ovarian reserve and ovarian response to exogenous gonadotrophins, while body weight has been identified as a determinant of the systemic exposure to follitropin delta (*Arce et al., 2013, 2016; Broer et al., 2014; Dewailly et al., 2014; Fleming et al., 2013; La Marca et al., 2010; La Marca and Sunkara, 2014; Nelson, 2013; Toner and Seifer, 2013*). The aim of the individualized dosing is to achieve a targeted number of oocytes, to improve the safety of ovarian stimulation by reducing the risk of poor or excessive ovarian response, in at-risk populations, and reducing the risk of ovarian hyperstimulation syndrome (OHSS), while at the same time maintaining efficacy. Even though individualization of gonadotrophin dose is common clinical practice in ovarian stimulation, dosing approach varies depending on the experience and subjective preference of the treating physician. Follitropin delta constitutes the first prospectively evaluated and validated biomarker-driven FSH dosing regimen. By incorporating a documented biomarker of ovarian response as well as a patient characteristic influencing exposure, the follitropin delta dosing regimen provides an improved precision in the prediction of ovarian response, reducing the variability in response across patients, as observed by an increased probability of a targeted response and a reduced risk of extreme ovarian responses.

The efficacy and safety of the individualized follitropin delta dosing regimen compared with conventional follitropin alfa dosing was evaluated in a large randomized controlled Phase 3 trial (*Nyboe Andersen and Nelson et al., 2017*). The trial demonstrated non-inferiority of individualized follitropin delta compared with conventional follitropin alfa with respect to the co-primary endpoints of ongoing pregnancy and ongoing implantation rates. At the same time, individualized follitropin delta stimulation in a fixed dosing regimen resulted in a more targeted response and an improved safety profile in terms of fewer cases of OHSS and/or OHSS preventive measures.

The present study was a safety trial examining the immunogenicity of follitropin delta following exposure in up to two repeated stimulation cycles, and was performed in patients who participated in the efficacy trial but failed to achieve an ongoing pregnancy. Therapeutic proteins may induce an immunological response, in particular during repeated exposure. Antibody formation towards the therapeutic protein may have clinical consequences, as neutralization of the therapeutic protein may result in lack of efficacy. Potentially, neutralizing antibodies could also be directed against the endogenous counterpart of the therapeutic protein. Factors influencing immunogenicity include molecular structure, contaminants/impurities in the preparation, duration of treatment and route of administration (*Kessler et al., 2006; Schellekens, 2005*). An immunogenic response is more likely when a therapeutic protein is given intermittently and administered subcutaneously. Both these factors apply to follitropin delta, necessitating the assessment of immunogenicity for confirmation of its safe use. Based on previous investigations on FSH preparations, the anticipated immunogenicity was expected to be low, around 0–2% (*Out et al., 1995; Recombinant Human FSH Study Group, 1995; Wadhwa and Thorpe, 2007*). In addition to immunogenicity, the trial investigated the efficacy of follitropin delta in repeated cycles in terms of ovarian response, pregnancy and live birth rates, as well as the safety of follitropin delta in an expanded dose range.

## MATERIALS AND METHODS

### Study design

The Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World 2 (ESTHER-2) trial was a controlled, assessor-blind, parallel groups, international, multicenter trial evaluating the immunogenicity of follitropin delta in patients undergoing repeated ovarian stimulation cycles. Participating sites and principal investigators are listed in **TABLE 1**.

The trial included women who had undergone a first ovarian stimulation cycle (cycle 1) in the Phase 3 efficacy trial ESTHER-1 (*Nyboe Andersen and Nelson et al., 2017*). Patients who did not achieve ongoing pregnancy in cycle 1 could continue to the current trial and undergo up to two repeated cycles of ovarian stimulation (cycle 2 and cycle 3).

The trial was conducted at 32 sites in 10 countries: Belgium, Brazil, Canada, Czech Republic, Denmark, Italy, Poland, Russia, Spain and the UK (some sites that included patients in cycle 1 did not include patients in the current trial due to a late start or recruitment stop). The trial protocol was approved by the local regulatory authorities and the independent ethics committees covering all participating centers. The trial was performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulatory requirements. All participants provided written informed consent prior to enrolment in cycle 2 (trial registration number: NCT01956123).

### Participants

Women who had participated in cycle 1 (women undergoing their first IVF/intracytoplasmic sperm injection (ICSI) cycle, 18–40 years of age, with regular menstrual cycles, diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility) and failed to achieve an ongoing pregnancy were eligible for cycle 2 and women who failed to achieve an ongoing pregnancy in cycle 2 were eligible for cycle 3. Patients with severe OHSS in a previous cycle, or patients with any clinically relevant change to any of the eligibility criteria or any clinically relevant medical history since the previous cycle were not eligible for enrolment.

### Treatment allocation

The participating patients had in cycle 1 been randomized 1:1 to treatment with either follitropin delta or follitropin alfa and remained on the same

