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ARTICLE

Establishing the follitropin delta dose that provides a comparable ovarian response to 150 IU/day follitropin alfa

BIOGRAPHY

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KEY MESSAGE

Analysis of two independent datasets comparing ovarian response in IVF/ICSI patients undergoing a GnRH antagonist protocol established that a daily dose of 10 µg follitropin delta provides a similar ovarian response to 150 IU/day follitropin alfa. This equivalence factor can help clinicians in evaluating follitropin delta in their conventional protocols.

ABSTRACT

Research question: The objective of this investigation was to determine the daily follitropin delta dose (µg) providing a similar ovarian response to 150 IU/day follitropin alfa.

Design: The study was a post-hoc analysis of ovarian response in 1591 IVF/intracytoplasmic sperm injection (ICSI) patients undergoing ovarian stimulation in a gonadotrophin-releasing hormone antagonist protocol in two recent randomized, assessor-blind, controlled trials in the development programme for follitropin delta: a phase II dose–response trial with a reference arm of a fixed daily dose of 150 IU follitropin alfa throughout stimulation, and a phase III efficacy trial with a comparator arm of 150 IU/day follitropin alfa as a starting dose.

Results: Daily follitropin delta doses of 10.0 µg (95% confidence interval [CI] 7.9–12.8) and 10.3 µg (95% CI 9.7–10.8) yielded the same number of oocytes as 150 IU/day follitropin alfa for all patients participating in the phase II and III trials, respectively. When analysing patients with either normal or high ovarian reserve (based on serum anti-Mullerian hormone ≥15 pmol/l) and no dose changes, the same number of oocytes was obtained with 150 IU/day follitropin alfa and daily doses of follitropin delta of 9.7 µg (95% CI 7.5–12.4) and 9.3 µg (95% CI 8.6–10.1) in the two trials. Daily follitropin delta doses in the range 9.5–10.4 µg were consistently estimated to correspond to 150 IU/day follitropin alfa for serum oestradiol concentration and number of follicles ≥12 mm at the end of stimulation across analysis populations in the phase III trial.

Conclusions: A daily follitropin delta dose of 10 µg provides a similar ovarian response to 150 IU/day follitropin alfa in IVF/ICSI patients.

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Declaration: J.-C. Arce and P. Larsson are employees of Ferring Pharmaceuticals. J.-C. Arce has patent applications on follitropin delta granted and pending. J. A. García-Velasco reports research grants and speaker fees from Ferring Pharmaceuticals, Merck, MSD, Gedeon Richter and Theramex.

KEY WORDS

Dose comparability
Dose equivalence factor
Follitropin alfa
Follitropin delta
IVF/intracytoplasmic sperm injection
Ovarian stimulation

INTRODUCTION

Historically, the biological activity of gonadotrophins is determined using the Steelman–Pohley bioassay, in which the FSH-induced increase in ovarian weight in rats is used as a measure of bioactivity and expressed in International Units (IU) (*Steelman and Pohley, 1953*). Most stimulation protocols and gonadotrophin dose regimens are provided in International Units, including those for daily recombinant FSH preparations filled by mass (µg protein content) (*Gonal-F, 2020*; *Wikland et al., 2006*). Clinicians have a long-standing familiarity with the expected clinical effects of gonadotrophin doses when defined in International Units, and reporting in International Units also allows for a more straightforward comparison of the responses to ovarian stimulation across patients and protocols. Acknowledging the long history of development of the gonadotrophin preparations for clinical use, the reluctance to adopt other ways of expressing gonadotrophin doses is understandable.

The Steelman–Pohley bioassay, which is based on changes in ovarian weight in rats *in vivo*, is not able to adequately characterize all gonadotrophins. For follitropin delta, a recombinant FSH derived from a human cell line (PER.C6), the Steelman–Pohley bioassay does not fully reflect the potency of follitropin delta in humans, but rather clearly underestimates it (*Olsson et al., 2014*). In this regard, it has been shown that the daily administration to women of 225 IU follitropin delta or 225 IU follitropin alfa (a recombinant FSH derived from a Chinese hamster ovary [CHO] cell line) resulted in significantly higher ovarian response with follitropin delta (*Olsson et al., 2014*). The explanation for this discrepancy between the rat bioassay and human data (i.e. human bioassay) in determining the potency is attributed to differences in glycosylation between follitropins derived from CHO or human cell lines, with some isoforms being rapidly cleared in rats but bioactive in humans (*WO 2009/127826 A1*). The potential implications of stating follitropin delta doses in International Units as per the rat bioassay would be a discrepancy between the expected and observed ovarian response and also a risk to patients' safety considering the compound's higher human potency. Consequently, follitropin delta doses are expressed by protein content (µg) and not by bioactivity (IU) (*Rekovelle, 2020*).

