Ferring and Reproductive Medicine and Maternal Health
A single commitment, dual approaches

Gaurang Daftary

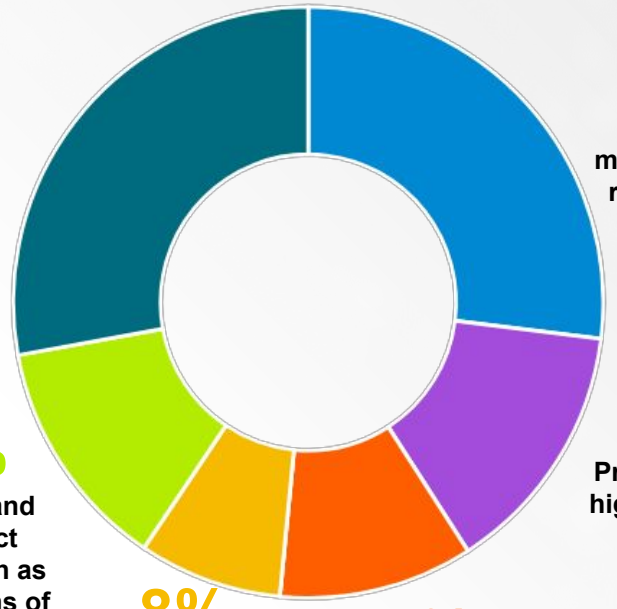
Global Scientific Vice President
Ferring Pharmaceuticals

FERRING
PHARMACEUTICALS

Heat-stable carbetocin

Post-partum haemorrhage impact

Leading causes of death among pregnant women[1*]



28%
Pre-existing medical conditions exacerbated by pregnancy (such as diabetes, malaria, HIV, obesity)

27%
Haemorrhage; more than two-thirds of reported deaths were classified as PPH

14%
Pregnancy-induced high blood pressure

13%
Embolism and other direct causes, such as complications of delivery and obstructed labour

8%
Abortion complications

11%
Sepsis

PPH is the leading direct cause of maternal deaths worldwide

Over **90% of deaths** from PPH occur in low and lower-middle income countries[2]

**Percentages have been rounded to the nearest whole number.*
PPH, post-partum haemorrhage.
1. Say L, et al. Lancet Glob Health 2014;2:e323–e333; 2. World Health Organization. Available at: https://www.who.int/medicines/areas/priority_medicines/Ch6_16PPH.pdf (Last accessed March 2022).

Unmet need in low and lower-middle income countries

The current standard-of-care medicine for PPH needs to be stored between **2–8°C** to maintain its effectiveness[1,2]

Over 90% of PPH deaths occur in low and lower-middle income countries,[3] where cold-chain storage can be difficult to achieve and maintain[1]

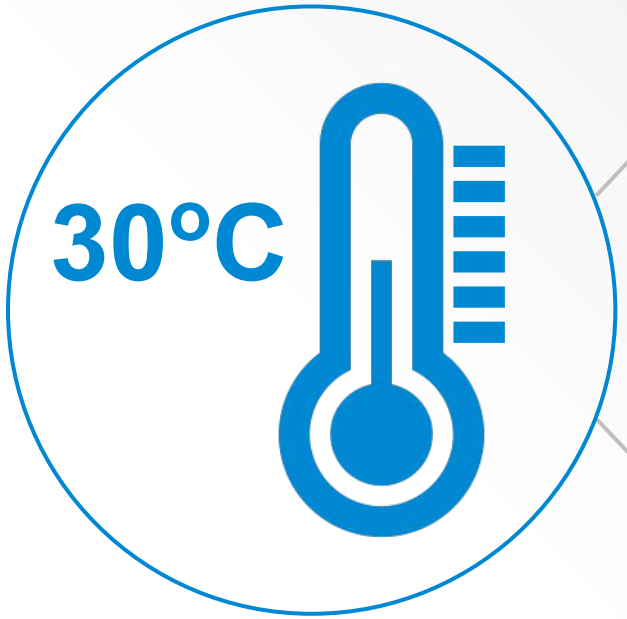
The majority of deaths from PPH due to uterine atony could be prevented[7,8]

22% of health facilities surveyed across 64 countries have no refrigerators[4]

Medicines can be exposed to 30°C.[5]
Only **1 in 4** healthcare staff may be trained to maintain cold storage and distribution[6]

1. Widmer M, et al. Trials 2016;17:143; 2. Torloni MR, et al. BJOG. 2016;123:2076–2086; 3. World Health Organization. Available at: https://www.who.int/medicines/areas/priority_medicines/Ch6_16PPH.pdf (Last accessed March 2022); 4. World Health Organization. Available at: http://www.who.int/immunization/programmes_systems/supply_chain/resources/WHO_CTC_Infographic.pdf?ua=1 (Last accessed March 2022); 5. Kartoglu U, et al. Biologicals 2017;50:117–124; 6. Immunization Supply Chain Policy Environment in Uganda. Available at: http://www.path.org/publications/files/APP_landscape_analysis_uganda_rpt.pdf (Last accessed: March 2022); 7. Ngwenya S. Int J Womens Health 2016;8:647–650; 8. World Health Organization. Available at: https://www.who.int/reproductivehealth/tranexamic-acid-pph-treatment/en/ (Last accessed March 2022).

Heat-stable carbetocin



Heat-stable carbetocin (Carbetocin Ferring) is the only injectable uterotonic for the prevention of uterine haemorrhage due to post-partum uterine atony that can be stored in humid and hot climates[1,2]

- Heat stable carbetocin remains stable for 3 years if stored below 30°C and 75% relative humidity[2] (approved storage conditions by Swissmedic)[3]
- Data are available supporting higher temperature deviations during transport[2]

Heat-stable carbetocin is long acting and effective as a single dose for the prevention of PPH*[1]

**Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to post-partum uterine atony.[1,2]*

1. Ferring Pharmaceuticals. PABAL® (carbetocin) Summary of Product Characteristics. 2019; 2. Malm M, et al. J Pept Sci 2018;24:e3082; 3. Swissmedic. Available at: https://www.swissmedic.ch/swissmedic/en/home/about-us/development-cooperation/marketing-authorisation-for-global-health-products.html (Last accessed April 2022).

A unique public–private partnership started in 2013[1]

- Conducted **CHAMPION** clinical trial: ~30,000 women in 10 countries
- Updated WHO PPH guidelines
- WHO Model Essential Medicines List

World Health Organization[2]

- Scientific and business expertise
- Financial resources
- Advocacy

MSD for Mothers[3,4]

- Heat-stable carbetocin for trial
- Scientific expertise
- Long-term commitment
- Regulatory submissions in L&LMICs
- Affordable and sustainable access price
- Sustainable supply to public sector in L&LMICs

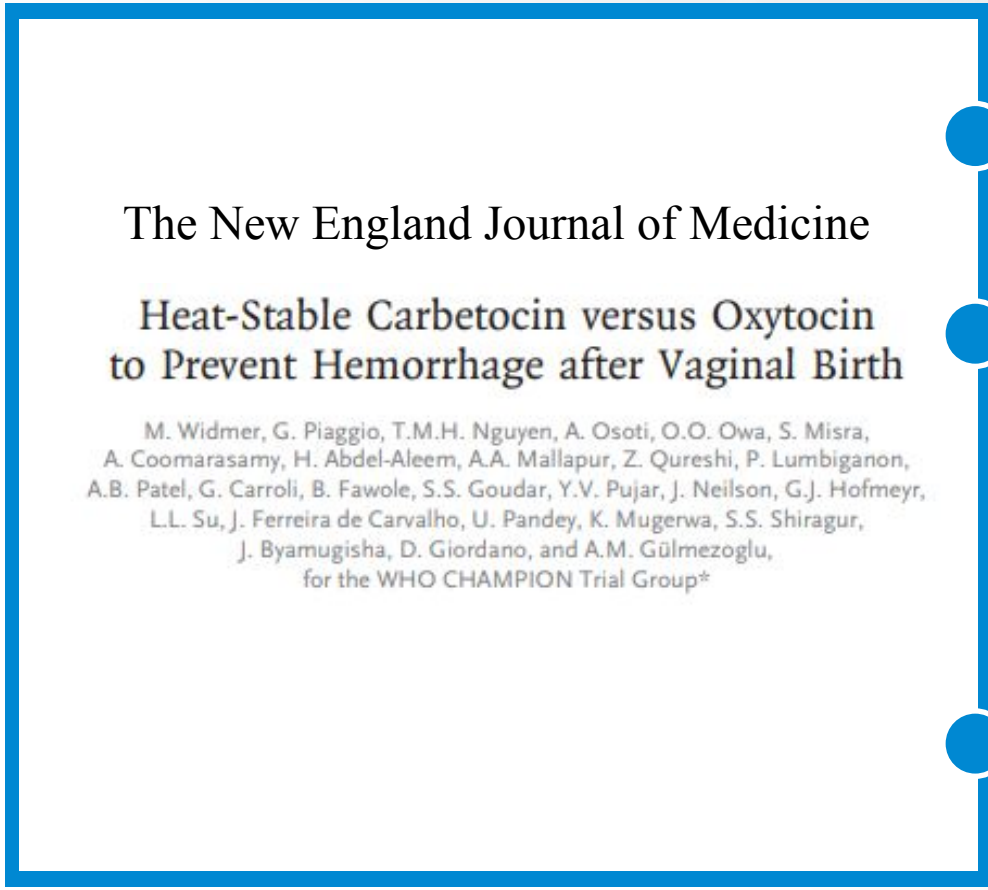
Ferring Pharmaceuticals[4]

As a leader in RMMH, Ferring is committed to the Project Family: Safe Birth initiative, following the vision that **No Woman Should Die Giving Life[5]**

L&LMIC, low and lower-middle income countries; PPH, post-partum haemorrhage; RMMH, reproductive medicine and maternal health.

1. World Health Organisation. Available at: http://apps.who.int/iris/bitstream/handle/10665/277278/WHO-RHR-18.29-eng.pdf?ua=1; 2. World Health Organisation. Available at: https://www.who.int/news/item/27-06-2018-who-study-shows-drug-could-save-thousands-of-women%e2%80%99s-lives; 3. Merck Pharmaceuticals. Available at: https://www.merck.com/news/msd-for-mothers-commits-10-million-and-business-expertise-to-the-global-financing-facility-to-help-end-preventable-deaths-of-mothers/; 4. Ferring Pharmaceuticals. Available at: https://www.ferring.com/ferring-pharmaceuticals-and-msd-announce-completion-of-largest-clinical-trial-ever-conducted-in-postpartum-haemorrhage/; 5. Ferring Pharmaceuticals. Available at: https://www.ferring.com/home-classic/people-and-families/reproductive-medecine-maternal-health/safe-birth/#:~:text=About%20%23ProjectFamily%3A%20safe%20birth,-No%20woman%20should&text=At%20Ferring%2C%20we're%20committed,no%20matter%20where%20she%20lives. (Last accessed April 2022).