**TABLE 1 PARTICIPATING SITES AND PRINCIPAL INVESTIGATORS**

| Country | Principal investigators |
|---|---|
| Belgium | Herman Tournaye, UZ Brussel; Petra De Sutter, UZ Gent; Wim Decleer, AZ Jan Palfijn AV, Gent |
| Brazil | Alvaro Petracco, Fertilitat–Centro de Medicina Reproductiva, Porto Alegre; Edson Borges, Fertility–Centro de Fertilizacao Assistida, São Paulo; Caio Parente Barbosa, Instituto Ideia Fértil de Saúde Reproductiva, São Paulo |
| Canada | Jon Havelock, Pacific Centre for Reproductive Medicine, Burnaby; Paul Claman, Ottawa Fertility Centre, Ottawa; Albert Yuzpe, Olive Fertility Centre, Vancouver |
| Czech Republic | Hana Višnová, IVF CUBE, Prague; Pavel Ventruba, Centre of Assisted Reproduction, Brno[a]; Petr Uher, Institute of Reproductive Medicine and Genetics, Karlovy vary; Milan Mrazek, GYNEM, Prague |
| Denmark | Anders Nyboe Andersen, The Fertility Clinic, Copenhagen University Hospital, Copenhagen; Ulla Breth Knudsen, The Fertility Clinic, Aarhus University Hospital, Skejby |
| France | Didier Dewailly, Department of Endocrine Gynaecology and Reproductive Medicine, Hôpital Jeanne de Flandre[a]; Anne Guivarc'h Leveque, Clinique Mutualiste La Sagesse[a] |
| Italy | Antonio La Marca, University of Modena and Reggio Emilia, Modena; Enrico Papaleo, Centro Natalità San Raffaele, Milan |
| Poland | Waldemar Kuczynski, Kriobank, Bialystok; Katarzyna Kozioł, nOvum Fertility Clinic, Warsaw |
| Russia | Margarita Anshina, Centre of Reproduction & Genetics–LLC, Moscow[a]; Irina Zazerskaya, Federal State Budgetary Institution 'Federal Centre of Heart, Blood & Endocrinology named after V.I. Almazov' of Ministry of Health of the Russian Federation, Saint-Petersburg; Alexander Gzgzyan, Institute of Russian Academy of Medical Science Scientific Research Institute of Gynaecology and Obstetrics named after D.O. Ott of North-West Department of RAMS, Saint-Petersburg; Elena Bulychova, State Budgetary Health Institution of Moscow Region 'Moscow Regional Scientific Research Institute of Obstetrics & Gynaecology'[a] |
| Spain | Victoria Verdú, Genefiv, Madrid; Pedro Barri, Hospital Universitario Quirón Dexeus, Barcelona; Juan Antonio García-Velasco, IVI Madrid, Madrid; Manuel Fernández-Sánchez, IVI Sevilla, Seville; Fernando Sánchez Martin, Ginemed, Seville; Ernesto Bosch, IVI Valencia, Valencia; José Serna, IVI Zaragoza, Zaragoza; Gemma Castillon; IVI Barcelona, Barcelona; Rafael Bernabeu, Instituto Bernabeu, Alicante; Marcos Ferrando, IVI Bilbao, Bilbao |
| UK | Stuart Lavery, Boston Place Clinic, London; Marco Gaudoin, Glasgow Centre for Reproductive Medicine, Glasgow |
| Other members of the ESTHER-2 study group | Scott M. Nelson, School of Medicine, University of Glasgow, Glasgow, UK; Bart C.J.M. Fauser, Division Woman & Baby, University Medical Centre Utrecht, Utrecht, the Netherlands; Bjarke M. Klein, Ferring Pharmaceuticals A/S, Biometrics, Global Clinical and Non-Clinical R & D, Denmark; Lisbeth Helmgaard, Vibeke Breinholt, Bernadette Mannaerts and Joan-Carles Arce, Ferring Pharmaceuticals A/S, Reproductive Health, Global Clinical and Non-Clinical R & D, Denmark |

[a] Did not include patients in the current trial.

gonadotrophin in cycles 2 and 3. The trial was assessor-blind and all investigators, embryologists and central laboratory personnel were blinded to treatment allocation.

### Study procedures

Ovarian stimulation was initiated with either follitropin delta (FE 999049, Ferring Pharmaceuticals) or follitropin alfa (Gonal-F, Merck Serono) on day 2–3 of the menstrual cycle. For both gonadotrophins, the daily dose/starting dose was dependent on the ovarian response in the previous cycle. If the predefined targeted response of 8–14 oocytes retrieved had been reached in the previous cycle, the same daily dose/starting dose was repeated. If the number of oocytes retrieved in the previous cycle was out of the predefined targeted range, the dose/starting dose was modified as detailed in TABLE 2. For follitropin alfa, the assessment of starting dose in the repeated cycles was in agreement with current clinical practice. For the individualized dosing algorithm for follitropin delta, dose modifications across cycles were expressed in relative terms (%), and the algorithm was constructed such that (similar to the follitropin alfa dosing regimen) an increase of (starting) dose in cycle 2, followed by a decrease in cycle 3 (or a decrease followed by an increase), would result in the same (starting) dose as in cycle 1.

The daily dose of follitropin delta was fixed throughout stimulation, while the daily dose of follitropin alfa could be adjusted from stimulation day 6 at the

**TABLE 2 DOSING REGIMEN OF FOLLITROPIN DELTA AND FOLLITROPIN ALFA IN CYCLES 2 AND 3**

| Oocytes retrieved in previous cycle | Follitropin delta daily dose compared with daily dose in previous cycle[a] | Follitropin alfa starting dose compared with starting dose in previous cycle[b] |
|---|---|---|
| <4[c] | + 50% | + 75 IU |
| 4–7 | + 25% | + 37.5 IU |
| 8–14 | Same | Same |
| 15–19 | – 20% | – 37.5 IU |
| ≥20[d] | – 33% | – 75 IU |

[a] Fixed throughout stimulation. Maximum daily dose in cycle 2 was 18 μg. Maximum daily dose in cycle 3 was 24 μg.

[b] Fixed for the first 5 days after which it could be adjusted by 75 IU based on the individual response. Maximum daily dose was 450 IU.

[c] Also including women with cycle cancellation due to poor ovarian response.