Nevertheless, given clinicians' intuitive understanding of International Units doses and their relation to expected ovarian response, it seems relevant to provide guidance on the follitropin delta microgram doses in the context of the more conventional International Units used for other follitropins. The limitations of the Steelman–Pohley bioassay means that the app ropriate quantification of the true human ovarian bioactivity can only be done based on data in humans. The scope of this investigation is to use the available evidence from IVF/intracytoplasmic sperm injection (ICSI) patients as obtained from randomized controlled trials to determine the daily follitropin delta dose (µg) providing the same biological response as 150 IU/day follitropin alfa in terms of ovarian response, taking into account not only oocytes retrieved, but also other FSH-related pharmacodynamic parameters such as follicular development and ovarian hormone response.

MATERIALS AND METHODS

This was a post-hoc analysis of the ovarian response data from 1591 IVF/ICSI patients included in two randomized, assessor-blind, controlled trials in the development programme for follitropin delta: a phase II dose-response trial (NCT01426386) and a phase III efficacy trial (NCT01956110). The phase II trial was conducted in 265 IVF/ICSI patients across seven investigational sites in four countries (*Arce et al., 2014*), and the phase III trial was conducted in 1326 IVF/ICSI patients across 37 investigational sites in 11 countries (*Nyboe Andersen and Nelson et al., 2017*). The trial protocols were approved by the local regulatory authorities and the independent ethics committees covering the participating centers. The trials were performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice and local regulatory requirements. All participants provided written informed consent. Details on trial design, assessor-blinding, population and results are available in the original references (*Arce et al., 2014*; *Nyboe Andersen and Nelson et al., 2017*).

Both trials were gonadotrophin-releasing hormone (GnRH) antagonist protocols with ovarian stimulation starting on day 2–3 of the menstrual cycle, and included women who were diagnosed with unexplained infertility, tubal infertility or endometriosis stage I/II (*American Society for Reproductive Medicine, 1997*), or had partners diagnosed with male factor infertility, and who were planning to undergo an IVF/ICSI cycle. In the phase II trial, women were randomly assigned, in a 1:1:1:1:1:1 ratio, to receive a fixed daily dose of either 5.2, 6.9, 8.6, 10.3 or 12.1 µg of follitropin delta (Rekovelle, Ferring Pharmaceuticals, Switzerland) or 150 IU (11 µg) of follitropin alfa (Gonal-F, Merck Serono, Switzerland), with no dose adjustments of either follitropin delta or follitropin alfa during stimulation. In the phase III trial, women were randomized in a 1:1 ratio to follitropin delta or follitropin alfa. In the follitropin delta group the daily dose was fixed throughout stimulation (after having been determined for each woman based on her serum AMH concentration and body weight; Supplemental Table 1), while the women in the follitropin alfa group received a daily starting dose of 150 IU (11 µg) for the first 5 days followed by potential dose adjustments as per the investigator's judgement.

Statistical analysis

For the phase II trial, the relationship between the dose of follitropin delta and the number of oocytes retrieved was approximated with a linear function (log-dose versus response), and the follitropin delta dose corresponding to 150 IU/day follitropin alfa was estimated by linear interpolation. The 95% confidence interval (CI) for the estimate was derived using the delta method on the log-dose scale followed by transformation to a linear scale. The linear approximation and interpolation were illustrated in a figure including estimated means and 95% CI for each dose. The analyses were made for all patients in the trial, as well as after excluding patients with low ovarian reserve and thereby focusing on those with either normal or high ovarian reserve (anti-Mullerian hormone [AMH] ≥15 pmol/l).