CHAMPION trial*


The New England Journal of Medicine

Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth

M. Widmer, G. Piaggio, T.M.H. Nguyen, A. Osoti, O.O. Owa, S. Misra, A. Coomarasamy, H. Abdel-Aleem, A.A. Mallapur, Z. Qureshi, P. Lumbiganon, A.B. Patel, G. Carroli, B. Fawole, S.S. Goudar, Y.V. Pujar, J. Neilson, G.J. Hofmeyr, L.L. Su, J. Ferreira de Carvalho, U. Pandey, K. Mugerwa, S.S. Shiragur, J. Byamugisha, D. Giordano, and A.M. Gülmezoglu, for the WHO CHAMPION Trial Group*

- Total of 29,645 women were included
- Heat-stable carbetocin was non-inferior to oxytocin for blood loss ≥500 mL or use of additional uterotonic agents, was a composite primary outcome in the trial

	Carbetocin n=14,771	Oxytocin n=14,768	Risk ratio (95% CI)
Blood loss ≥500 mL or use of additional uterotonic agents	14.5%	14.4%	1.01 (0.95–1.06)

- Adverse event rates were similar between treatment groups

**CHAMPION Australian New Zealand Clinical Trials Registry number, ACTRN12614000870651; EudraCT number, 2014-004445-26; and Clinical Trials Registry–India number, CTRI/2016/05/006969.*

Widmer M, et al. N Engl J Med 2018;379:743–752.

Network meta-analysis conducted in 2018 by Gallos et al.

Cochrane Database of Systematic Reviews

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review)

Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A

In a network meta-analysis of 140 randomised controlled trials (N=88,947 women), heat-stable carbetocin was:[1,2]

- The highest ranked single uterotonic agent for the prevention of blood loss ≥500 mL[1]
- Linked with a reduction in the use of additional uterotonics[1]
- Associated with the most favourable side effect profile among uterotonics to prevent PPH* (similar to oxytocin)[1]

Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to post-partum uterine atony.[2]

1. Gallos ID, et al. Cochrane Database Syst Rev 2018;4:CD011689; 2. Ferring Pharmaceuticals. PABAL® (carbetocin) Summary of Product Characteristics. 2019.

Heat-stable carbetocin is included in the WHO Essential Medicines List

World Health Organisation Model List of Essential Medicines: 21st list 2019

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE	
22.3. Uterotonics	
Carbetocin	Injection (heat-stable): 100 micrograms/mL
Mifepristone – misoprostol Where permitted under national law and where culturally acceptable	Tablet 200 mg – tablet 200 micrograms Co-package containing: mifepristone 200 mg tablet [1] and misoprostol 200 microgram tablet [4]
Misoprostol	Tablet: 200 micrograms • Management of incomplete abortion and miscarriage • Prevention and treatment of post-partum haemorrhage where oxytocin is not available or cannot be safely used Vaginal tablet: 25 micrograms*
Oxytocin	Injection: 10 IU in 1 mL

**Only to be used for induction of labour where appropriate facilities are available.*

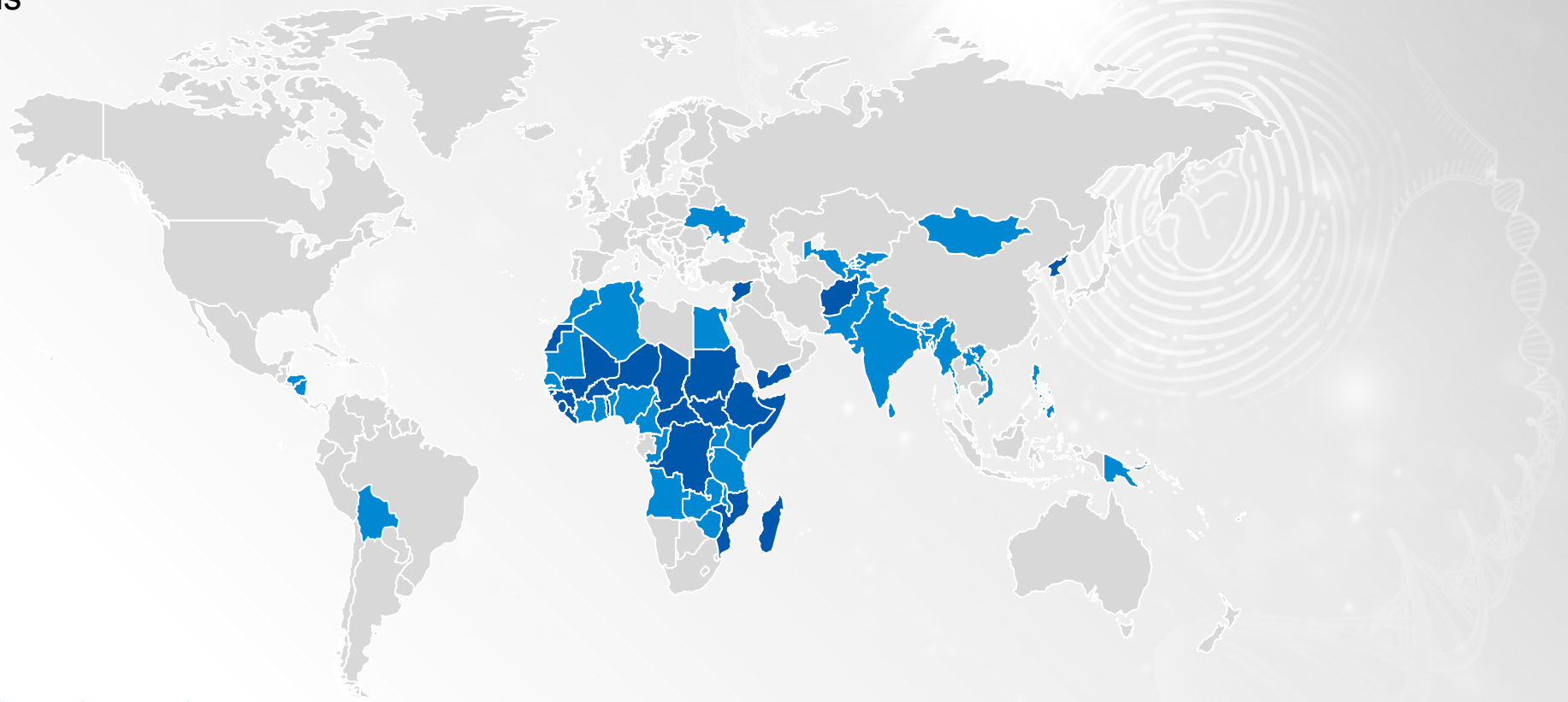
World Health Organization Model List of Essential Medicines: 21st list 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06eng.pdf (Last accessed March 2022)

Focus of Project Family: Safe Birth

Heat-stable Carbetocin Ferring will be made available at a sustainable **access price*** for public-sector healthcare facilities in low and lower-middle income countries, and select upper-middle income countries with a maternal mortality rate >140 per 100,000 live births[1]

World Bank 2020 criteria[2]

- Low income
- Lower middle income



**IDA Global Product Catalogue USD 0.44 / ampoule ex-warehouse.*

1. Ferring Pharmaceuticals. Data on file; 2. The World Bank. Available at: https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html (Last accessed March 2022).

Major milestone: Heat-stable carbetocin first patient

Monday 26 July 2021 – The first patient receives heat stable Carbetocin outside of clinical trials. This first dose was administered at the KLE Academy of Higher Education and Research, Belagavi, which was the lead Indian centre in the CHAMPION trial

1. Ferring Pharmaceuticals. Available at: https://www.ferring.com/women-in-india-are-the-first-in-the-world-to-receive-new-heat-stable-carbetocin-formulation-to-prevent-excessive-bleeding-after-childbirth/#:~:text=Saint%2DPrex%2C%20Switzerland%20%E2%80%93%2026,as%20postpartum%20haemorrhage%20(PPH) (Last accessed March 2022).

Project Family: Safe Birth

FERRING PHARMACEUTICALS

Our mission

Protect the lives of 20 million women and their families by 2030 through sustainable access to heat-stable carbetocin[2]

1. Ferring Pharmaceuticals. Available at: https://www.ferring.com/women-in-india-are-the-first-in-the-world-to-receive-new-heat-stable-carbetocin-formulation-to-prevent-excessive-bleeding-after-childbirth/ (Last accessed March 2022); 2. Ferring Pharmaceuticals. Available at: https://www.ferring.com/gender-health-and-racial-inequalities-to-be-tackled-in-flagship-ferring-grant-programme/ (Last accessed March 2022).

Follitropin delta

FERRING
PHARMACEUTICALS

Follitropin delta:
The only human cell line-derived rFSH

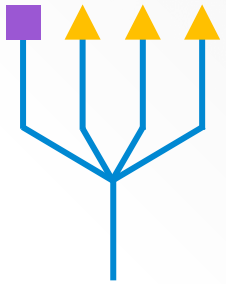
rFSH, recombinant follicle-stimulating hormone.

1. United States Patent Application Publication. Pub no: US 2015/0065695 A1. March 2015; 2. REKOVELLE Summary of Product Characteristics (Europe) 2022.

Follitropin delta: The only human cell line-derived rFSH

▲ 2,3-linked sialic acid
■ 2,6-linked sialic acid

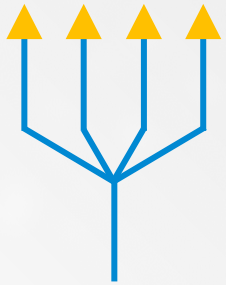
Follitropin delta



Asn

Mix of α2,3 and α2,6 sialic acid-linked residues, consistent with natural human FSH[1,2]

Follitropin alfa



Asn

Only α2,3 sialic acid-linked residues[1,2]

Compared with other rFSH products:[1,3]

- Follitropin delta more closely resembles the glycosylation pattern of natural human FSH
- Follitropin delta is likely to closely mimic the physiochemical and pharmacokinetic profiles of human urinary products

Created from the text of United States Patent Application Publication 2015 and Rekovelle SmPC 2022.

Asn, asparagine.

1. United States Patent Application Publication. Pub no: US 2015/0065695 A1. March 2015; 2. REKOVELLE Summary of Product Characteristics (Europe) 2022; 3. Smitz J, et al. Reprod Sci 2016;23:706–716.

Are there pharmacokinetic consequences?

Phase 1: Olsson et al

The Journal of Clinical Pharmacology
54(11) 1299–1307

DOI: 10.1002/jcph.328

Different Pharmacokinetic and Pharmacodynamic Properties of Recombinant Follicle-Stimulating Hormone (rFSH) Derived From a Human Cell Line Compared With rFSH From a Non-Human Cell Line

Håkan Olsson, PhD, Rikard Sandström, PhD, and Lars Grundemar, MD, PhD

Abstract

Pharmacokinetic and pharmacodynamic properties of a novel recombinant follicle-stimulating hormone (rFSH) preparation (FE 999049), expressed by a human cell line (PER.C6), was compared with an rFSH preparation (follitropin α) expressed by a Chinese hamster ovary (CHO) cell line in healthy pituitary-suppressed women. Following single intravenous administration of 225 IU (Steelman–Pohley assay), the clearance was lower, 0.31 versus 0.44 L/h, for FE 999049 than for follitropin α. Likewise, the apparent clearance after repeated daily subcutaneous administrations was lower, 0.58 versus 0.99 L/h, and AUC and C_{max} higher, 1.7- and 1.6-fold. The absolute bioavailability after a single subcutaneous dose of 450 IU was similar for both preparations, 60–65%. After repeated subcutaneous administration the elimination half-life was approximately 30 and 24 hours for FE 999049 and follitropin α. The ovarian responses by number of follicles and serum concentrations of inhibin B and estradiol, were higher with FE 999049 than with follitropin α, AUC and C_{max} for the two latter being >1.6-fold greater with FE 999049 than with follitropin α. These results indicate that administration of equal doses of FE 999049, expressed in a human cell line, and follitropin α, expressed in a CHO cell line, display different pharmacokinetic and pharmacodynamic properties in humans.

