525

COCO: A Randomised Controlled Trial comparing Ovarian Responses with Conventional Follitropin Delta 10/15 µg versus Follitropin Alfa 150/225 IU starting doses in a Long GnRH Agonist Protocol

Yingpu Sun,[1] Jianqiao Liu,[2] Jichun Tan,[3] Zhaolian Wei,[4] Hong Ye,[5] Qianhong Ma,[6] Lifeng Tian,[7] Xiaoming Teng,[8] Xueru Song,[9] Yunshan Zhang,[10] Yanwen Xu,[11] Lihan Zhou,[12] Eugene Zheng,[13] Yu Bagger,[14] Rita Lobo[14]

[1]The First Affiliated Hospital of Zhengzhou University; [2]The Third Affiliated Hospital of Guangzhou Medical University; [3]Shengjing Hospital of China Medical University; [4]The First Affiliated Hospital of Anhui Medical University; [5]Chongqing Maternal and Child Health Hospital; [6]West China Second University Hospital of Sichuan University; [7]Jiangxi Maternal and Child Health Hospital; [8]Shanghai First Maternal and Infant Health Hospital; [9]Tianjin Medical University General Hospital; [10]Tianjin Central Hospital of Gynecology Obstetrics; [11]The First Affiliated Hospital of Sun Yat-sen University; [12]Medical Science Department, Ferring Pharmaceuticals, Shanghai, China; [13]Biometrics, Ferring Pharmaceuticals, Shanghai, China; [14]Global Research and Medical, Ferring Pharmaceuticals, Kastrup, Denmark.

OBJECTIVE

To compare ovarian responses and safety of conventional follitropin delta versus follitropin alfa in a long gonadotropin-releasing hormone (GnRH) agonist protocol

KEY TAKEAWAYS

1. Conventionally dosed follitropin delta, at starting doses 10 or 15 µg per day showed non-inferiority to follitropin alfa 150 or 225 IU per day in the mean oocyte yield in Chinese participants
2. A numerically higher trend was observed with follitropin delta vs follitropin alfa across key efficacy endpoints, including ongoing pregnancy and live birth rates
3. Average oocyte yields, as well as pregnancy rates and live births from a fresh transfer, were slightly higher in a GnRH agonist protocol than observed in previous trial for follitropin delta with an GnRH antagonist protocol[1]

BACKGROUND

- Follitropin delta was approved for ovarian stimulation in China based on data from the registration trial, GRAPE, which evaluated individualised dosing, determined by serum AMH and bodyweight, within a GnRH antagonist protocol[1]
- In China, long GnRH agonist protocols are frequently used for ovarian stimulation due to improved endometrial receptivity compared with GnRH antagonist protocols, as well as more synchronised follicular development and tighter control of the stimulation timeline[2–5]
- This trial was designed to compare ovarian responses using conventionally dosed follitropin delta (10 or 15 µg per day [10/15 µg/day]) versus follitropin alfa (150 or 225 IU per day [150/225 IU/day]) in a long GnRH agonist protocol in women undergoing ovarian stimulation

METHODS

- COCO was randomised, multicentre and assessor-blinded, comparing efficacy and safety of starting doses of 10/15 µg/day follitropin delta with 150/225 IU/day follitropin alfa (dose adjustments allowed after stimulation Day 5) in a long GnRH agonist protocol. Investigators decided whether participants received the low (follitropin delta 10 µg or follitropin alfa 150 IU) or high (follitropin delta 15 µg or follitropin alfa 225 IU) starting dose based on their clinical judgment
- Participants, 18-40 years with serum AMH ≤35 pmol/L undergoing IVF/ICSI enrolled at 11 specialist reproductive clinics in China between 02-APR-2024 and 27-FEB-2025
- The primary endpoint was the number of oocytes retrieved. Pregnancies from the first fresh transfer (on Day 3 after oocyte retrieval) were followed to live birth. Adverse events, including ovarian hyperstimulation syndrome (OHSS) rates, were monitored
- The number of oocytes retrieved was compared using a negative binomial model with treatment and gonadotropin dose stratum as factors. Prespecified non-inferiority was confirmed if the lower limit of the 95% confidence interval for the difference between treatments was less than or equal to –3.00 for the FAS and the PP analysis set. Pregnancy and live birth rates were compared using a linear logistic regression model with treatment and starting dose as the model factor. 95% CIs were derived from the model estimates using the delta method