[d] Also including women with cycle cancellation due to excessive ovarian response and women with triggering of final follicular maturation with GnRH agonist.

discretion of the treating physician, based on ovarian response. The maximum daily dose of follitropin delta was 18 μg and 24 μg in cycles 2 and 3, respectively. The maximum daily starting dose of follitropin alfa was 225 IU and 300 IU in cycles 2 and 3, respectively, with a maximum daily dose of 450 IU after dose adjustments in both cycles of ovarian stimulation. On stimulation day 6, a gonadotrophin-releasing hormone (GnRH) antagonist (cetrorelix acetate, Cetrotide, Merck Serono) 0.25 mg/day was initiated, and continued throughout stimulation. When three or more follicles ≥17 mm in diameter were observed, triggering of final follicular maturation was performed with either 250 μg recombinant human chorionic gonadotrophin (HCG; choriogonadotrophin alfa, Ovitrelle, Merck Serono) or 0.2 mg GnRH agonist (triptorelin acetate, Gonapeptyl, Ferring Pharmaceuticals), depending on number of follicles ≥12 mm (<25 follicles: HCG triggering; 25–35 follicles: GnRH agonist triggering or cycle cancellation per investigator's discretion). In case of >35 follicles ≥12 mm or the investigator judging that three or more follicles ≥17 mm could not be reached by day 20, the cycle was canceled. Oocytes were retrieved 36 ± 2 h after triggering of final follicular maturation and were inseminated by IVF or ICSI. Blastocyst transfer was performed on day 5 for women who received HCG (women who received GnRH agonist had all blastocysts cryopreserved). In cycle 2, women had single blastocyst transfer if they had a good-quality blastocyst (grade 3BB or higher *[Gardner and Schoolcraft, 1999]*) available, and double blastocyst transfer if they had no good-quality blastocyst available (and if two blastocysts were available). In cycle 3, women could have single or double blastocyst transfer, independent of blastocyst quality. Surplus blastocysts could be cryopreserved for use after trial completion. Vaginal progesterone tablets (Endometrin, Ferring Pharmaceuticals) 3 × 100 mg daily for luteal phase support were provided from the day after oocyte retrieval until the day of HCG test (13–15 days after transfer). Clinical and ongoing pregnancy were confirmed by ultrasound at 5–6 weeks and 10–11 weeks after transfer, respectively. All pregnancies were followed until birth and 4 weeks after live birth, if applicable.

Blood sampling for evaluation of anti-FSH antibodies was performed on stimulation day 1 (pre-dosing), 7–10 and 21–28 days (first and second post-dosing) after the last dose of follitropin delta or follitropin alfa. The time points for the first and second post-dosing assessments were chosen to assess a potential immunoglobulin M (IgM) response and a fully mounted IgG immune response, respectively (*FDA, 2009*). A tiered approach to immunogenicity testing was applied in line with guidance from EMA and FDA (*EMA, 2007; FDA, 2009, 2014*), with a screening assay followed by a confirmatory assay and subsequent additional characterization as applicable (including titre, neutralizing antibody and cross-reactivity assays). The screening, confirmation, titration and cross-reactivity assays were bridging immunoassays using electrochemiluminescence (ECL) as detection system (Meso Scale Discovery platform, MSD, Rockville, MD, USA). For assessing the neutralizing capability of antibodies in confirmed positive samples, a cell-based assay based on human embryonic kidney (HEK 293) cells that stably express the human FSH receptor was used. All assays were validated according to recommendations in current guidance and white papers (*EMA, 2007; FDA, 2009, 2014; Gupta et al., 2011; Shankar et al., 2008*). A treatment-induced anti-FSH antibody response was defined as a negative pre-dosing sample followed by at least one positive post-dosing sample or a positive pre-dosing sample followed by at least one post-dosing sample with a predefined fold increase in titre. Women with a treatment-induced anti-FSH antibody response were to be followed (for up to 2 years) until the response had returned to pre-dosing levels, as confirmed by two consecutive assessments.

Adverse events were recorded from signed informed consent until end-of-cycle in cycle 2, and again from screening until end-of-cycle in cycle 3, if applicable.

### Study outcomes

The primary endpoint was the proportion of women with treatment-induced anti-FSH antibodies after up to two repeated cycles of ovarian stimulation. Secondary immunogenicity endpoints covered the proportion of women with neutralizing antibodies, and treatment-induced antibodies by cycle (overall and neutralizing). Other secondary endpoints included pregnancy and live birth rates, ovarian response, embryology, adverse events and OHSS (including OHSS of moderate/severe grade, classified using Golan's system [*Golan et al., 1989*]) and/or OHSS preventive measures (cycle cancellations due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist, and/or administration of a dopamine agonist [if 20 or more follicles ≥12 mm]).

### Statistical analysis

The primary objective was to evaluate the immunogenicity of follitropin delta and follitropin alfa based on the presence of treatment-induced anti-FSH antibodies and their neutralizing capacity in women undergoing repeated ovarian stimulation. The statistical analysis was limited to descriptive statistics, and no formal comparisons of the treatment groups were planned. Further, no formal sample size calculations were performed, as the number of eligible patients would be determined by the outcome of cycle 1. Based on expected ongoing pregnancy and drop-out rates, it was estimated that 400 and 200 women would participate in cycles 2 and 3, respectively, with equal distribution between the treatment groups. This sample size would result in a reasonable precision of the estimated proportions, given that the proportions related to the primary endpoint were expected to be 0–2% (*Out et al., 1995; Recombinant Human FSH Study Group, 1995; Wadhwa and Thorpe, 2007*).

## RESULTS

### Baseline characteristics

The trial was conducted between 26 March 2014 and 26 June 2015, with live birth follow-up completed on 26 January 2016. In cycle 2, 513 women were enrolled and exposed; 252 to follitropin delta and 261 to follitropin alfa. In cycle 3, 189 women were enrolled, of whom 188 were exposed; 95 to follitropin delta and 93 to follitropin alfa. The trial participant flow for cycles 2 and 3 are shown in FIGURE 1.

Treatment groups were generally balanced with regard to baseline characteristics in both cycle 2 and cycle 3. In the overall trial population, the proportion of women ≥35 years increased (from 51% to 57%) and the proportion of women with serum AMH <15 pmol/l increased (from 53% to 57%) from cycle 2 to cycle 3. The proportion of women who had double blastocyst transfer increased from 22% in cycle 2 to 61% in cycle 3 (equally distributed between the treatment groups in both cycles), reflecting the less rigid transfer policy in the third stimulation cycle.