Keywords

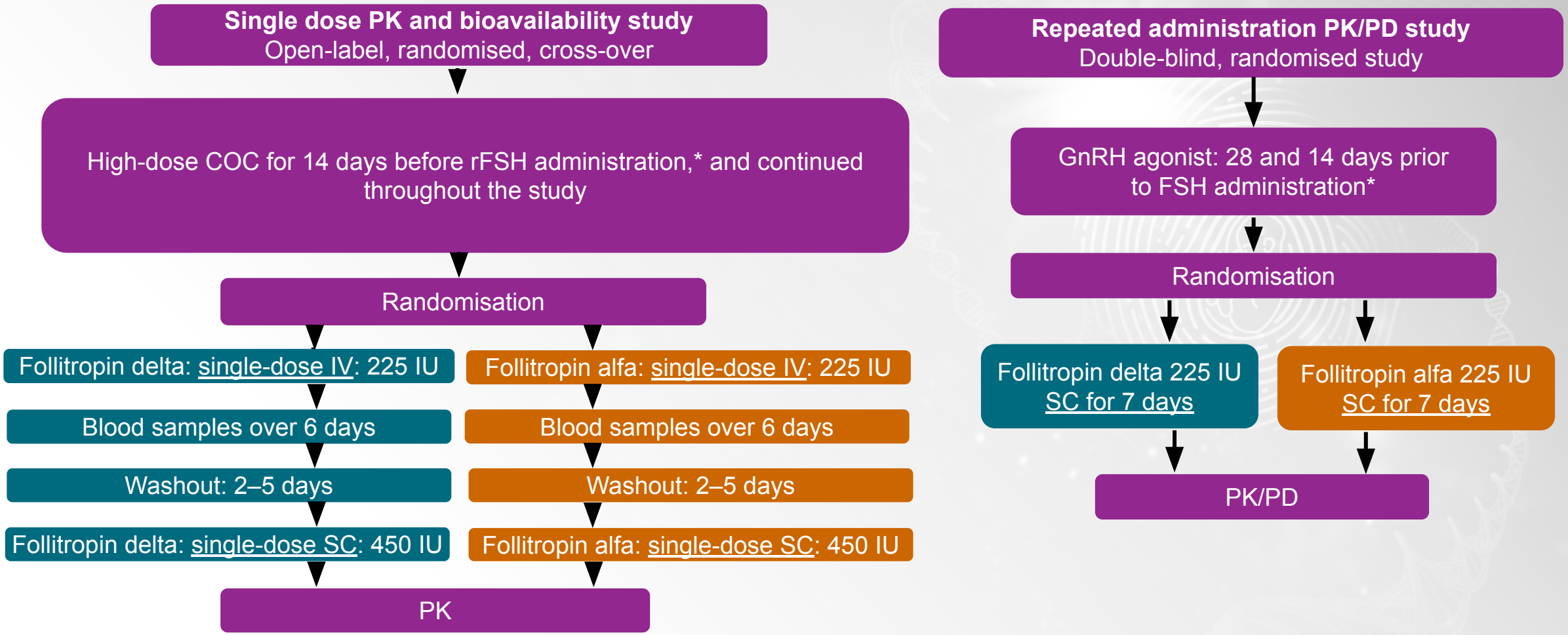
recombinant FSH, human cell line, pharmacokinetics, pharmacodynamics, bioavailability

Follicle-stimulating hormone (FSH) is produced in the anterior pituitary gland and is a key hormone in both male and female reproductive functions. In females, it stimulates growth and maturation of ovarian follicles[1] while in males it promotes spermatogenesis.[2] The synthesis and release of FSH is mainly controlled by the secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus. Information of on the subsequent fate of FSH are limited, but animal data indicate that in addition to the ovaries, FSH is distributed mainly to the kidney and liver,[3,4] and predominantly eliminated by the kidney.[4–6]

FSH is a glycoprotein composed of 2 non-covalently bound polypeptide chains, denoted α and β. The α-subunit, which is common to pituitary FSH, pituitary luteinizing hormone (LH), pituitary thyroid-stimulating hormone (TSH), and placental chorionic gonadotropin as well as the level of sialylation.[7,8] It has been demonstrated that the composition of the carbohydrate moieties has a significant impact on the in vivo activity of FSH by affecting the clearance, the binding properties to the FSH receptor in the target organs, and its ability to activate the receptors. Generally, less acidic isoforms have a higher clearance,[9–11] while the biological activity in vitro and in vivo has commonly been reported to be increased compared with isoforms with a higher number of sialic acid residues.[9,12–15]

Recombinant FSH (rFSH) has been widely used in the treatment of infertility since the introduction in the mid-1990s. To date, the currently available rFSH products

Phase 1: Olsson et al



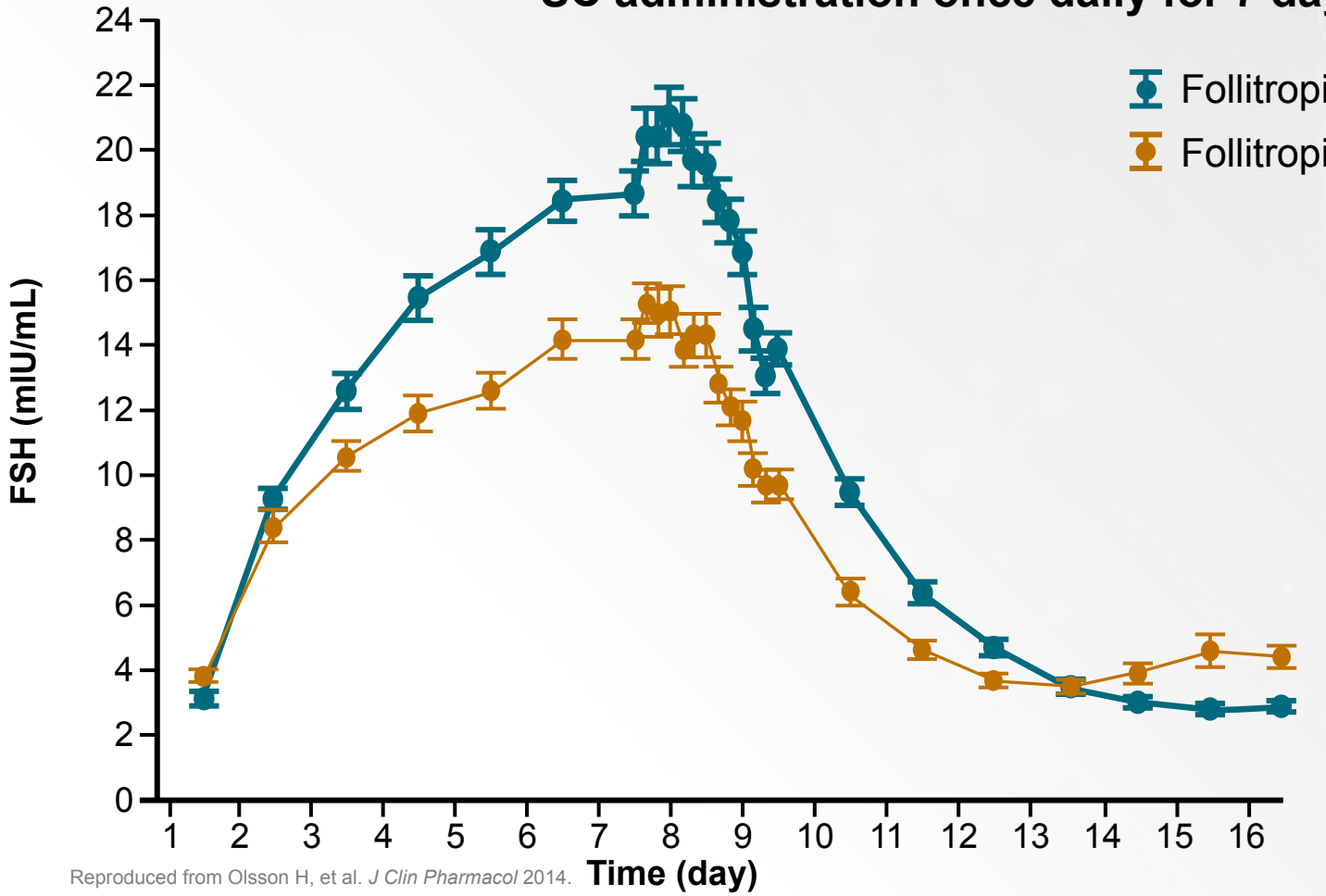
The FSH level was analysed before rFSH administration, and was required to be <5 IU/L, or <5IU/L and ≤50 pg/mL in case of double-blind randomized study, for the subject to be eligible.

COC, combined oral contraceptive; GnRH, gonadotrophin-releasing hormone; IU, international unit; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous.

Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

Phase 1: Divergent pharmacokinetic responses after human administration

SC administration once daily for 7 days consecutively*



Reproduced from Olsson H, et al. *J Clin Pharmacol* 2014.

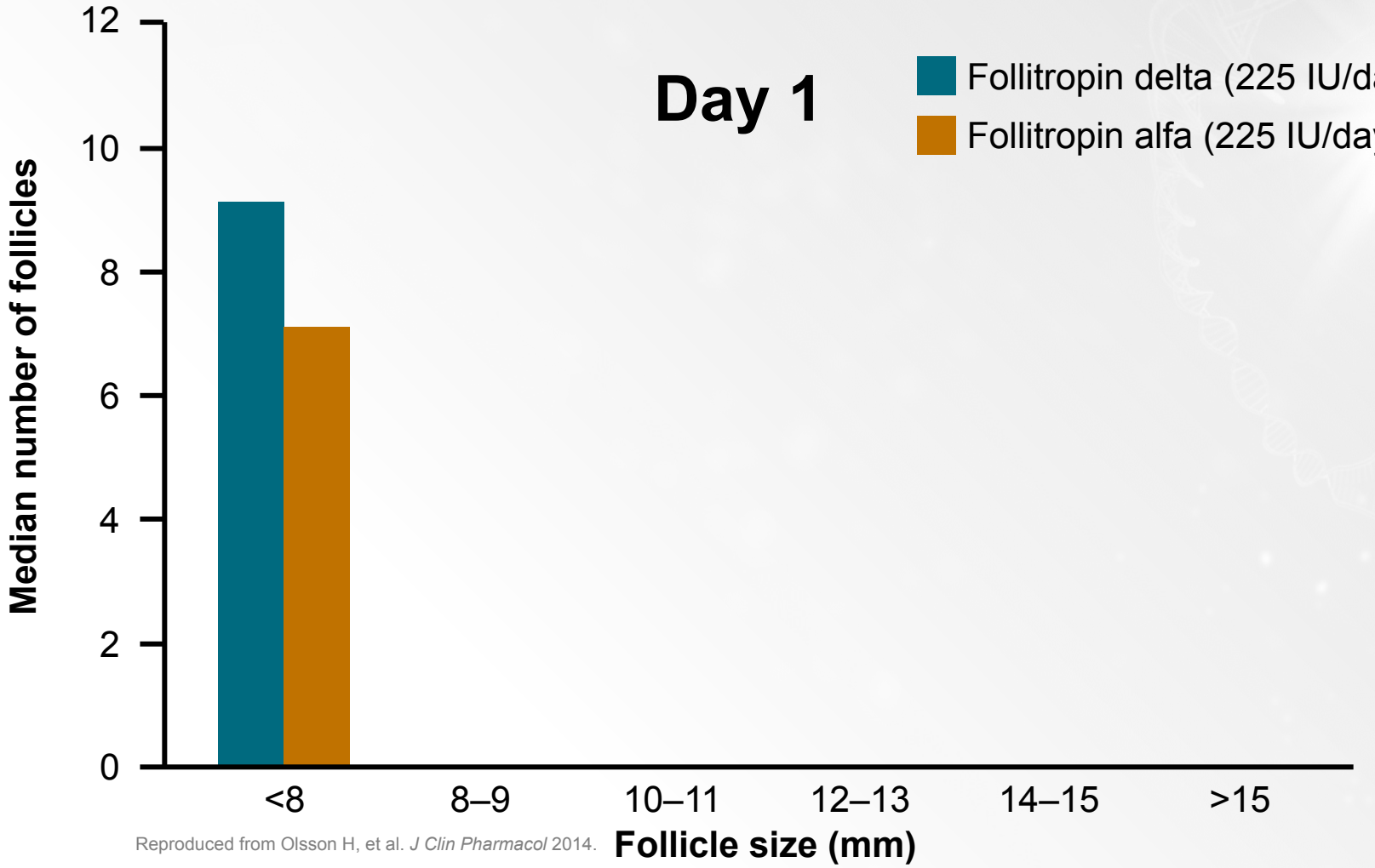
Follitropin delta versus follitropin alfa resulted in significantly:

- Higher AUC
- Higher C_{max}
- Lower clearance
- Longer half-life

*Concentrations on Days 1–6 are pre-dose values. Bars represent standard error.
AUC, area under the curve; C_{max}, maximum concentration.
Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

Pharmacodynamic results

Phase 1: Divergent pharmacodynamic responses after human administration

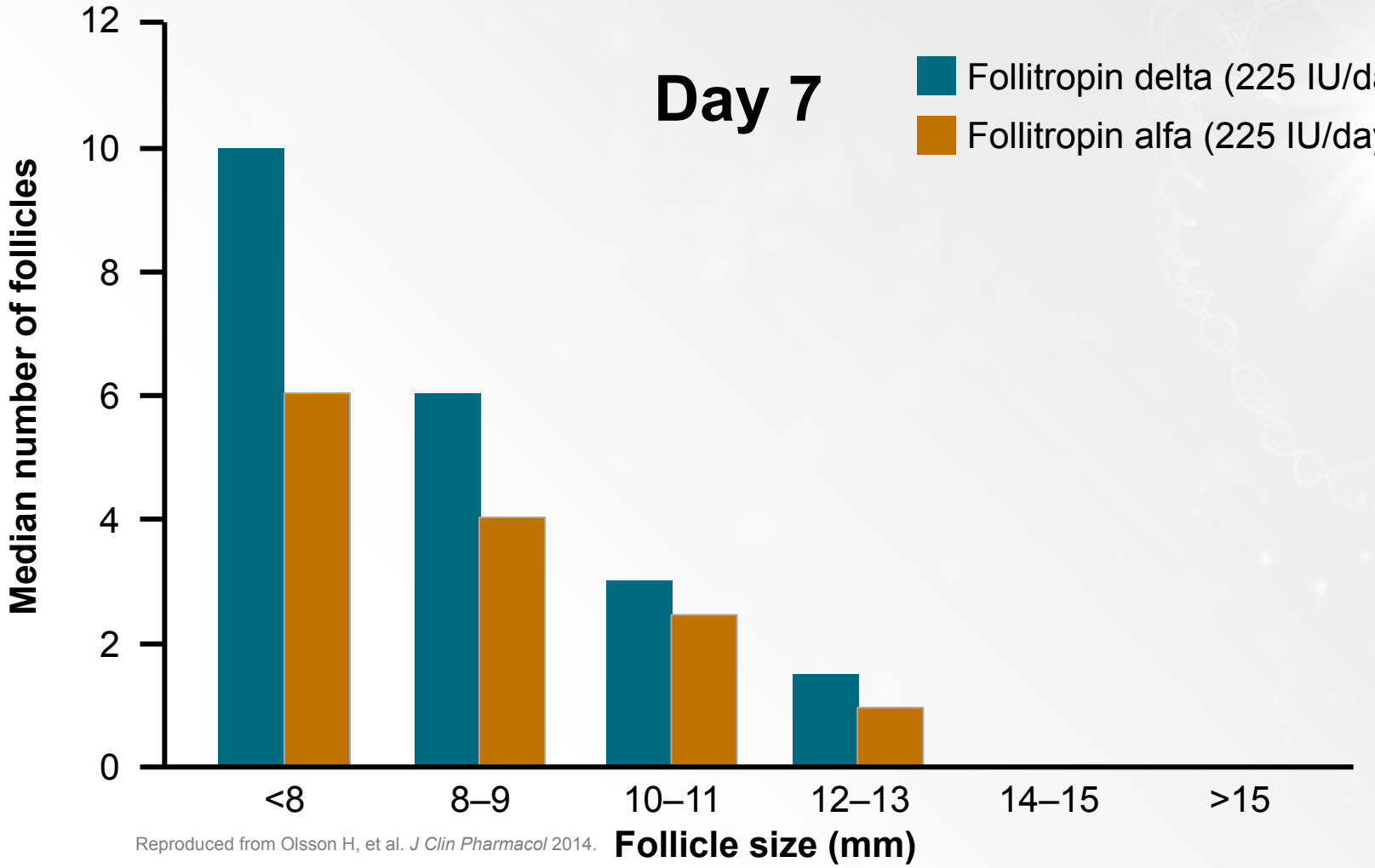


Reproduced from Olsson H, et al. *J Clin Pharmacol* 2014.

The median number of follicles in different size categories over the course of administration was also assessed

Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

Phase 1: Divergent pharmacodynamic responses after human administration

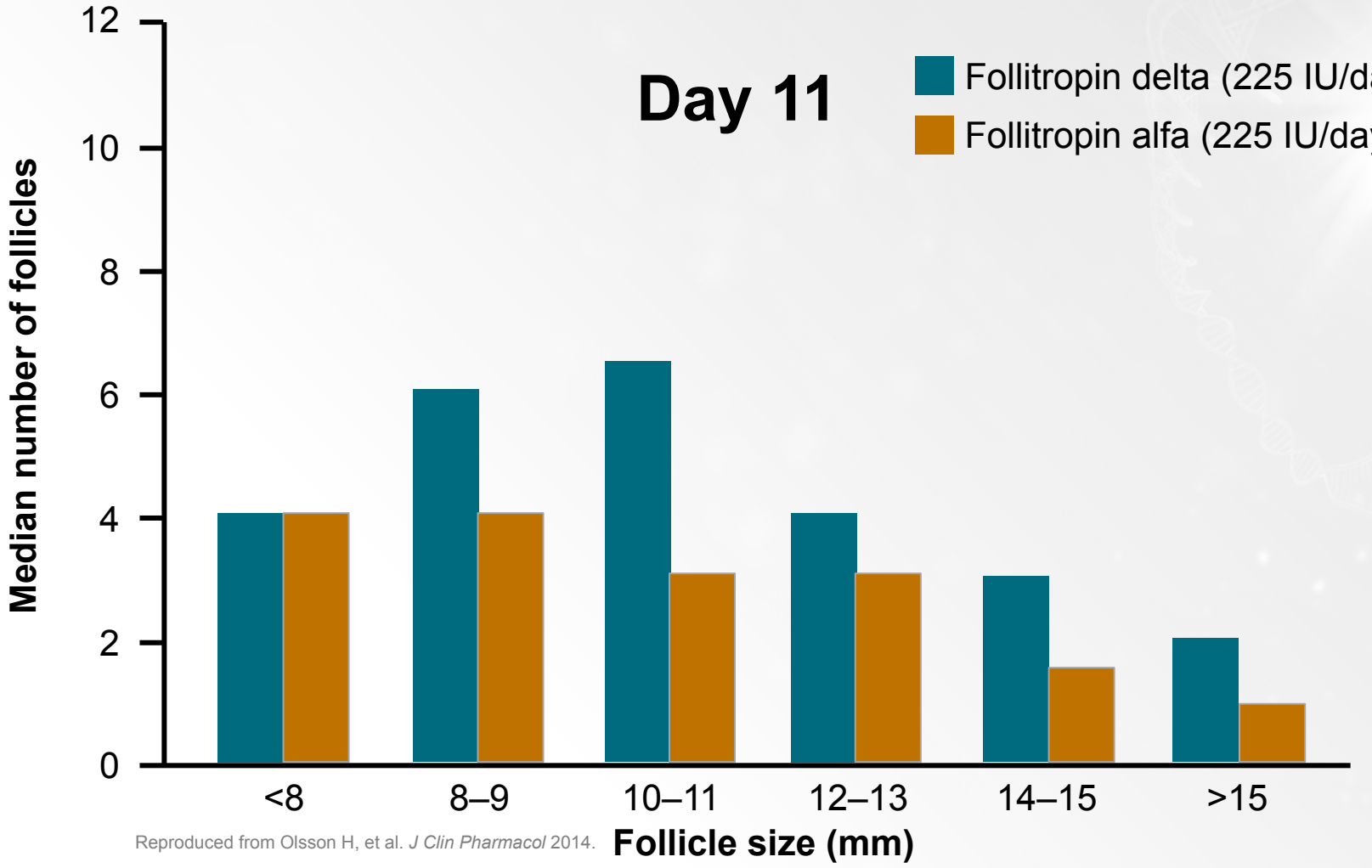


Reproduced from Olsson H, et al. *J Clin Pharmacol* 2014.

Both the number and the size distribution of growing follicles changed during the treatment period of 7 days

Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

Phase 1: Divergent pharmacodynamic responses after human administration

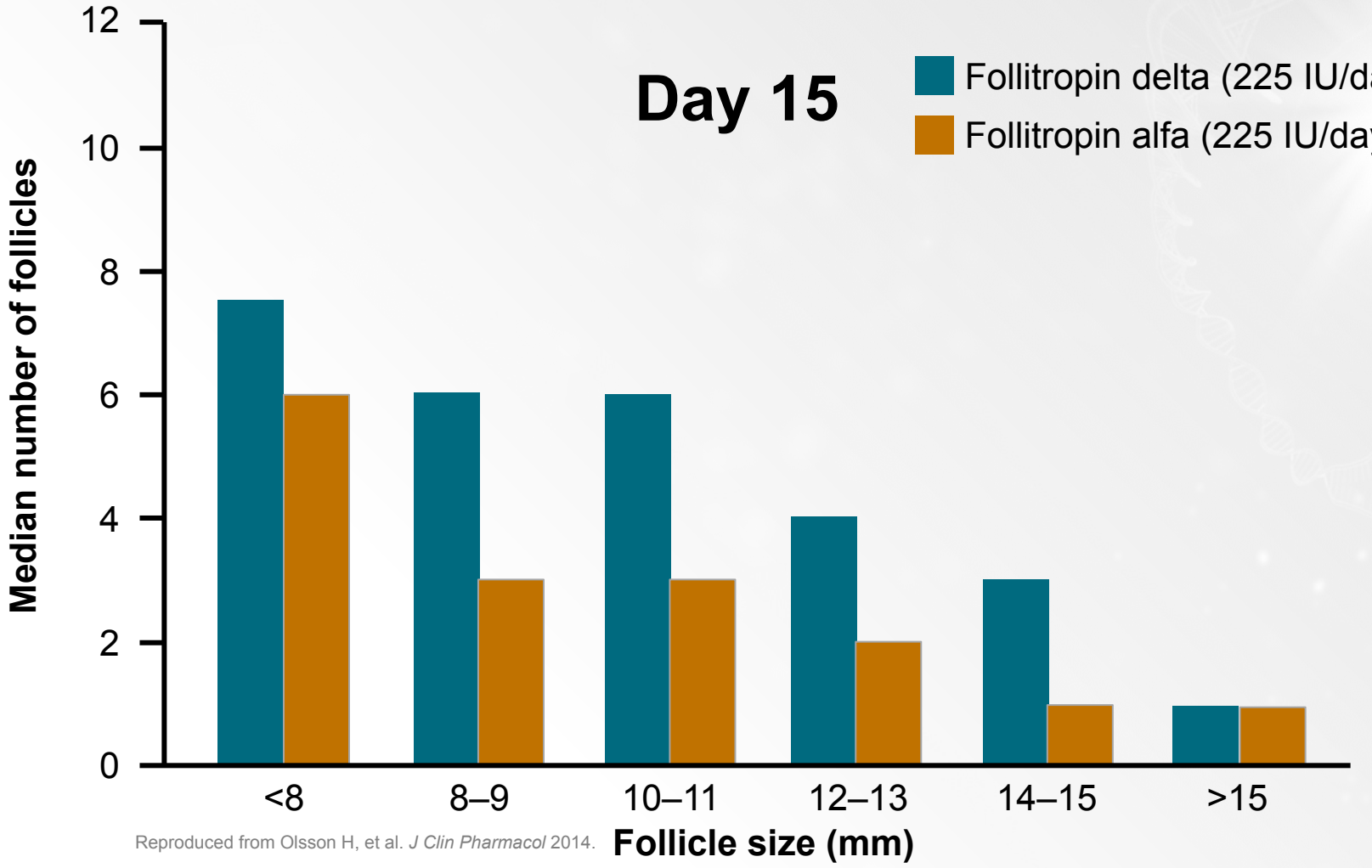


Reproduced from Olsson H, et al. *J Clin Pharmacol* 2014.

There was a significantly higher number of follicles with follitropin delta compared with follitropin alfa (32 vs 20, $p<0.05$)

Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

Phase 1: Divergent pharmacodynamic responses after human administration

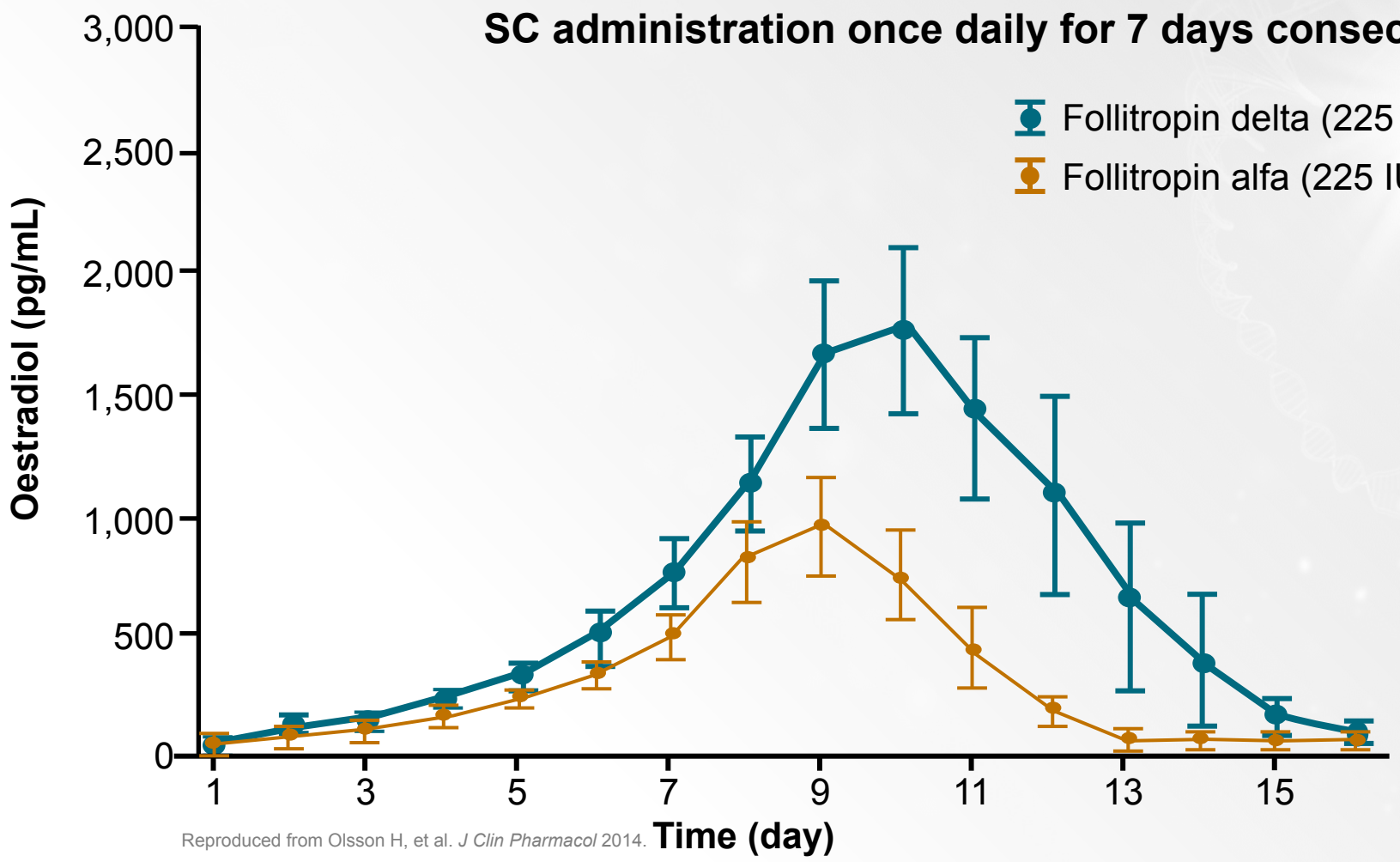


Reproduced from Olsson H, et al. *J Clin Pharmacol* 2014.

There was a significantly higher number of follicles with follitropin delta compared with follitropin alfa (33 vs 19, $p<0.05$)

Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

Phase 1: Divergent pharmacodynamic responses after human administration



Reproduced from Olsson H, et al. *J Clin Pharmacol* 2014.

AUC and C_{max} for oestradiol were significantly higher (p=0.017 and p=0.023, respectively) for follitropin delta compared with follitropin alfa

**Concentrations on Days 1–7 are pre-dose values.*
Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307.

What next……?

A conversion factor would establish dosage parity… but not highlight the differential potency of Rekovelle

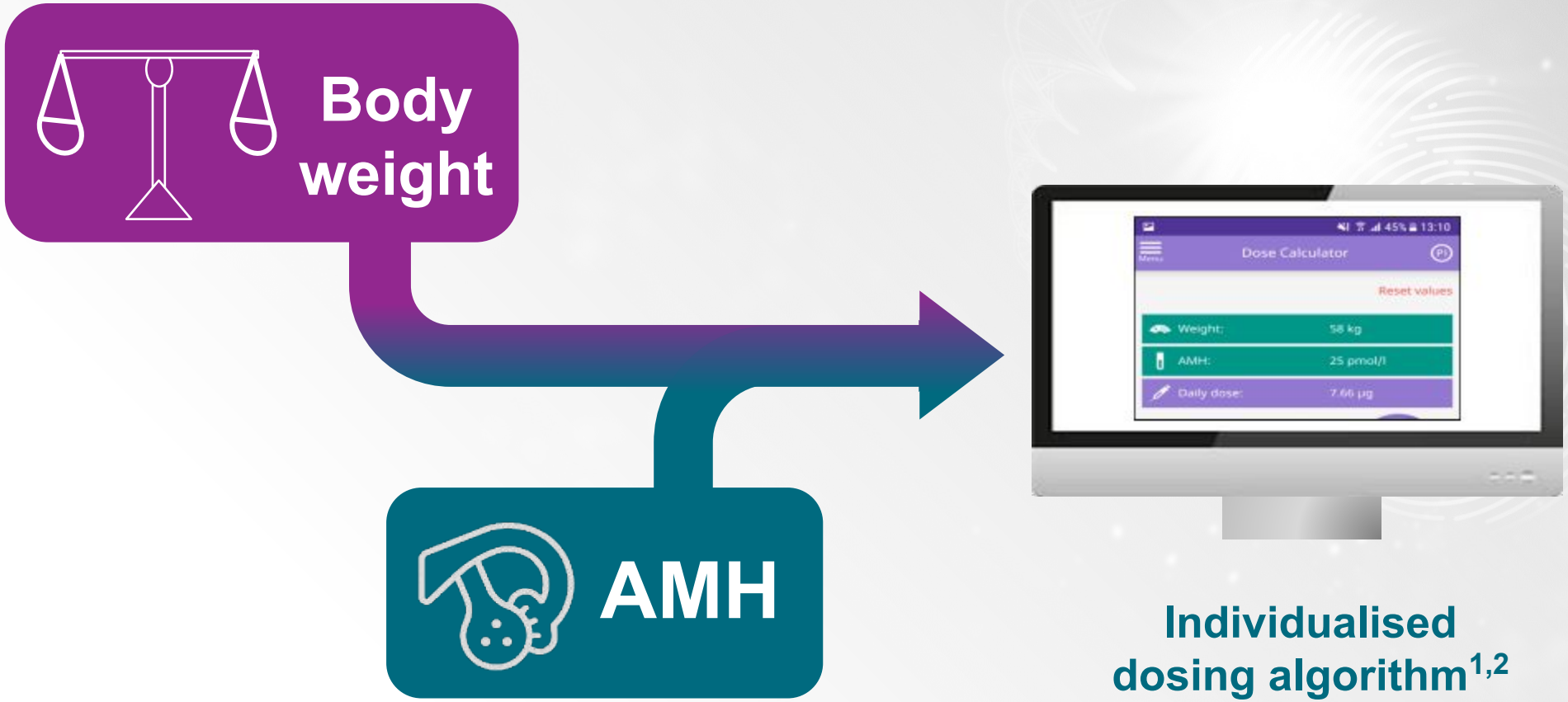
ART protocols are based on conventions and experience that require frequent monitoring and often lead to unexpected responses

Could mcg dosing be aligned more closely with contemporary treatment paradigms?

An approach based on stratified medicine using biomarkers was employed after extensive input from practicing physicians

What is the dosing algorithm and what is the benefit of using the algorithm to guide dosing decisions?

Individualised dosing algorithm



Individualised dosing algorithm[1,2]

AMH, anti-Müllerian hormone.

1. Rose TH, et al. Drugs R D 2016;16:173–180; 2. Arce JC, et al. In Anti-Müllerian Hormone (Nova Science Publishers, 2016):83–102.