For the phase III trial, the relationship between the dose of follitropin delta and the ovarian response parameter was approximated by a linear function (log-dose versus response) for the group of patients randomized and exposed to follitropin delta. For the group of patients randomized and exposed to follitropin alfa, a similar approximation was applied based on the follitropin

TABLE 1 THE DAILY FOLLITROPIN DELTA DOSE (μG) (95% CI) ACHIEVING THE SAME OVARIAN RESPONSE AS A FIXED DOSE OF 150 IU/DAY FOLLITROPIN ALFA IN THE PHASE II DOSE–RESPONSE TRIAL

Parameter	All patients (*n* = 265)	Patients with either normal or high ovarian reserve (*n* = 150)
Oocytes retrieved	10.0 (7.9–12.8) μg	9.7 (7.5–12.4) μg
Follicles ≥12 mm[a]	10.2 (7.6–13.6) μg	9.8 (7.4–13.1) μg
Oestradiol[a]	9.0 (7.0–11.7) μg	9.2 (7.3–11.6) μg

In this trial, the dose of 150 IU/day follitropin alfa in the reference group was fixed throughout stimulation.

Normal and high ovarian response were as determined by baseline serum AMH ≥15 pmol/l.

95% CI, two-sided 95% confidence interval.

[a] At the end of stimulation.

delta dose these women would have received, as determined by their serum AMH and body weight, if they had been randomized to treatment with follitropin delta. It was expected that the line for follitropin delta would be almost horizontal, with the minimal slope indicating that, with the individualized follitropin delta dosing regimen, the ovarian response is harmonized across doses, and that the line for follitropin alfa would have a negative slope because all patients were treated with a conventional starting dose of 150 IU/day follitropin alfa regardless of AMH and body weight. The point where the two regression lines intersected was the dose of follitropin delta estimated to correspond to a starting dose of 150 IU/day follitropin alfa. The 95% CI for the estimate was derived using the delta method on the log-dose scale followed by transformation to the linear scale. The linear approximations were illustrated in figures including estimated means and 95% CI for subgroups based on follitropin delta doses rounded to integers. For each dose level subgroup, the comparison between follitropin delta and follitropin alfa was randomization-based, and therefore reflects the true difference in number of oocytes retrieved between the dose of follitropin delta shown on the *x*-axis in these figures and 150 IU/day follitropin alfa in this subgroup of patients.

The analyses were made for all patients in the trial and for the following relevant subpopulations: (i) patients with no dose changes (which for the follitropin delta group corresponds to the women for whom the investigator did not request a dose change, and for the follitropin alfa group corresponds to the women remaining on the starting dose of 150 IU/day); (ii) patients with either normal or high ovarian reserve (AMH ≥15 pmol/l); and (iii) the combination of these two populations, i.e. patients with either normal or high ovarian reserve and no dose changes. Ovarian response parameters included number of oocytes retrieved, number of follicles with a diameter of 12 mm or more at the end of stimulation, and serum concentrations of oestradiol at the end of stimulation.

RESULTS

Baseline

The demographics and baseline characteristics of the 1591 patients contributing to this investigation were comparable across treatment groups within each trial and also across the two trials (Supplemental Tables 2 and 3). More than half of the patients (55%) had an ovarian reserve indicative of a predicted normal to high response to gonadotrophin therapy, as reflected by a serum AMH concentration of 15 pmol/l or more.

Dataset 1: phase II dose–response trial

The dose–response trial demonstrated a linear relationship between the dose of follitropin delta (log-scale) and the number of oocytes retrieved. In this trial, a fixed dose of 150 IU/day follitropin alfa resulted in a mean ± standard deviation of 10.4 ± 5.2 oocytes retrieved for all patients who started stimulation, and 12.4 ± 5.4 for patients with either a normal or high ovarian reserve (based on serum AMH ≥15 pmol/l). Based on the dose–response curve for follitropin delta, the same ovarian response was achieved with a daily follitropin delta dose of 10.0 μg (95% CI 7.9–12.8) for all patients who started stimulation (TABLE 1, FIGURE 1A) and a follitropin delta dose of 9.7 μg (95% CI 7.5–12.4) for patients with either a normal or high ovarian reserve (TABLE 1, FIGURE 1B). An analysis of follicular development and ovarian hormone response yielded observations in line with those for oocytes retrieved for both analysis populations (TABLE 1).