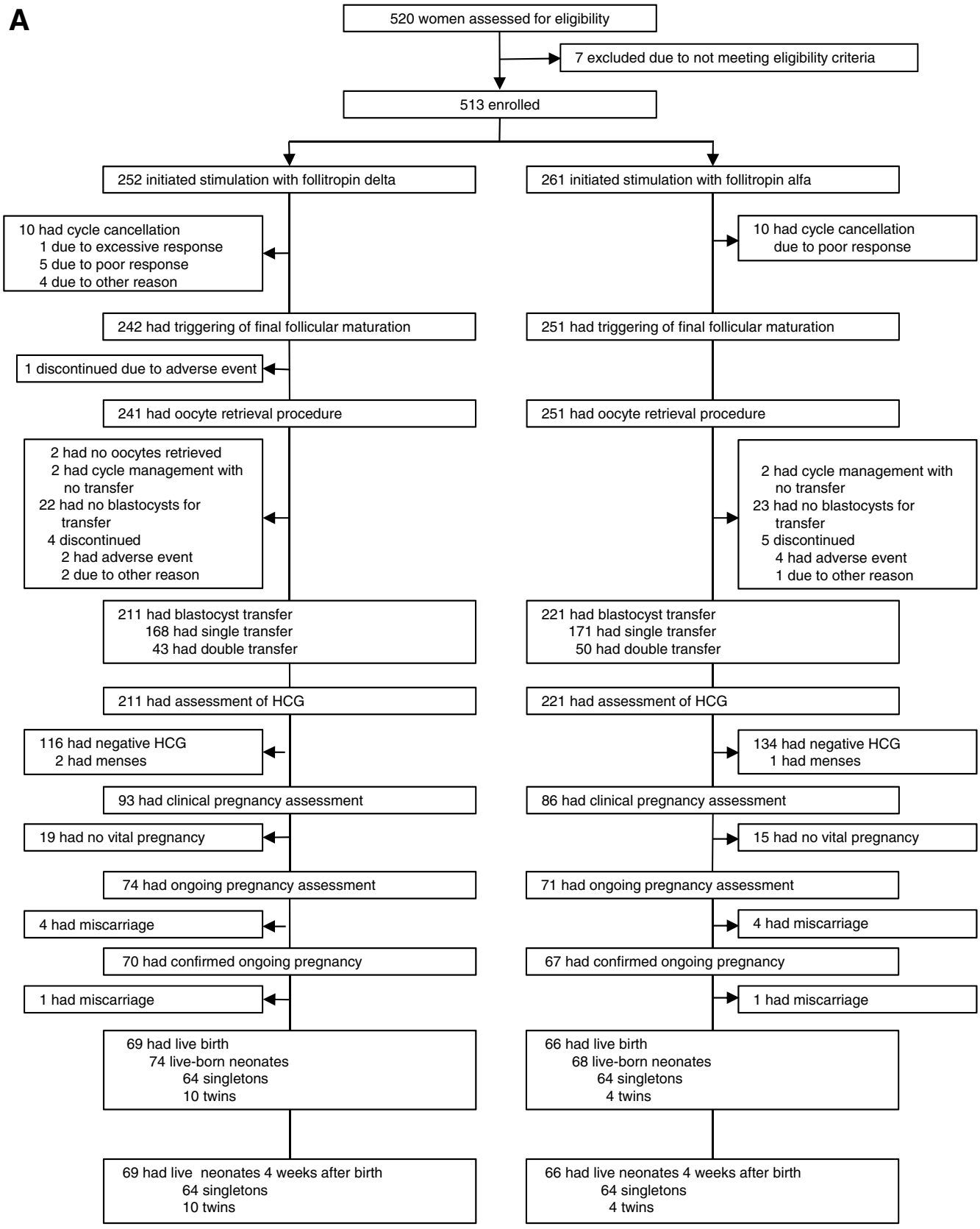


**FIGURE 1** (A) Trial and participant flow – cycle 2. (B) Trial and participant flow – cycle 3.

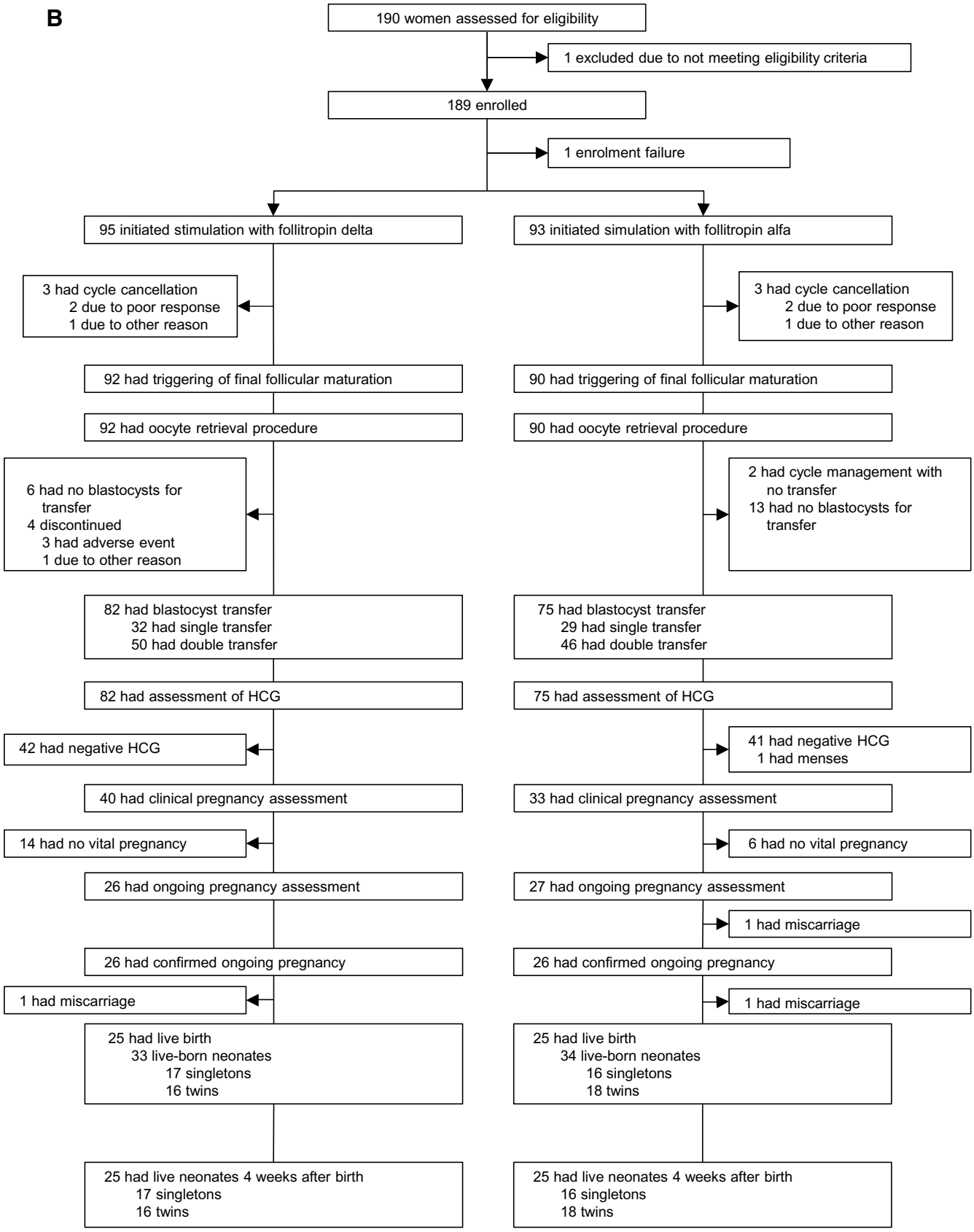


**FIGURE 1** (Continued)

**TABLE 3 IMMUNOGENICITY IN REPEATED OVARIAN STIMULATION CYCLES**

| | Cycle 1[a] | | Cycle 2 | | Cycle 3 | |
|---|---|---|---|---|---|---|
| | Follitropin delta *n* = 665 | Follitropin alfa *n* = 661 | Follitropin delta *n* = 252 | Follitropin alfa *n* = 261 | Follitropin delta *n* = 95 | Follitropin alfa *n* = 93 |
| Pre-existing anti-FSH antibodies[b] | 9 (1.35) | 6 (0.91) | 4 (1.59) | 2 (0.77) | 0 | 0 |
| Treatment-induced anti-FSH antibodies, total | 7 (1.05) | 5 (0.76) | 2 (0.79) | 1 (0.38) | 1 (1.05) | 1 (1.08) |
| Treatment-induced anti-FSH antibodies, new[c] | – | – | 1 (0.40) | 1 (0.38) | 0 | 0 |
| Treatment-induced anti-FSH antibodies of neutralizing capacity | 0 | 0 | 0 | 0 | 0 | 0 |

Values are presented as number (percentage).

[a] Cycle 1 was the initial stimulation cycle in the preceding efficacy trial (described in *Nyboe Andersen and Nelson et al., 2017*).

[b] Positive anti-FSH antibody samples at pre-dosing.

[c] Women with treatment-induced anti-FSH antibodies who did not have treatment-induced anti-FSH antibodies in the previous treatment cycle.

### Immunogenicity of follitropin delta

TABLE 3 displays immunogenicity data from cycles 2 and 3, and also shows results from cycle 1 for comparison. In cycle 1, in total 15 women (1.13%) had pre-existing anti-FSH antibodies (i.e. their pre-dosing samples were positive for anti-FSH antibodies prior to the first gonadotrophin exposure).

In cycle 2, six women (1.17%) had their pre-dosing samples positive for anti-FSH antibodies. Of these, two women (one in each treatment group) had also had positive pre-dosing samples in cycle 1, while the other four did not have anti-FSH antibodies detected in the preceding cycle. None of the six women developed treatment-induced anti-FSH antibodies.