Follitropin delta – individualised dosing

AMH value is rounded to the nearest integer[1]

Follitropin delta dosing:[1-3]

All patients with **AMH <15 pmol/L** are given the same daily dose of 12 mcg

For patients with **AMH ≥15 pmol/L**, dose is adjusted based on AMH and body weight, with a maximum daily dose of 12 mcg

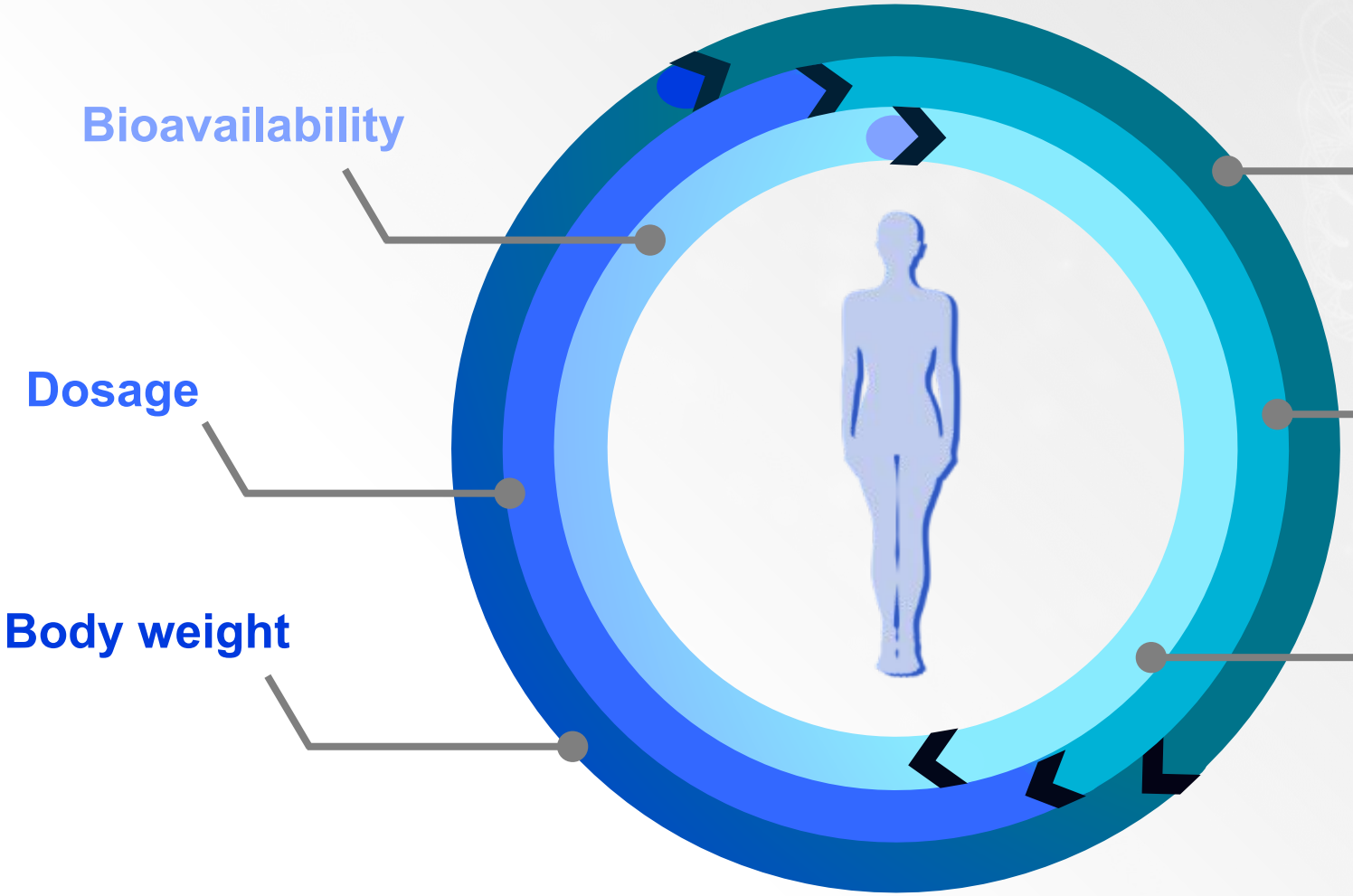
AMH (pmol/L)	Fixed daily dose[2]
<15	12 mcg
15–16	0.19 mcg/kg
17	0.18 mcg/kg
18	0.17 mcg/kg
19–20	0.16 mcg/kg
21–22	0.15 mcg/kg
23–24	0.14 mcg/kg
25–27	0.13 mcg/kg
28–32	0.12 mcg/kg
33–39	0.11 mcg/kg
≥40	0.10 mcg/kg

Reproduced from Nyboe Andersen A, et al. *Fertil Steril* 2017.

Please refer to the REKOVELLE Summary of Product Characteristics for dosing information.[3]

1. Arce JC, et al. In Anti-Müllerian Hormone (Nova Science Publishers, 2016):83–102; 2. Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4; 3. REKOVELLE Summary of Product Characteristics (Europe) 2022.

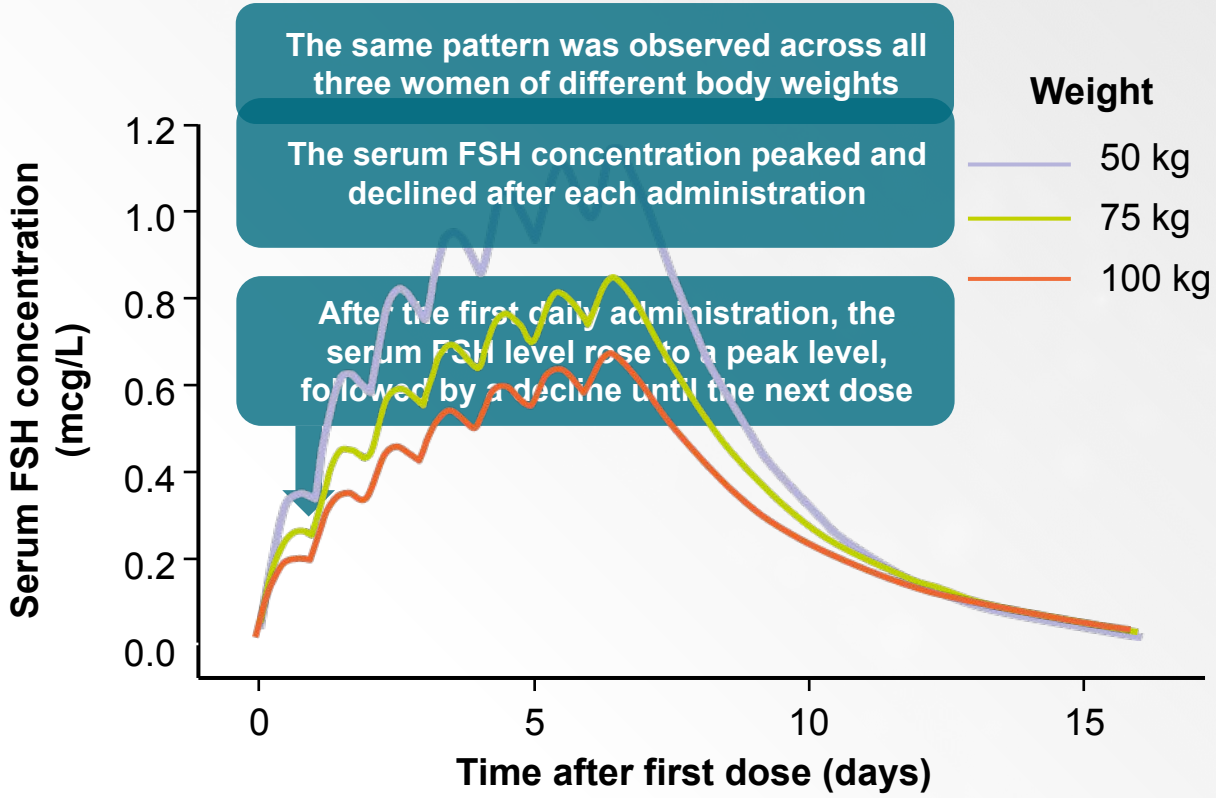
Building a new paradigm for individualised treatment



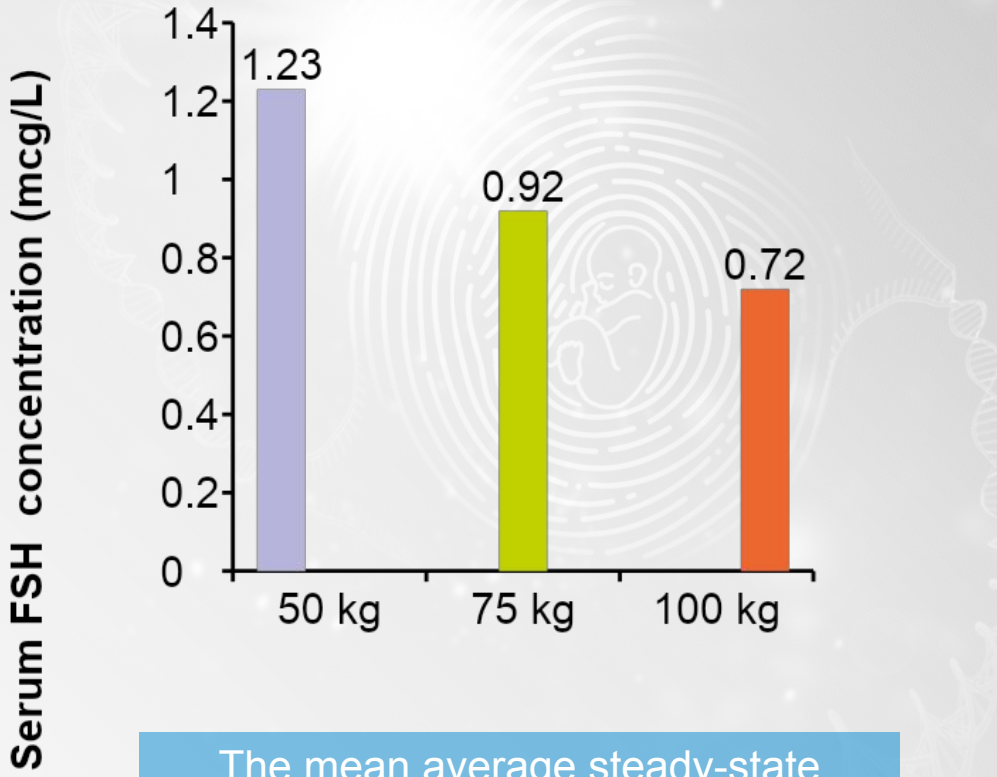
Optimising **dosage** based on **ovarian reserve** in each **individual** patient[1–3]

1. Olsson H, et al. J Clin Pharmacol 2014;54:1299–1307; 2. Rose TH, et al. Drugs R D 2016;16:173–180;
3. Arce JC, et al. In Seifer DB, Tal R eds. Nova Science Publishers, Inc., 2016.

Follitropin delta: Building the algorithm



Simulation of the typical expected FSH concentration after multiple doses of follitropin delta 10 mcg for three subjects with different body weights



The mean average steady-state concentrations based on 1,000 simulations

FSH, follicle-stimulating hormone.

Rose TH, et al. Drugs R D 2016;16:173–180.