Dataset 2: phase III efficacy trial

In the large phase III efficacy trial, a daily follitropin delta dose of 10.3 μg (95% CI 9.7–10.8) was estimated to provide the same number of oocytes retrieved as a starting dose of 150 IU/day follitropin alfa (TABLE 2, FIGURE 2A), when analysing all patients who started stimulation. Graphically, this is represented by

TABLE 2 THE DAILY FOLLITROPIN DELTA DOSE (μG) (95% CI) ACHIEVING THE SAME OVARIAN RESPONSE AS AN 150 IU/DAY FOLLITROPIN ALFA STARTING DOSE IN THE PHASE III EFFICACY TRIAL

Parameter	All patients (*n* = 1326)	Patients with no dose changes (*n* = 862)	Patients with either normal or high ovarian reserve (*n* = 570)	Patients with no dose changes and either normal or high ovarian reserve (*n* = 485)
Oocytes retrieved	10.3 (9.7–10.8) μg	10.3 (9.6–11.1) μg	9.5 (8.9–10.2) μg	9.3 (8.6–10.1) μg
Follicles ≥12 mm[a]	10.1 (9.4–10.7) μg	10.0 (9.0–11.1) μg	9.5 (8.7–10.4) μg	9.6 (8.5–10.9) μg
Oestradiol[a]	10.4 (9.5–11.5) μg	10.3 (9.2–11.5) μg	10.3 (8.9–11.9) μg	10.0 (8.7–11.5) μg

Patients with no dose changes are the women for whom the investigator did not request a dose change in the follitropin delta group and the women who remained on the starting dose of 150 IU/day in the follitropin alfa group.

Normal and high ovarian response were as determined by baseline serum AMH ≥15 pmol/l.

95% CI, two-sided 95% confidence interval.

[a] At the end of stimulation.