In cycles 2 and 3, the incidence of treatment-induced anti-FSH antibodies was in the same range for follitropin delta and follitropin alfa, below the incidence of pre-dosing antibodies, and similar to the incidence of treatment-induced anti-FSH antibodies in cycle 1 (TABLE 3). No new patients developed treatment-induced anti-FSH antibodies in cycle 3, thus the cumulative incidence of treatment-induced anti-FSH antibodies after up to two repeated cycles of ovarian stimulation (cycles 2 and 3) with follitropin delta was 0.79%. All samples with treatment-induced anti-FSH antibodies had titres below the limit of quantification, and no treatment-induced anti-FSH antibodies were of neutralizing capacity in any treatment cycle. Follow-up of women with treatment-induced anti-FSH antibodies confirmed that the immunological response was transient.

Further evaluation of each woman with treatment-induced or pre-dosing anti-FSH antibodies indicated serum FSH levels within the normal range and individual ovarian responses that were in line with expectations based on the women's serum AMH and gonadotrophin dose. Based on all cycles in women with pre-dosing or treatment-induced anti-FSH antibodies, mean duration of stimulation was 8.7 days, mean number of oocytes retrieved was 10.5 and mean number of blastocysts was 3.4, which was similar to the overall population, thereby showing that presence of anti-FSH antibodies did not affect the ovarian response. None of the women with anti-FSH antibodies had immune-related adverse events or related skin reactions at the site of injection.

### Exposure, ovarian response, pregnancy, live birth and safety

The dosing in cycles 2 and 3 was determined based on the ovarian response in the previous cycle. FIGURE 2 displays the dosing for women in cycles 2 and 3, as based on the ovarian response in the previous cycle. The proportion of women who retained the same dose/starting dose in the repeated cycles was 40.9% versus 33.3% in the follitropin delta and follitropin alfa groups, respectively, in cycle 2, and 43.2% versus 41.9%, respectively, in cycle 3 (FIGURE 2).