AMH is a better predictor of ovarian response than other parameters when used with body weight

A dose–response model indicated that AMH and body weight measurements only are sufficient to predict the ovarian response following follitropin delta treatment[1]

Impact of baseline parameters on the number of oocytes retrieved estimated in a PD model[1]

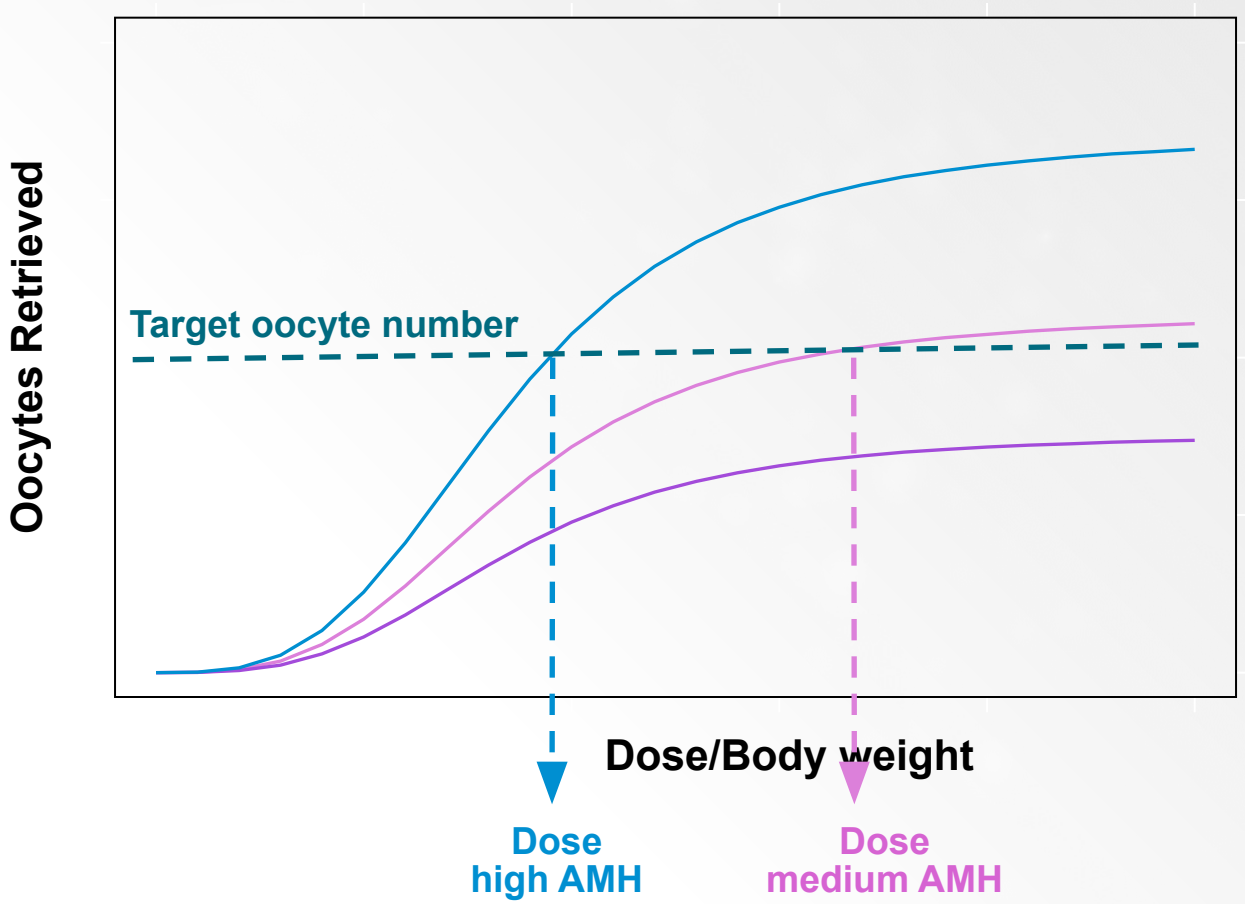
Covariate	Explained variation
Dose by body weight	
+ AMH	35%
+ Basal FSH	23%
+ Inhibin B	17%
+ AFC	26%
+ Age	15%
Dose by body weight + AMH	
+ Basal FSH	38%
+ Inhibin B	35%
+ AFC	38%
+ Age	35%

The model showed that AMH was a better predictor of oocytes retrieved, compared with basal FSH, inhibin B, AFC and age[1]

The model showed that there was no added value of combining AMH and body weight with other parameters[1]

The PD model was a sigmoid Emax model (Emax = expected maximal number of oocytes retrieved), evaluating the contribution of covariates, individually and combined, in explaining the variation in the data. Data are based on Arce et al. 2014.2
AFC, antral follicle count.
1. Arce JC, et al. In Seifer DB, Tal R eds. Nova Science Publishers, Inc., 2016; 2. Arce JC, et al. Fertil Steril 2014;102:1633–1640.e5.

Building the algorithm



Examples of patients with:

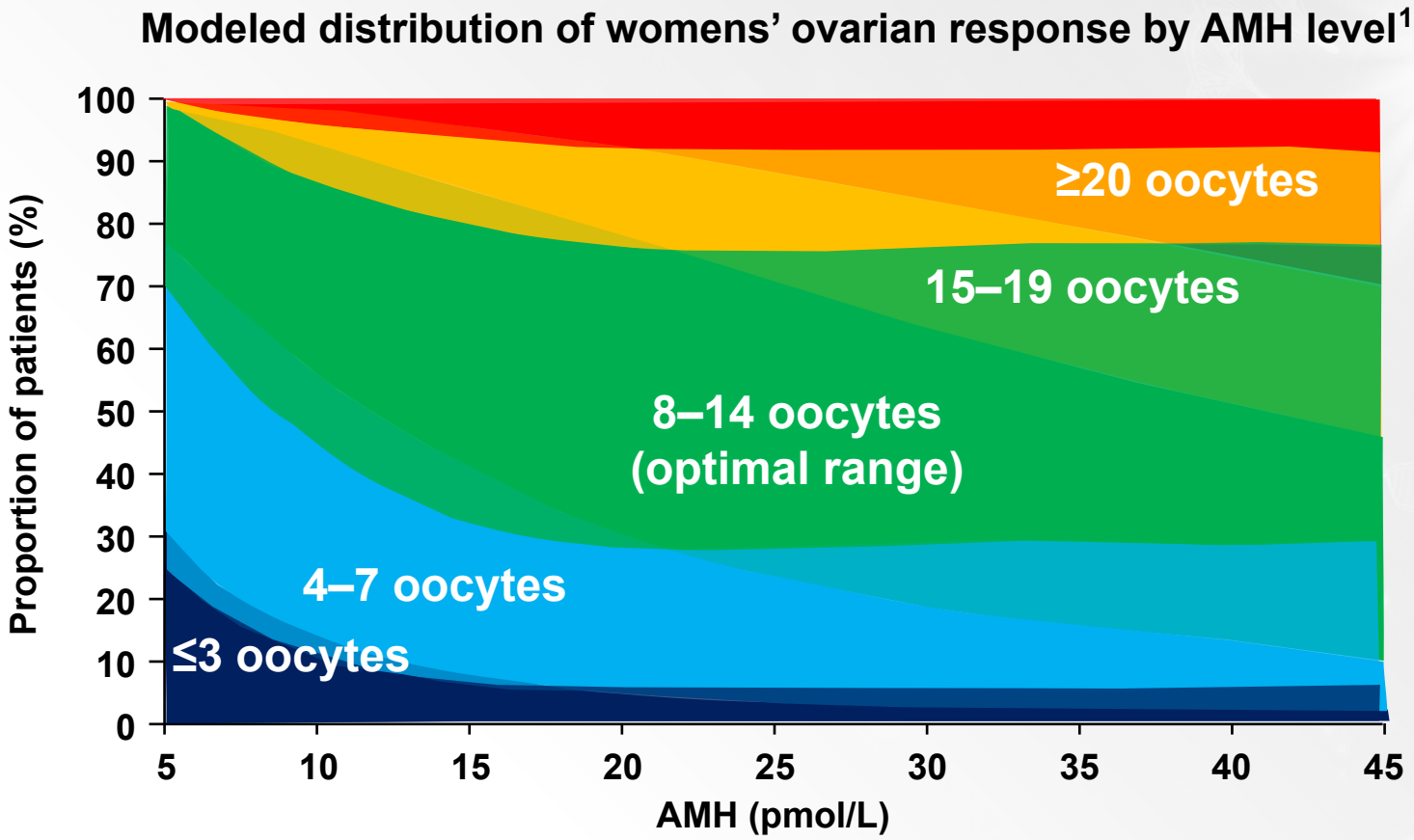
High AMH

Medium AMH

Low AMH

Ferring Pharmaceuticals, data on file.

Follitropin delta dosing regimen is predicted to give a more uniform ovarian response



Individualised dosing regimen (9 mcg)

Arce JC, et al. In Seifer DB, Tal R eds. Nova Science Publishers, Inc., 2016.

Clinical validation: ESTHER-1

Phase 3 ESTHER-1 study: Nyboe Anderson & Nelson et al

Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial

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Objective: To compare the efficacy and safety of follitropin delta, a new human recombinant FSH with individualized dosing based on serum antimüllerian hormone (AMH) and body weight, with conventional follitropin alfa dosing for ovarian stimulation in women undergoing IVF.
Design: Randomized, multicenter, assessor-blinded, noninferiority trial (ESTHER-1).
Setting: Reproductive medicine clinics.
Patient(s): A total of 1,329 women (aged 18–40 years).
Intervention(s): Follitropin delta (AMH < 15 pmol/L: 12 μg/d; AMH ≥ 15 pmol/L: 0.10–0.19 μg/kg/d; maximum 12 μg/d), or follitropin alfa (150 IU/d for 5 days, potential subsequent dose adjustment; maximum 450 IU/d).
Main Outcome Measure(s): Ongoing pregnancy and ongoing implantation rates; noninferiority margins −8.0%.
Result(s): Ongoing pregnancy (30.7% vs. 31.6%; difference −0.9% [95% confidence interval (CI) −5.9% to 4.1%]), ongoing implantation (35.2% vs. 35.8%; −0.6% [95% CI −6.1% to 4.8%]), and live birth (29.8% vs. 30.7%; −0.9% [95% CI −5.8% to 4.0%]) rates were similar for individualized follitropin delta and conventional follitropin alfa. Individualized follitropin delta resulted in more women with target response (8–14 oocytes) (43.3% vs. 38.4%), fewer poor responses (fewer than four oocytes in patients with AMH < 15 pmol/L) (11.8% vs. 17.9%), fewer excessive responses (≥ 15 or ≥ 20 oocytes in patients with AMH ≥ 15 pmol/L) (27.9% vs. 35.1% and 10.1% vs. 15.6%, respectively), and fewer measures taken to prevent ovarian hyperstimulation syndrome (2.3% vs. 4.5%), despite similar oocyte yield (10.0 ± 5.6 vs. 10.4 ± 6.5) and similar blastocyst numbers (3.1 ± 2.8 vs. 3.5 ± 3.2), and less gonadotropin use (30.0 ± 25.1 vs. 103.7 ± 73.6 μg).
Conclusion(s): Optimizing ovarian response in IVF by individualized dosing according to pretreatment patient characteristics results in similar efficacy and improved safety compared with conventional ovarian stimulation.

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Supported by Ferring Pharmaceuticals. The study was designed by the sponsor in collaboration with the academic investigators. Data collection and study sites were monitored by an independent clinical research organization. The data were collected by the sponsor and analyzed as per the prespecified statistical analysis plan and validated by an independent statistician.
Presented in part at the 32nd Annual Meeting of the European Society of Human Reproduction and Embryology, July 3–6, 2016, Helsinki, Finland.
A.N.A. and S.M.N. should be considered similar in author order.
Reprint requests: Joan-Carles Arce, M.D., Ph.D., Ferring Pharmaceuticals A/S, Reproductive Health, Global Clinical & Non-Clinical R&D, Kay Fiskers Plads 11, Copenhagen DK-2300, Denmark (E-mail: jca@ferring.com).