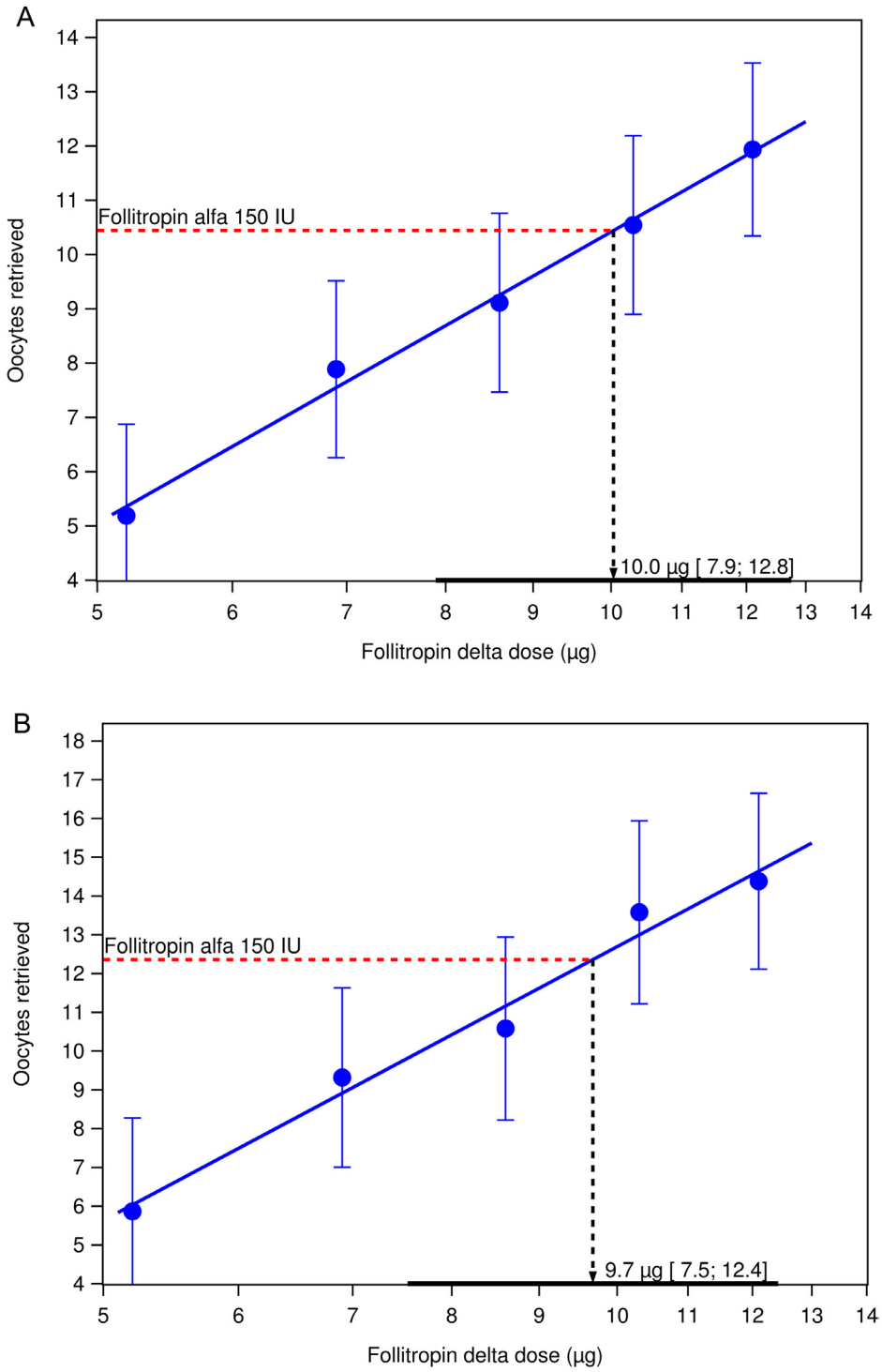

FIGURE 1 Number of oocytes retrieved for follitropin delta and 150 IU/day follitropin alfa in the phase II dose–response trial. (A) All patients (n = 265). (B) Patients with either normal or high ovarian reserve as determined by a baseline serum anti-Müllerian hormone concentration ≥15 pmol/l (n = 150). Estimated means (circles) with 95% confidence intervals (95% CI) and a regression line fitted to the log-dose versus the number of oocytes retrieved (blue line). The mean number of oocytes retrieved for 150 IU follitropin alfa (A, 10.4 oocytes; B, 12.4 oocytes) is indicated by the dashed horizontal red line, and the dose of follitropin delta estimated to have the same response as 150 IU follitropin alfa is indicated by the dashed vertical black line. The estimate and its 95% CI are indicated by the arrow and the solid horizontal black line on the x-axis.