TABLE 4 shows exposure, ovarian response, embryology, pregnancy and live birth in cycles 2 and 3. In both cycles, treatment groups were similar in ovarian response in terms of number of follicles at end of stimulation and overall number of oocytes retrieved, and in both treatment groups, the proportion of women reaching the targeted ovarian response (8–14 oocytes) increased slightly from cycle 2 to 3. Of the women who in cycle 2 received an increased (starting) dose compared with the previous cycle, 30.7% with follitropin delta and 30.1% with follitropin alfa reached the targeted response, and of the women who received a decreased (starting) dose compared with the previous cycle, 44.1% and 48.8%, respectively, reached the targeted response. In cycle 3, the proportion of women reaching the targeted response was 41.9% and 37.0%, respectively, among women with increased (starting) dose and 50.0% and 42.9%, respectively, among women with decreased (starting) dose.

Fertilization rate and average number of embryos and blastocysts (total and good quality) were also similar between treatment groups in both cycles. The average total dose of follitropin delta was significantly ($P < 0.001$) lower compared with follitropin alfa in cycle 2, but similar in cycle 3. As per protocol, no dose adjustments were implemented with follitropin delta, while with follitropin alfa, 43.7% and 40.9% of women had dose adjustments implemented in cycles 2 and 3, respectively, the majority of which were dose increases.

In terms of clinical outcome, pregnancy and live birth rates were comparable between treatment groups in both stimulation cycles (TABLE 4). The increase in double blastocyst transfers in cycle 3 was reflected as notably higher multiple pregnancy rates in cycle 3.

The increase in maximum daily dose and mean total dose of follitropin delta from cycle 2 to 3 had no apparent effect on the incidence of adverse events. The frequencies of adverse events were 47.2% and 47.5% with follitropin delta and follitropin alfa, respectively, in cycle 2 and 48.4% and 45.2%, respectively, in cycle 3. In the follitropin delta group, the incidence of moderate/severe

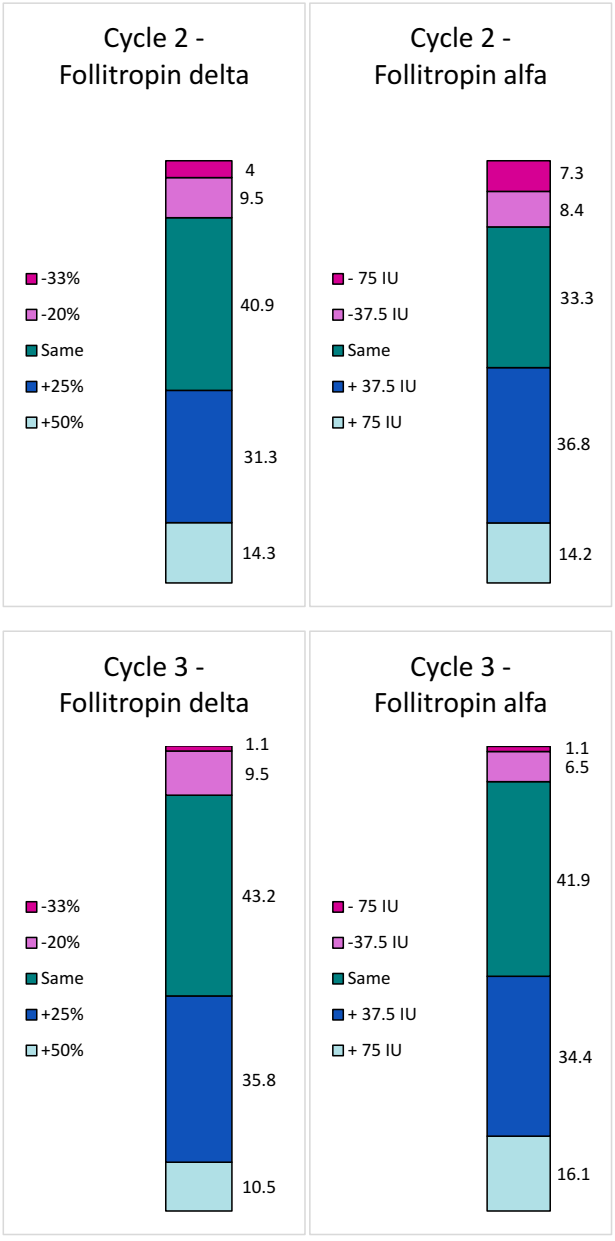


**FIGURE 2** Start dose based on ovarian response in previous cycle – women in cycles 2 and 3. The participants' dose/starting dose in cycles 2 and 3 were dependent on the ovarian response in the previous cycle. The figure displays the proportion (%) of women in cycle 2 and cycle 3 who received a dose/starting dose that was increased by 50% or 75 IU for follitropin delta and follitropin alfa, respectively (light blue), increased by 25% or 37.5 IU, respectively (dark blue), remained the same (green), was reduced by 20% or 37.5 IU, respectively (light purple), or was reduced by 33% or 75 IU, respectively (dark purple), compared with the dose/starting dose in the previous cycle.

OHSS and/or preventive interventions for OHSS was 1.6% and 0% in cycles 2 and 3, respectively, while the incidence with follitropin alfa was 4.2% and 2.2%, respectively. No cases of moderate/severe OHSS were observed with follitropin delta in cycles 2 and 3, while there were eight cases with follitropin alfa.