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ESTHER-1: Study locations

ESTHER: n=1,329
Belgium
Brazil
Canada
Czechia
Denmark
France
Italy
Poland
Russia
Spain
UK

Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

ESTHER-1: Trial design[1,2]

ESTHER-1: Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World
Randomised, controlled, assessor-blind, multicentre, non-inferiority trial of individualised follitropin delta versus conventional follitropin alfa dosing

37 sites (11 countries): Belgium, Brazil, Canada, Czechia, Denmark, France, Italy, Poland, Russia, Spain and the UK[1]

Age: 18–40 years; first IVF/ICSI cycle; regular cycles

1:1 stratified randomisation by age: <35, 35–37, 38–40 years
Investigators, embryologists and central lab personnel blinded

Individualised follitropin delta

Fixed daily SC dose:
AMH <15 pmol/L: 12 mcg
AMH ≥15 pmol/L: 0.10–0.19 mcg/kg
Maximum daily dose: 12 mcg

Blinded investigators made decisions to alter the daily dose based on response. These decisions were, however, per protocol, these instructions were implemented for subjects in the follitropin alfa arm and ignored for subjects in the follitropin delta arm by an unblinded nurse

Concentional follitropin alfa

Fixed daily dose of 150 IU/day (11 mcg) for 5 days, after which it could be adjusted up to a maximum of 450 IU/day

GnRH antagonist: Day 6
Trigger:* rhCG/GnRH agonist and freeze all/cancel[†]

Oocyte retrieval; IVF/ICSI;
SET: D5 blastocyst for all <37 years, or if quality >3BB for those ≥38 years (2 blastocysts if quality <3BB);
freeze untransferred; Endometrin® 100 mg TID until pregnancy test, ongoing pregnancy rate at 10–11 weeks

*BMI: 17.5–32 kg/m^2; *≥3 follicles ≥17 mm; [†]with <25 follicles ≥12 mm: rhCG; with 25–35 follicles ≥12 mm: GnRH agonist and freeze all/cancel; >35 follicles ≥12 mm: cancel.*
rhCG, recombinant human chorionic gonadotrophin; SET, single embryo transfer; TID, three times a day.
1. Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4; 2. Bosch E, et al. Reprod Biomed Online 2019;38:195–205.

ESTHER-1: Select inclusion and exclusion criteria

Select inclusion criteria

- Age 18−40 years
- BMI 17.5−32.0 kg/m^2
- First cycle
- Regular menstrual cycles of 24−35 days
- Diagnosis of tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility

Select exclusion criteria

- Endometriosis stage III−IV
- History of recurrent miscarriage
- Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation

Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

ESTHER-1: Select endpoints

Co-primary endpoints

- Ongoing pregnancy rate (at least one intrauterine foetus 10–11 weeks after transfer)
- Ongoing implantation rate (the number of intrauterine foetuses 10–11 weeks after transfer divided by blastocysts transferred)

Key secondary endpoints

- Pregnancy outcomes
  - Live birth rates
- Targeted ovarian response (8–14 oocytes)
- Extreme ovarian response (<4, ≥15 or ≥20 oocytes)
- Embryology
- Safety and adverse events

Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

ESTHER-1: Dosing

1,326 subjects

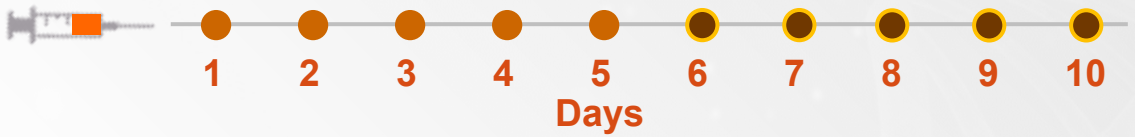
n=665
Follitropin delta – individualised dosing regimen based on AMH and body weight

FIXED DOSE (no dose adjustments allowed)

n=661
Follitropin alfa – conventional dosing regimen

STARTING DOSE
of 150 IU (11 mcg) filled-by-mass for the first 5 stimulation days

DOSE ADJUSTMENTS
based on individual responses with 450 IU as the maximum daily dose



Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

ESTHER-1: Baseline characteristics

	Individualised follitropin delta (n=665)	Conventional follitropin alfa (n=661)
Age (years)	33.4 ± 3.9	33.2 ± 3.9
<35 years	59%	59%
35–37 years	24%	25%
38–40 years	17%	15%
Body weight (kg)	64.7 ± 10.7	63.4 ± 10.4
BMI (kg/m^2)	23.7 ± 3.4	23.3 ± 3.3
FSH (IU/L)	7.5 (6.2–9.2)	7.7 (6.5–9.4)
AMH (pmol/L)	16.3 (9.0–24.8)	16.0 (9.1–25.5)
AFC	14.7 ± 6.9	14.4 ± 6.8

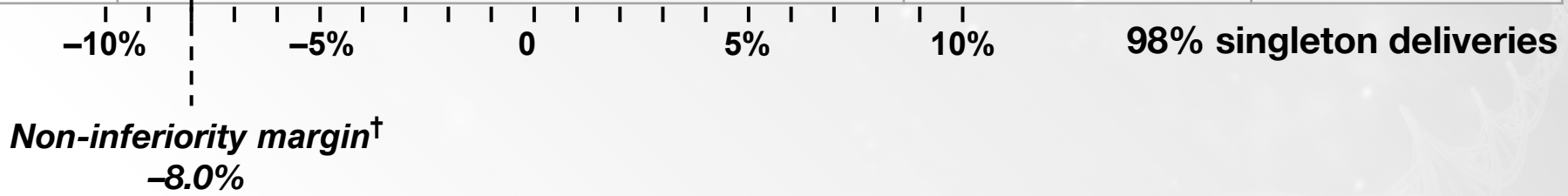
Reproduced from Nyboe Andersen A, et al. *Fertil Steril* 2017.

Data are mean ± SD, median (interquartile range) or percentage.
SD, standard deviation.
Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

Follitropin delta in RCT: ESTHER-1 registration trial

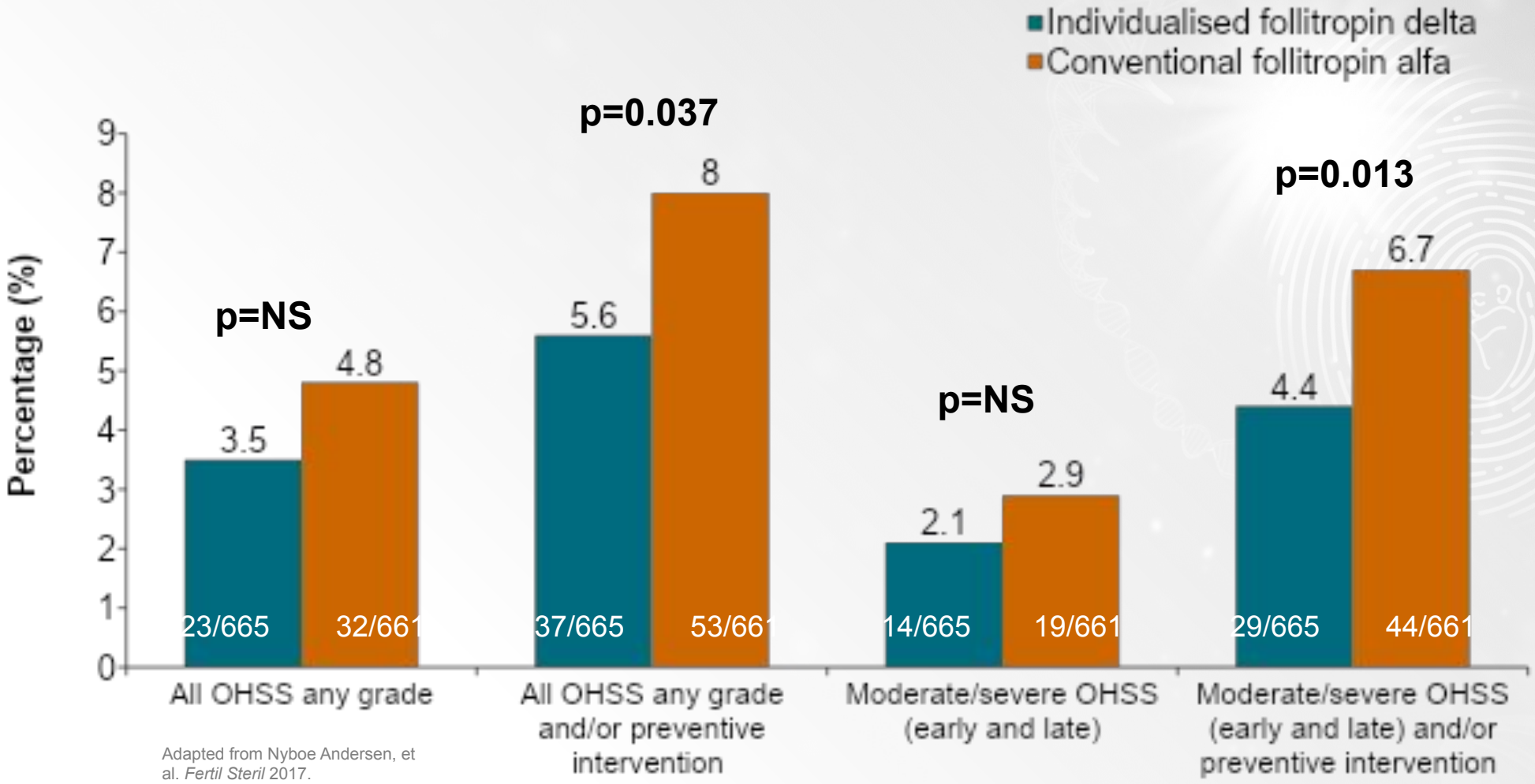
	Difference (95% CI)	Observed rates	
		Individualised follitropin delta (n=665)	Conventional follitropin alfa (n=661)
Ongoing pregnancy*	–0.9 [–5.9 to 4.1]	30.7%	31.6%
Ongoing implantation*	–0.6 [–6.1 to 4.8]	35.2%	35.8%
Live birth	–0.9 [–5.8 to 4.0]	29.8%	30.7%
Live neonates at 4 weeks	–0.6 [–5.5 to 4.3]	29.8%	30.4%

Adapted from Nyboe Andersen, et al. *Fertil Steril* 2017.



**Co-primary endpoints.*
†The noninferiority limit for the risk difference between the two treatments was prespecified at –8.0% for both co-primary endpoints. For each binary endpoint, a two-sided 95% confidence interval was established using the Mantel-Haenszel method to combine results across age-strata.
Live birth outcomes were secondary outcomes. This study was neither designed nor powered to assess results based on secondary outcomes and no final conclusions can be derived from those results.
CI, confidence interval; RCT, randomised controlled trial.
Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

ESTHER-1: OHSS



Adapted from Nyboe Andersen, et al. *Fertil Steril* 2017.

Safety was a secondary outcome. This study was neither designed nor powered to assess results based on secondary outcomes and no final conclusions can be derived from those results.
NS, non-significant; OHSS, ovarian hyper-stimulation syndrome.
Nyboe Andersen A and Nelson S, et al. Fertil Steril 2017;107:387–396.e4.

Thank You