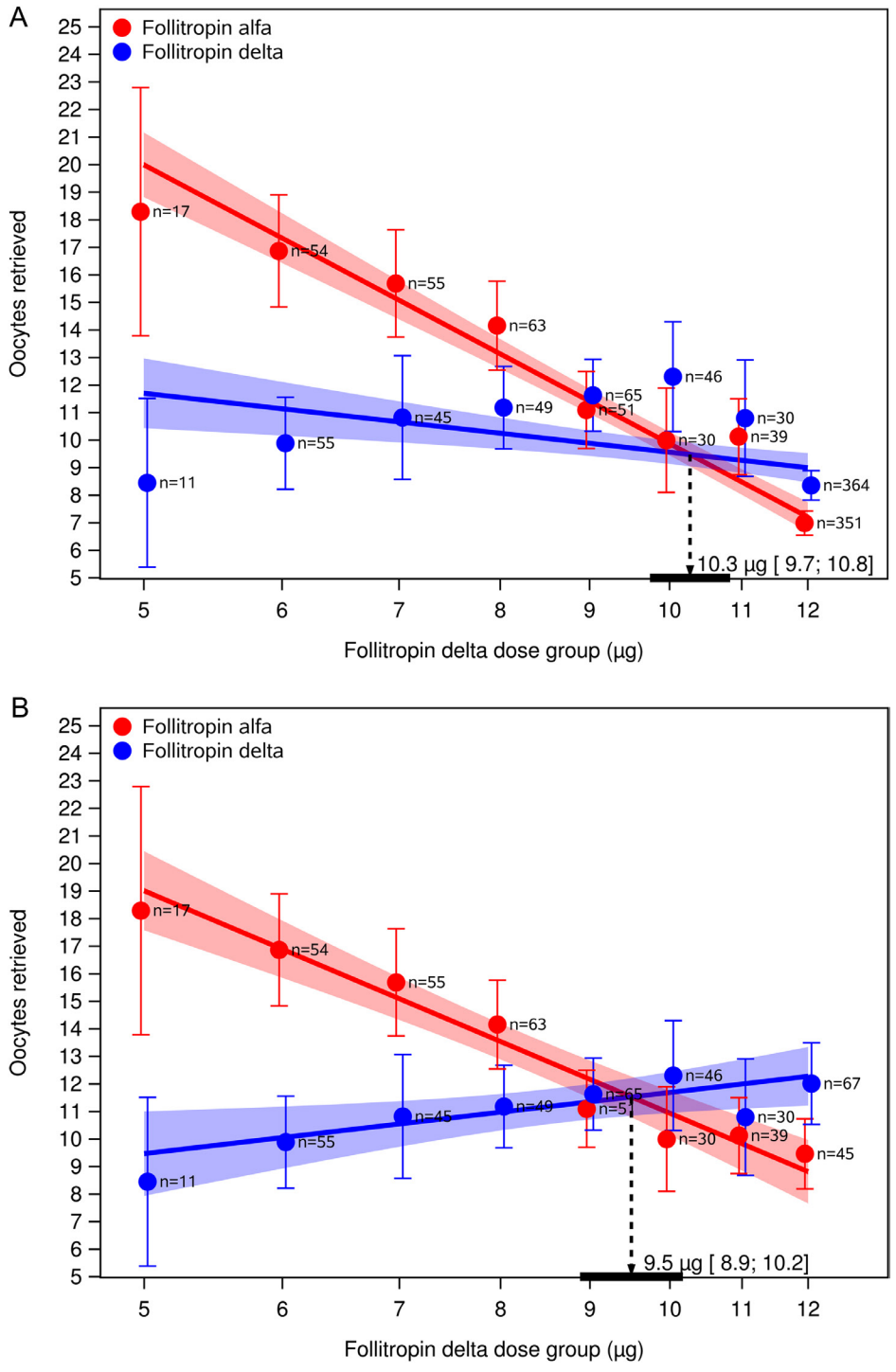

FIGURE 2 Number of oocytes retrieved for follitropin delta and 150 IU/day follitropin alfa in the phase III efficacy trial. (A) All patients (n = 1326). (B) Patients with either normal or high ovarian reserve as determined by baseline serum anti-Müllerian hormone (AMH) concentration ≥15 pmol/l (n = 570). Estimated means (circles) with 95% confidence intervals (95% CI) and number of patients for the subgroups based on the dose of follitropin delta corresponding to the patients' AMH concentrations and body weight. For example, for 7 µg on the x-axis, the circle for follitropin delta indicates that approximately 11 oocytes were retrieved in patients treated with follitropin delta, while the circle for follitropin alfa indicates that approximately 16 oocytes were retrieved in patients with the same baseline characteristics (AMH and body weight) but treated with a starting dose of 150 IU/day follitropin alfa. The intersection of the regression lines for follitropin delta (blue) and follitropin alfa (red) indicates the dose of follitropin delta estimated to have the same response as 150 IU of follitropin alfa. The estimate and its 95% CI are indicated by the arrow and the solid horizontal black line on the x-axis.

the intersection of the two regression lines representing follitropin delta and follitropin alfa. Similar observations were made for the subpopulations of patients with no dose changes at 10.3 µg follitropin delta (TABLE 2), patients with either normal or high ovarian reserve at 9.5 µg follitropin delta (TABLE 2, FIGURE 2B) and the combination of patients with either normal or high ovarian reserve and no dose changes at 9.3 µg follitropin delta (TABLE 2).

Further evaluation of comparability of ovarian response included follicular development and ovarian hormone response parameters at the end of stimulation (TABLE 2). The analysis of follicular development, as represented by the number of follicles with a diameter of 12 mm or greater, gave an estimate that was consistent with the estimate for oocytes retrieved, with a mean daily follitropin delta dose of 10 1 µg (95% CI 9.4–10.7) corresponding to a starting dose of 150 IU/day follitropin alfa. For the ovarian hormone response represented by serum oestradiol, the mean daily follitropin delta dose that achieved the same serum concentrations as a starting dose of 150 IU/day follitropin alfa was 10.4 µg (95% CI 9.5–11.5). Consistent observations for the number of follicles measuring 12 mm or more and serum oestradiol concentration at the end of stimulation were made in the subgroup analyses of patients with no dose changes, patients with either normal or high ovarian reserve, and the combination of patients with either normal or high ovarian reserve and no dose changes (TABLE 2).