RESULTS

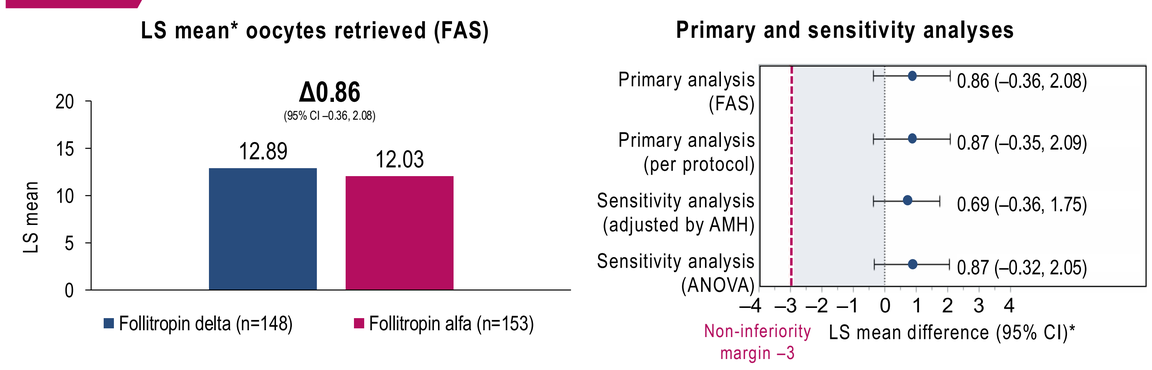
Table 1 COCO Trial: Demographics and Baseline Characteristics (FAS)

	Follitropin delta Starting dose 10 or 15 µg per day, n=148	Follitropin alfa Starting dose 150 or 225 IU per day, n=153
Age, years	32.5 ± 3.6	32.2 ± 3.8
<35 years	106 (71.6)	106 (69.3)
Bodyweight, kg	57.5 ± 8.3	57.5 ± 7.7
BMI, kg/m^2	22.4 ± 3.0	22.6 ± 2.8
Primary reason for infertility		
Tubal infertility	90 (60.8)	102 (66.7)
Unexplained infertility	25 (16.9)	20 (13.1)
Mild/moderate male factor	15 (10.1)	9 (5.9)
Severe male factor	18 (12.2)	19 (12.4)
Endometriosis stage I/II	0	3 (2.0)
Primary infertility	69 (46.6)	86 (56.2)
Duration of infertility, months	40.2 ± 31.8	38.7 ± 29.3
AFC	12.9 ± 4.5	12.4 ± 4.6
Previous ovarian stimulation cycle	19 (12.8)	15 (9.8)
Serum AMH at screening, pmol/l	17.0 ± 6.8	16.6 ± 7.1
Low / high gonadotropin starting dose	47 (31.8) / 101 (68.2)	51 (33.3) / 102 (66.7)

Data are mean ± standard deviation or n (%).

- Demographic and baseline characteristics were comparable between treatments groups

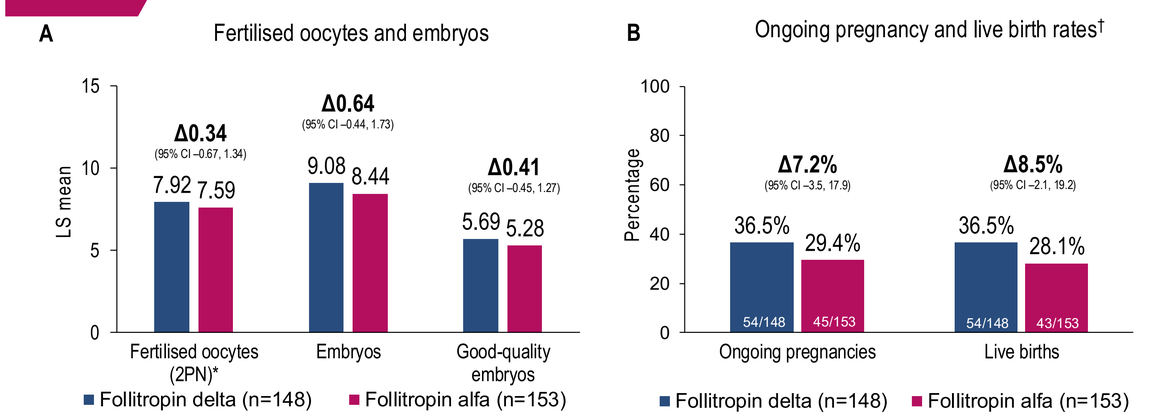
Figure 1 Oocytes Retrieved (Primary Endpoint)



*LS mean differences between treatments and the associated 95% CI were estimated from the model, assumed to have a negative binomial distribution, with treatment and starting dose as fixed factors. The LS means for the treatments in log scale were first estimated and then back transformed into the original scale. The standard error in the original scale for mean difference is derived using delta method to calculate the 95% CI.
Low starting dose stratum: follitropin delta 10 µg/day, n=47; follitropin alfa 150 IU/day, n=51. High starting dose stratum: follitropin delta 15 µg/day, n=101; follitropin alfa 225 IU/day, n=102.