## DISCUSSION

This large clinical trial thoroughly investigated the immunogenicity of follitropin delta, with baseline assessments of anti-FSH antibodies prior to each stimulation cycle and post-dosing assessments at two occasions after stimulation to capture any potential primary or secondary immune responses. The immunogenicity assessment strategy consisted of anti-FSH antibody screening and confirmatory assays, measurement of antibody titre, determination of neutralizing antibodies, and analysis of cross-reactivity of antibodies to native FSH according to the relevant guidelines (*EMA, 2007; FDA, 2009, 2014*). The incidence of treatment-induced anti-FSH antibodies following follitropin delta administration in repeated cycles was low (0.8% in cycle 2 and 1.1% in cycle 3) and similar to the incidence in cycle 1 (1.1%). Previous studies on the immunogenicity of follitropin alfa and follitropin beta have not shown any anti-FSH antibody production (*Out et al., 1995; Recombinant Human FSH Study Group, 1995*) but anti-FSH antibody assays have improved considerably

**TABLE 4 OVARIAN RESPONSE, EMBRYOLOGY, PREGNANCY AND LIVE BIRTH IN REPEATED OVARIAN STIMULATION CYCLES**

| | Cycle 2 | | Cycle 3 | |
|---|---|---|---|---|
| | **Follitropin delta *n* = 252** | **Follitropin alfa *n* = 261** | **Follitropin delta *n* = 95** | **Follitropin alfa *n* = 93** |
| Ovarian response, embryology | | | | |
| Duration of stimulation (days) | 9.0 ± 1.9 | 9.0 ± 1.8 | 8.9 ± 1.9 | 8.8 ± 1.4 |
| Daily dose (μg) | 12.0 ± 3.6 | 13.5 ± 3.5 | 14.6 ± 5.1 | 15.1 ± 4.4 |
| Total dose (μg) | 107.7 ± 39.2[a] | 121.7 ± 44.3 | 130.0 ± 57.5 | 132.7 ± 44.4 |
| Women with investigator-requested gonadotrophin dose adjustments during stimulation[b] | 85 (33.7) | 114 (43.7) | 34 (35.8) | 38 (40.9) |
| Women with dose adjustments implemented during stimulation | 0 (0.0) | 114 (43.7) | 0 (0.0) | 38 (40.9) |
| Follicles (≥12 mm) at end of stimulation (*n*) | 10.2 ± 5.2 | 9.9 ± 4.9 | 8.9 ± 4.5 | 9.8 ± 4.8 |
| Oocytes retrieved[c] (*n*) | 9.2 ± 4.8 | 8.6 ± 4.3 | 8.3 ± 4.0 | 8.9 ± 4.2 |
| Target ovarian response (8–14 oocytes retrieved)[c] | 112 (46.5) | 118 (47.0) | 45 (48.9) | 45 (50.0) |
| Fertilization rate[d] (%) | 56.8 ± 23.5 | 52.6 ± 24.3 | 56.3 ± 20.6 | 49.7 ± 24.9 |
| Embryos, day 3[d] | | | | |
| Total (*n*) | 5.1 ± 3.3 | 4.3 ± 2.8 | 4.4 ± 2.4 | 4.4 ± 3.3 |
| Good quality (*n*)[e] | 3.9 ± 3.1 | 3.3 ± 2.4 | 3.2 ± 2.2 | 3.3 ± 3.0 |
| Blastocysts, day 5[d] | | | | |
| Total (*n*) | 2.8 ± 2.4 | 2.4 ± 2.1 | 2.2 ± 1.8 | 2.4 ± 2.3 |
| Good quality (*n*)[f] | 1.4 ± 1.7 | 1.2 ± 1.6 | 1.2 ± 1.5 | 1.2 ± 1.8 |
| Pregnancy and live birth[g] | | | | |
| Positive HCG[h] | 95 (37.7) | 87 (33.3) | 40 (42.1) | 34 (36.6) |
| Clinical pregnancy[i] | 82 (32.5) | 79 (30.3) | 31 (32.6) | 30 (32.3) |
| Vital pregnancy[j] | 74 (29.4) | 71 (27.2) | 26 (27.4) | 27 (29.0) |
| Ongoing pregnancy[k] | 70 (27.8) | 67 (25.7) | 26 (27.4) | 26 (28.0) |
| Implantation[l] | 88/254 (34.6) | 83/271 (30.6) | 38/132 (28.8) | 39/121 (32.2) |
| Ongoing implantation[m] | 73/254 (28.7) | 69/271 (25.5) | 33/132 (25.0) | 35/121 (28.9) |
| Women with live birth[n] | 69 (27.4) | 66 (25.3) | 25 (26.3) | 25 (26.9) |
| Women with live neonate(s) at 4 weeks after birth[o] | 69 (27.4) | 66 (25.3) | 25 (26.3) | 25 (26.9) |
| Multiple pregnancy[p] | 5 (7.1) | 2 (3.0) | 8 (30.8) | 10 (38.5) |

Values are presented as mean ± SD, or number (percentage), unless otherwise stated. Data are for all women unless otherwise stated.

[a] $P < 0.001$ (compared with follitropin alfa).

[b] Investigators were blinded to the trial medication and could request dose adjustment for both treatment groups based on transvaginal ultrasound assessment of follicular response. The follitropin delta dose was however fixed throughout stimulation and no dose adjustments were implemented, while the follitropin alfa dose could be adjusted down or up to a maximum of 450 IU.

[c] For women who received triggering of final follicular maturation.

[d] For women with oocytes retrieved.

[e] An embryo with six or more blastomeres and fragmentation ≤20%.

[f] A blastocyst of grade 3BB or higher.

[g] Outcome per started cycle.

[h] Positive according to the local laboratory's reference ranges.

[i] At least one gestational sac 5–6 weeks after transfer.

[j] At least one intrauterine gestational sac with fetal heart beat 5–6 weeks after transfer.

[k] At least one intrauterine viable fetus 10–11 weeks after transfer.

[l] Number of gestational sacs 5–6 weeks after transfer divided by number of blastocysts transferred.

[m] Number of intrauterine viable fetuses 10–11 weeks after transfer divided by number of blastocysts transferred.

[n] The birth of at least one live neonate.