DISCUSSION

The analysis of two independent datasets that jointly included more than 1500 patients undergoing ovarian stimulation for IVF/ICSI in a GnRH antagonist protocol led to the establishment of a dose equivalence factor, with 10 µg follitropin delta providing a similar ovarian response as 150 IU/day follitropin alfa. Customized statistical approaches suitable for the different trial designs were applied, and the analyses provided concordant findings in the range of 9.3–10.3 µg follitropin delta across trials and populations in relation to the number of oocytes retrieved. The estimates for follicular development and ovarian hormone response parameters aligned with those obtained for number of oocytes retrieved. The observation that a daily dose of 10 µg follitropin delta was comparable to the conventional dose of 150 IU/day follitropin alfa (which is also labelled as 11 µg follitropin alfa *[Gonal-F, 2020]*), indicates that follitropin delta provides a higher ovarian response in humans when administered not only at equal units of biological activity as in the rat in vivo Steelman–Pohley assay (*Olsson et al., 2014*), but also at the same microgram weight dose (*Arce et al., 2014*).

The novel methodological approach used here gives a more precise estimate of the dose equivalence factor than a head-to-head equivalence trial comparing one dose of follitropin delta to 150 IU/day follitropin alfa could ever provide. While the findings from the phase II trial with a fixed dose provided, early on in the development programme, an indication of the equivalence factor between the doses of follitropin delta and follitropin alfa, the point estimate was associated with a relatively wide 95% CI because of the study's sample size. The analysis of the phase III efficacy trial, which had a sample size more than five times greater than the dose–response trial and was therefore associated with more precision and narrower 95% CI, confirmed the phase II findings. Together, the two independent datasets provide a consistent body of evidence. The inclusion of patients with a low ovarian reserve in the analysis could lead to an underestimation of the differences in ovarian response between follitropins because these women are less sensitive to small variations in gonadotrophin doses (*Arce et al., 2014*). Therefore, subgroup analyses were performed excluding these patients and focusing on women with either normal or high ovarian reserve. In both trials, using only the data from patients with ovarian reserve indicative of a normal to high response (i.e. patients with a baseline serum AMH ≥15 pmol/l) did not lead to substantially different observations from the general trial populations.

With the abundance of clinical protocols for ovarian stimulation, it is crucial to have a common reference unit to understand the doses being proposed with different gonadotrophins. This is not only essential for clinicians, but also beneficial for patients, especially when they have a treatment history involving different protocols and different gonadotrophins. The present investigation brings clarity to this topic by establishing the dose comparability between follitropin delta and follitropin alfa in terms of ovarian response in the best possible human bioassay, i.e. IVF/ICSI patients, and thereby also facilitating the extrapolation of doses within the dose range used in clinical practice.

The daily follitropin delta dose is derived from a dosing algorithm using body weight and serum AMH concentrations, aiming to obtain an ovarian response of around 11 oocytes retrieved. The dose is stated in micrograms, and until now clinicians have not been able to determine the biological activity of the dose administered to patients. Having the knowledge that a daily dose of 10 µg follitropin delta will provide a comparable ovarian response to 150 IU/day follitropin alfa means an increased understanding of what to expect; for example, if the algorithm results in a dose of 9 µg, the clinician can anticipate a slightly lower oocyte yield and serum oestradiol concentration than would have been expected with 150 IU/day follitropin alfa.

Applying the equivalence factor described here of a daily dose of 10 µg follitropin delta corresponding to 150 IU/day follitropin alfa, it is possible to speculate that doses such as 75, 225 and 300 IU follitropin alfa would be expected to provide a comparable ovarian response to 5, 15 or 20 µg follitropin delta. Although this is an extrapolation from the findings of this study, it represents an important step towards improving the interpretation of the clinical effects of conventional protocols and biomarker-based personalized protocols using various follitropin preparations expressed in different units (*Arce et al., 2016*, *2014*; *La Marca et al., 2012*; *Nelson et al., 2009*; *Nyboe Andersen and Nelson et al., 2017*; *Papaleo et al., 2016*).