- Non-inferiority of follitropin delta versus follitropin alfa was demonstrated for the FAS and per-protocol (PP) analyses, with comparable ovarian responses between treatments
- The two sensitivity analyses demonstrate robustness of results

Figure 2 Fertilised Oocytes, Embryos, Ongoing Pregnancy Rates and Live Birth Rates (FAS)



*Fertilised oocytes with two visible pronuclei were counted on Day 1 after insemination; however, the two pronuclei are not always visible at the normal time of assessment.
†For treatment differences for the pregnancy and live birth rates, a linear logistic regression model was applied with treatment and starting dose as the model factors. Then the results in terms of odds in log-scale for pregnancy were transformed back into proportions and difference in proportions. The 95% confidence interval for difference in proportions was calculated using the delta method.
Low starting dose stratum: follitropin delta 10 µg/day, n=47; follitropin alfa 150 IU/day, n=51. High starting dose stratum: follitropin delta 15 µg/day, n=101; follitropin alfa 225 IU/day, n=102.

- The number of fertilised oocytes and embryos were comparable between treatment groups, and the observed ongoing pregnancy and live birth rates from the first fresh embryo transfer were numerically higher in the follitropin delta group compared with the follitropin alfa group

Table 2 Adverse Event Summary (Safety Set)

	Follitropin delta Starting dose 10 or 15 µg per day, n=148	Follitropin alfa Starting dose 150 or 225 IU per day, n=153
Adverse events	75 (49.3)	87 (56.9)
Serious adverse events	4 (2.7)	11 (7.2)
AEs leading to discontinuation	9 (6.1)	10 (6.5)
Adverse drug reactions	16 (10.8)	25 (16.3)
Severe adverse events	4 (2.7)	5 (3.3)
Adverse events leading to death	0	0
Treatment emergent adverse events (≥5% in either group)		
Biochemical pregnancy	8 (5.4)	15 (9.8)
Morning sickness	12 (8.1)	10 (6.5)
Spontaneous abortion	9 (6.1)	9 (5.9)
Threatened spontaneous abortion	8 (5.4)	10 (6.5)
Hydrometra	9 (6.1)	7 (4.6)
Pelvic discomfort	8 (5.4)	8 (5.2)
OHSS, any grade*	6 (4.1)	9 (5.9)
Early OHSS, moderate/severe (Grades 3–5)	4 (2.7)	8 (5.2)
Upper respiratory tract infection	9 (6.1)	5 (3.3)

Data are n (%). *OHSS was graded according to Golan et al. (1989).[6]

- Adverse event profiles were similar between treatment groups and there were low rates of early OHSS

Table 3 Neonatal Outcomes at Birth (Safety Set)

	Follitropin delta Starting dose 10 or 15 µg per day, n=148	Follitropin alfa Starting dose 150 or 225 IU per day, n=153
Live births	54 (36.5)	43 (28/1)
Number of neonates born	67	48
Singletons	41	38
Twins	13	5
Gestational age, weeks	37.7 ± 2.09	38.4 ± 1.98
Gender		
Boy	32 (47.8)	24 (50.0)
Girl	35 (52.2)	24 (50.0)
Birth weight, g	2883 ± 672	3053 ± 519
Apgar score at 5 minutes	9.8 ± 0.5	9.9 ± 0.6
Admission to NICU or NCU >2hrs	18 (26.9)	9 (18.8)
Congenital anomaly present	8 (11.9)	4 (8.3)

Data are mean ± standard deviation or n (%).

- Neonatal health statuses at birth were comparable between treatment groups

References

1. Qiao et al. *Hum Reprod* 2021;36: 2452-2462.
2. Hu et al. *Front Endocrinol (Lausanne)* 2020;11:458.
3. Guo et al. *Shengzhi Yixue* 2025;34:571-579.
4. Xu et al. *Hum Reprod* 2020;35:1306-1318.
5. Cai et al. *Reprod Fertil* 2025;6:e250045.
6. Golan et al. *Obstet Gynecol Surv* 1989;44:430-440.

Acknowledgments

Medical writing assistance was provided by Celia J. Parkyn and was funded by Ferring Pharmaceuticals A/S. Ferring Pharmaceuticals A/S funded the trial.

Disclosures

SL, **JL**, **JT**, **ZW**, **HY**, **QM**, **LT**, **XT**, **ZS**, **YZ**, **and YX:** None declared.
LZ, **EZ**, **YB**, **PP** and **RL** are employees of Ferring Pharmaceuticals.

Contact information

For questions and comments, contact Rita Lobo at rita.lobo@ferring.com.

Abbreviations

AFC, antral follicle count; **AMH**, anti-Müllerian hormone; **ANOVA**, analysis of variance; **CI**, confidence interval; **FAS**, full analysis set; **GnRH**, gonadotropin-releasing hormone; **IU**, international units; **ICSI**, intracytoplasmic sperm injection; **IVF,** in vitro fertilisation; **LS**, least square; **NICU/NCU**, neonatal (intensive) care unit; **OHSS**, ovarian hyperstimulation syndrome; **PP**, per protocol.