[o] At least one live neonate 4 weeks after birth.

[p] Rate per ongoing pregnancy.

over time and are far more sensitive nowadays. In the current trial, none of the post-dosing samples of women with treatment-induced anti-FSH antibodies following follitropin delta stimulation had neutralizing capacity, which is in agreement with the more recent immunogenicity studies, where no neutralizing antibodies were reported, neither for daily administration nor for long-acting rFSH preparations (*Norman et al., 2011; Rettenbacher et al.,*

2015; Strowitzki et al., 2016). Baseline assessments of anti-FSH antibodies were performed for all patients in the preceding efficacy trial (Nyboe Andersen et al., 2017) prior to the first stimulation cycle (cycle 1), and confirmed the occurrence of natural anti-FSH antibodies in the infertile population (Gobert et al., 2001; Haller-Kikkatalo et al., 2012; Shatavi et al., 2006). In the follitropin delta group, 1.4% of the women had pre-existing anti-FSH antibodies. Thus, the combined data from all three treatment cycles in the trial program show that the incidence of treatment-induced anti-FSH antibodies in repeated stimulation with follitropin delta is low and similar to the incidence of pre-existing anti-FSH antibodies. Women with treatment-induced anti-FSH antibodies following follitropin delta treatment showed a transient immune response with low antibody titres without FSH neutralizing capacity and without clinical impact.

The current trial also evaluated a dosing regimen for follitropin delta in repeated cycles. In the first stimulation cycle, cycle 1, patients had been randomized to either follitropin delta or follitropin alfa, with follitropin delta dosing based on serum AMH and body weight and follitropin alfa dosed according to the prescribing information (Nyboe Andersen and Nelson et al., 2017). Patients who continued into subsequent cycles remained in the same treatment group and had their starting dose determined based on the ovarian response in the previous cycle. The similar number of patients in each treatment group continuing into the repeated cycles, the maintained blinding throughout both cycles, and the similar construction of the dosing regimens for follitropin delta and follitropin alfa, allowed for an accurate comparison of the two preparations in repeated stimulation. The comparative clinical data of the two treatment groups from the repeated cycles support the appropriateness of the follitropin delta dosing regimen applied in cycles 2 and 3. The overall number of oocytes retrieved, as well as the ongoing pregnancy and live birth rates, were comparable between treatment groups in both stimulation cycles.

Comparing the results throughout all three stimulation cycles in the trial program, a trend towards overall lower average number of oocytes in the repeated cycles was observed, with overall means of 10.2 oocytes, 8.9 oocytes and 8.6 oocytes in cycles 1, 2 and 3, respectively. In addition, the success rates decreased slightly in the repeated cycles, with overall ongoing pregnancy rates of 31.1%, 26.7% and 27.7% in cycles 1, 2 and 3, respectively, which is consistent with the discontinuation of young, good-prognosis patients becoming pregnant during the trial program, as also reflected by higher proportions of older women and women with lower AMH in the repeated cycles. The reduced pregnancy rates in the repeated cycles can also be explained by the fact that trial participants could choose to undergo cryopreserved cycles instead of continuing to a new ovarian stimulation cycle. This option would be more applicable for women with a surplus of good-quality blastocysts from the initial stimulation cycle, i.e. women with a better prognosis. Reduced pregnancy rates in repeated stimulation cycles have been described previously (Rabinson et al., 2009; Rettenbacher et al., 2015; Strowitzki et al., 2016), but sustained pregnancy rates during repeated stimulation were also reported (Norman et al., 2011).

By comparing the FSH starting doses, it was shown that in both cycle 2 and cycle 3, the majority of women received either the same (starting) dose or received an increased dose as compared with the previous cycle. Only a small fraction of women received a reduced dose. As a consequence, and in line with previous reports from repeated stimulation cycles (Eppsteiner et al., 2014; Rabinson et al., 2009; Strowitzki et al., 2016), the mean total dose increased for each cycle in both treatment groups. Comparing the total FSH dose, it is noteworthy that while the follitropin delta dose was fixed throughout stimulation, dose increments during stimulation were applied quite extensively in the follitropin alfa group in all cycles. Nevertheless, the overall ovarian response was similar for the two treatments. Dose increases during stimulation do not seem to affect the number of oocytes (Khalaf et al., 2002; van Hooff et al., 1993) and thus the choice of an appropriate starting dose is critical for the ultimate ovarian response in that cycle. Staying on the same dose throughout a whole stimulation cycle, as stipulated by the follitropin delta dosing regimen, may be advantageous for the patients, and require less frequent monitoring.

The frequency of adverse events did not increase in the repeated cycles, despite the gradual increase in daily and total dose in cycles 2 and 3, supporting safe use of follitropin delta also in an expanded dose range up to 24 μg.

In relation to ovarian response and risk of OHSS, individualized follitropin delta dosing compared with conventional follitropin alfa dosing in the first treatment cycle resulted in an improved OHSS risk management, revealed as lower incidences of preventive measures for OHSS as well as preventive measures and/or OHSS (Nyboe Andersen and Nelson et al., 2017). The observations from the repeated cycles suggest that the improved safety of follitropin delta treatment with regard to OHSS management in first cycle patients is carried over also to the next treatment cycle, demonstrated as a reduction in the number and severity of observed OHSS cases.

The current trial was adequately designed with robust, validated and sensitive assessments of immunogenicity. The trial population was representative of the typical patient population undergoing ovarian stimulation for IVF/ICSI in clinical practice.

In conclusion, no increase in immunogenicity was observed following follitropin delta exposure in repeated ovarian stimulation cycles. Similar ovarian response, pregnancy and live birth rates were observed as compared with follitropin alfa in both treatment cycles, supporting the appropriateness of the evaluated dosing regimen, with the advantage of being fixed, in repeated stimulation cycles. Follitropin delta was safe to use in an expanded dose range, with a continued improved safety profile as compared with follitropin alfa in terms of OHSS risk.

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