In conclusion, the equivalence factor identified in this study can help clinicians in evaluating follitropin delta in their conventional protocols and also increase the understanding of the doses applied in the existing microgram-based individualized dosing. Application of this dose equivalence factor will also ease patients' transition between protocols with different gonadotrophins in

successive cycles and reduce the risk of dose misinterpretations.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2020.07.006.

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SUPPLEMENTAL TABLES

SUPPLEMENTAL TABLE 1 INDIVIDUALIZED FOLLITROPIN DELTA DOSING REGIMEN USED IN THE PHASE 3 EFFICACY TRIAL

AMH (pmol/L)	<15	15-16	17	18	19-20	21-22	23-24	25-27	28-32	33-39	≥40
Fixed daily dose of follitropin delta (µg/kg)	12 µg	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.10

AMH concentration was rounded off to the nearest integers before determination of dose.

With the exception of 12 µg for AMH <15 pmol/L, all doses are expressed as µg/kg.

Maximum daily dose was 12 µg.

SUPPLEMENTAL TABLE 2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS IN THE PHASE 2 DOSE-RESPONSE TRIAL

	Follitropin delta 5.2 µg (N = 42)	**Follitropin delta 6.9 µg (N = 45)**	**Follitropin delta 8.6 µg (N = 44)**	**Follitropin delta 10.3 µg (N = 44)**	**Follitropin delta 12.1 µg (N = 47)**	**Follitropin alfa 150 IU (N = 43)**
Age (years)	33.6 ± 2.2	32.3 ± 3.5	32.8 ± 2.4	32.3 ± 3.2	32.6 ± 3.0	32.4 ± 3.0
Body weight (kg)	62.4 ± 10.1	63.0 ± 9.2	62.8 ± 8.2	60.5 ± 8.2	61.1 ± 8.2	66.1 ± 10.8
BMI (kg/m^2)	23.0 ± 3.5	23.2 ± 3.2	23.2 ± 2.8	22.4 ± 2.6	22.3 ± 2.5	24.2 ± 3.6
Duration of infertility (years)	3.3 ± 2.0	3.1 ± 2.2	3.4 ± 2.3	3.3 ± 2.3	3.4 ± 2.4	2.8 ± 1.4
Primary infertility (%)	67	71	68	80	70	58
AFC	13.7 ± 4.4	13.2 ± 4.7	13.5 ± 4.4	14.5 ± 4.4	14.3 ± 4.5	14.0 ± 4.2
AMH (pmol/L)	16 (9-23)	18 (9-27)	16 (10-22)	16 (11-25)	16 (10-29)	19 (10-28)
AMH <15 pmol/L (%)	45	42	43	45	43	42
AMH ≥15 pmol/L (%)	55	58	57	55	57	58
FSH (IU/L)	6.4 (5.1-7.7)	7.0 (5.8-7.8)	6.6 (6.1-8.1)	6.9 (5.8-8.0)	7.0 (6.1-9.4)	6.8 (5.4-8.1)
Estradiol (pmol/L)	136 (121-171)	149 (121-171)	140 (116-193)	145 (123-178)	126 (101-156)	134 (106-166)

Values are mean ± standard deviation, median (25th-75th interquartile range) or percentage.

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone.

SUPPLEMENTAL TABLE 3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS IN THE PHASE 3 EFFICACY TRIAL

	Follitropin delta (N = 665)	**Follitropin alfa (N = 661)**
Age (years)	33.4 ± 3.9	33.2 ± 3.9
Body weight (kg)	64.7 ± 10.7	63.4 ± 10.4
BMI (kg/m^2)	23.7 ± 3.4	23.3 ± 3.3
Duration of infertility (years)	2.9 ± 2.0	2.9 ± 1.8
Primary infertility (%)	71	71
AFC	14.7 ± 6.9	14.4 ± 6.8
AMH (pmol/L)	16 (9-25)	16 (9-26)
AMH <15 pmol/L (%)	45	46
AMH ≥15 pmol/L (%)	55	54
FSH (IU/L)	7.5 (6.2-9.2)	7.7 (6.5-9.4)
Estradiol (pmol/L)	158 (128-199)	162 (130-201)

Values are mean ± standard deviation, median (25th-75th interquartile range) or percentage.

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone.