

# How clinical practices in ovarian stimulation is developing; Future of IVF treatment



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# Why do we need new developments in ovarian stimulation

To provide the most optimal treatment

1. Efficient

High pregnancy rates

2. Safe

Low risk for OHSS

3. Patient friendly

Shorter stimulation  
Fewer injections

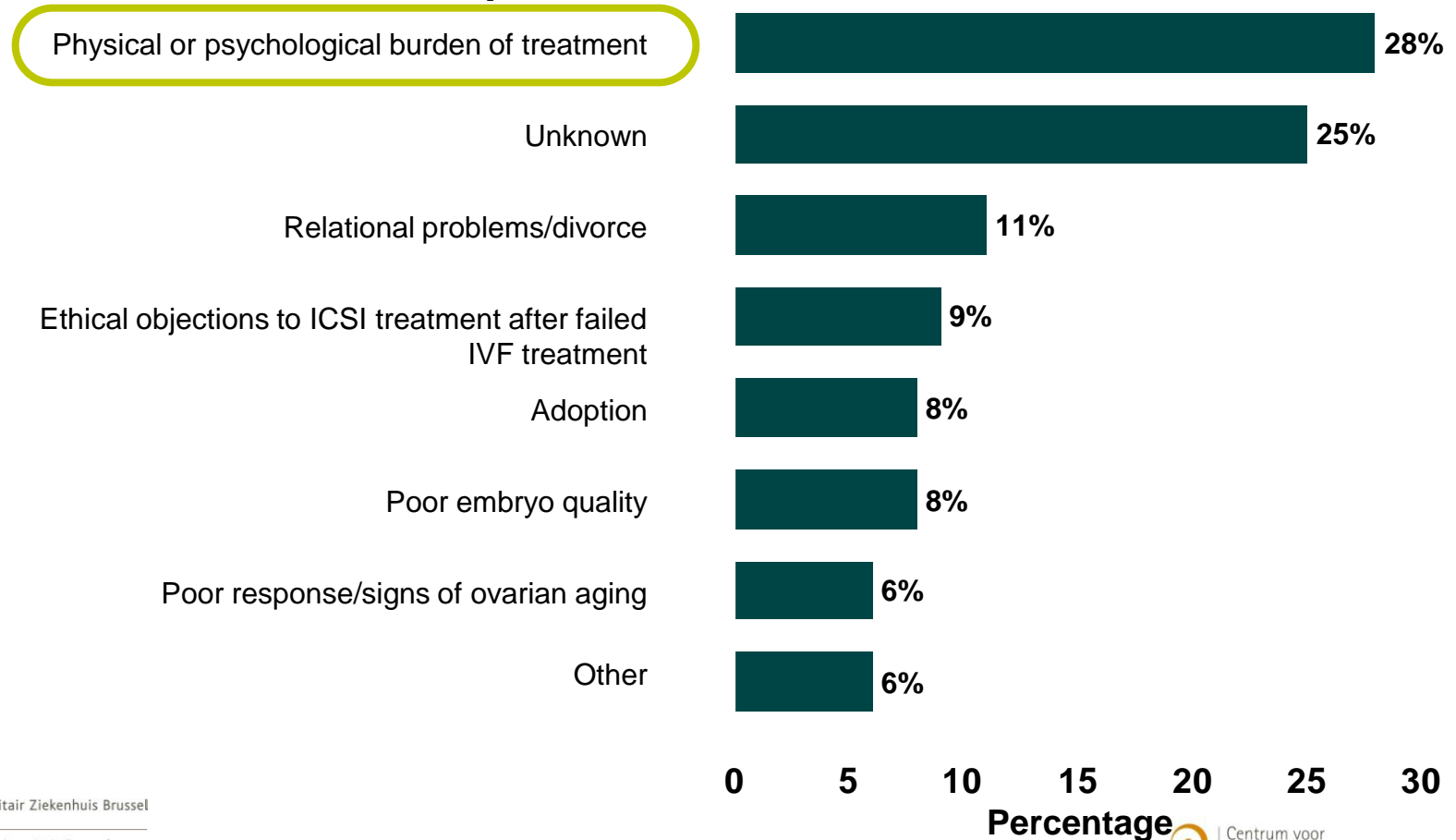
# Why do we need to also focus on patient friendliness?

To avoid patients dropping out of treatment

# Physical or Psychological Treatment Burden Is a Primary Reason for Dropout

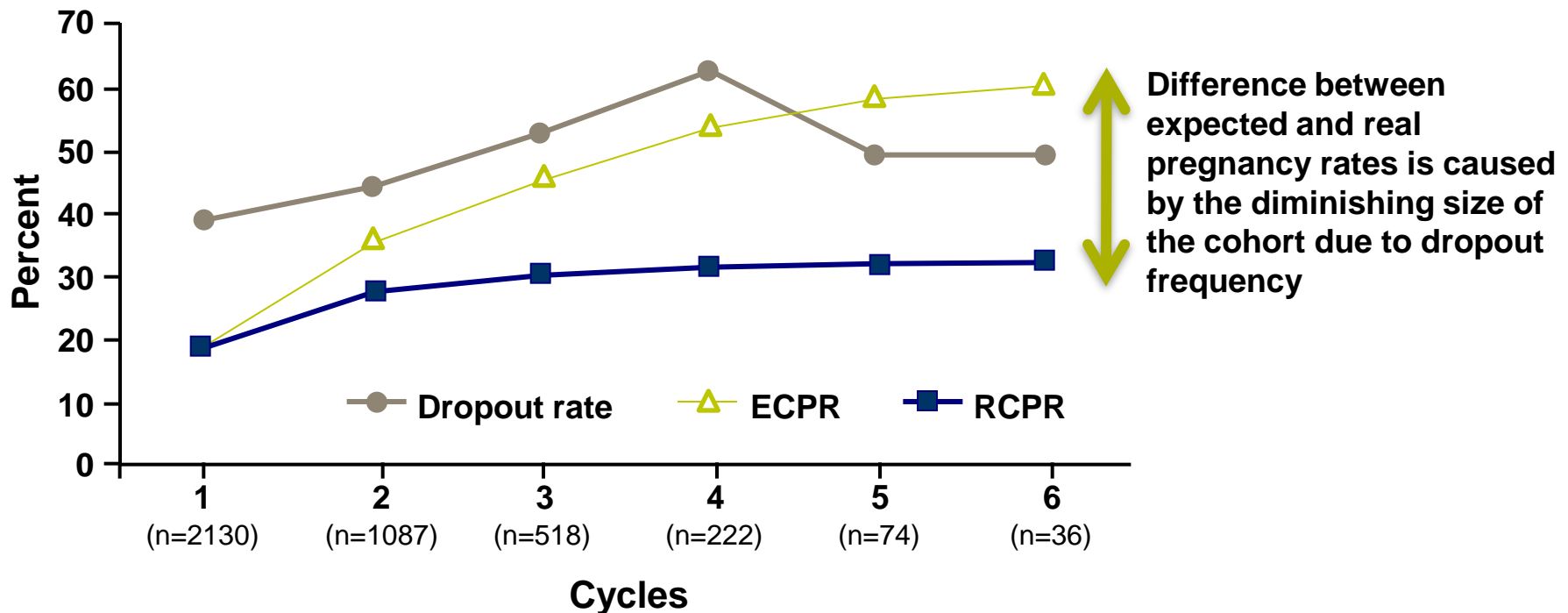
Among 384 couples undergoing IVF treatment, 65 (17%) dropped out

## Reason for Dropout



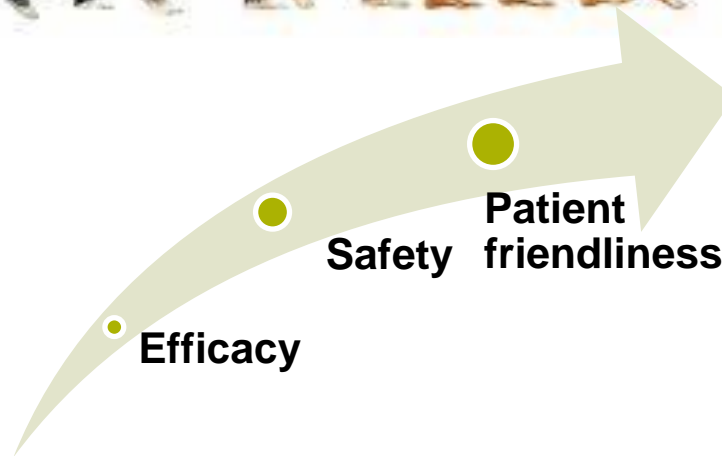
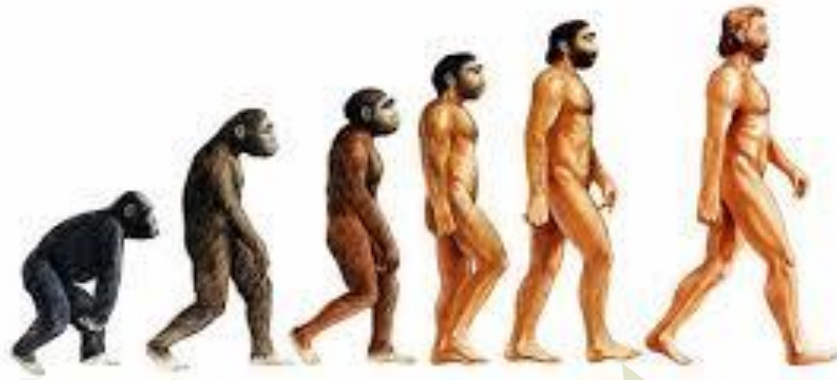
# Dropouts Negatively Impact Real Cumulative Pregnancy Rates

## Data from 4102 IVF cycles in 2130 women



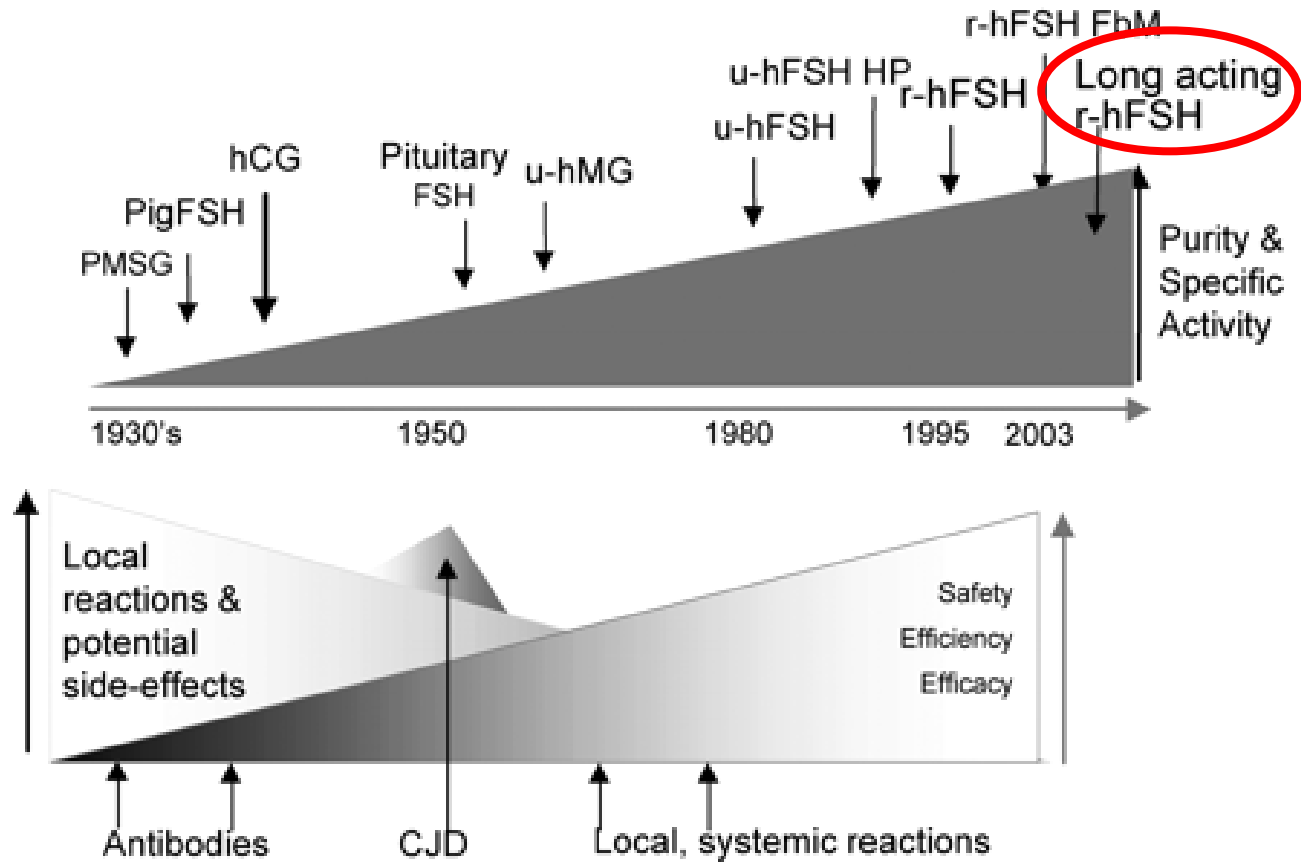
ECPR = expected cumulative pregnancy rate; RCPR = real cumulative pregnancy rate.  
Schroder et al. *RBM Online*. 2004;8:600.

# The evolution in ovarian stimulation



# The evolution in gonadotropins

## THE CONTINUING QUEST FOR QUALITY & CONSISTENCY



*Lunenfeld: Hum Reprod Update 10:453–467, 2004*

# Corifollitropin alfa: the long-acting FSH

$\alpha$  Subunits

$\beta$  Subunits

Human FSH

92 aa

111 aa

$t_{1/2}$  Puregon = 30 h

hCG

92 aa

145 aa

28aa

Corifollitropin alfa

92 aa

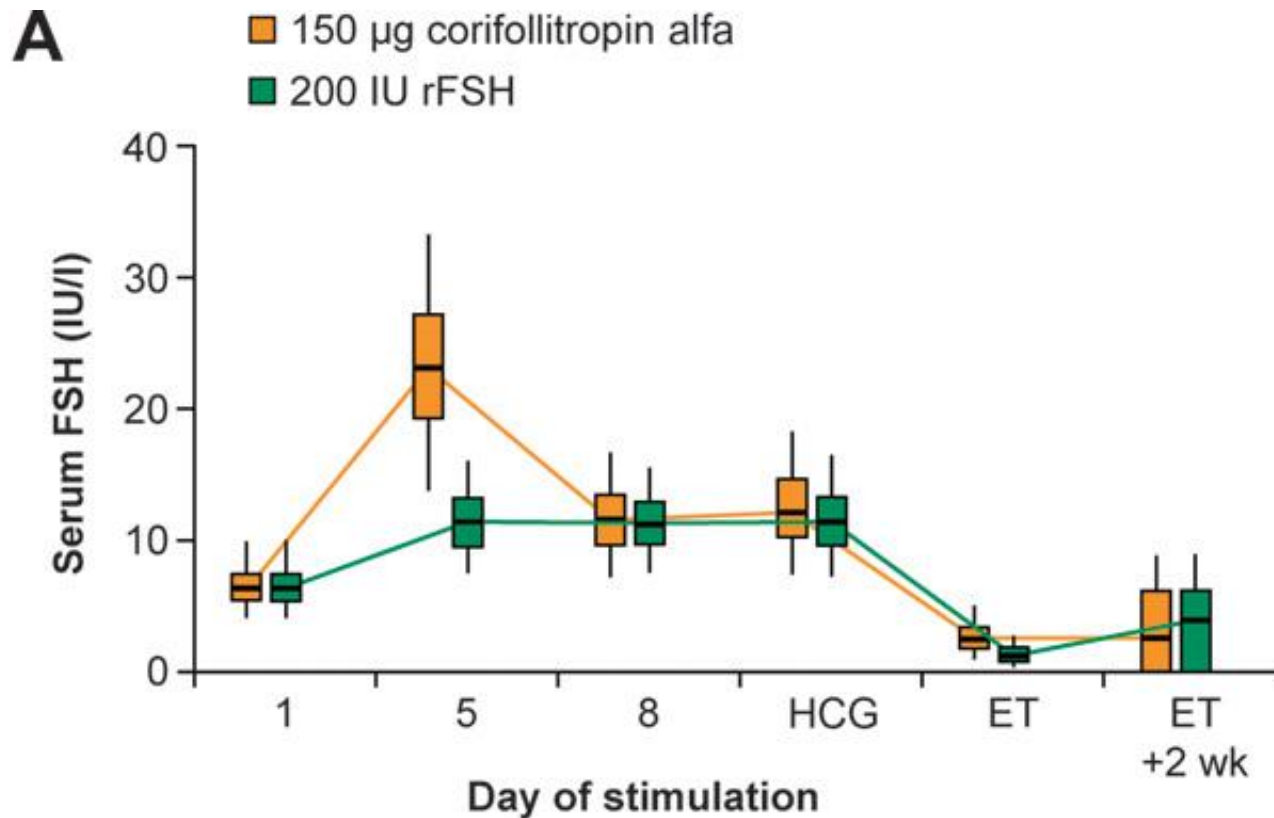
111 aa

$t_{1/2}$  corifollitropin alfa = 69 h

FSH = follicle-stimulating hormone; aa = amino acids;  $t_{1/2}$  = half life.

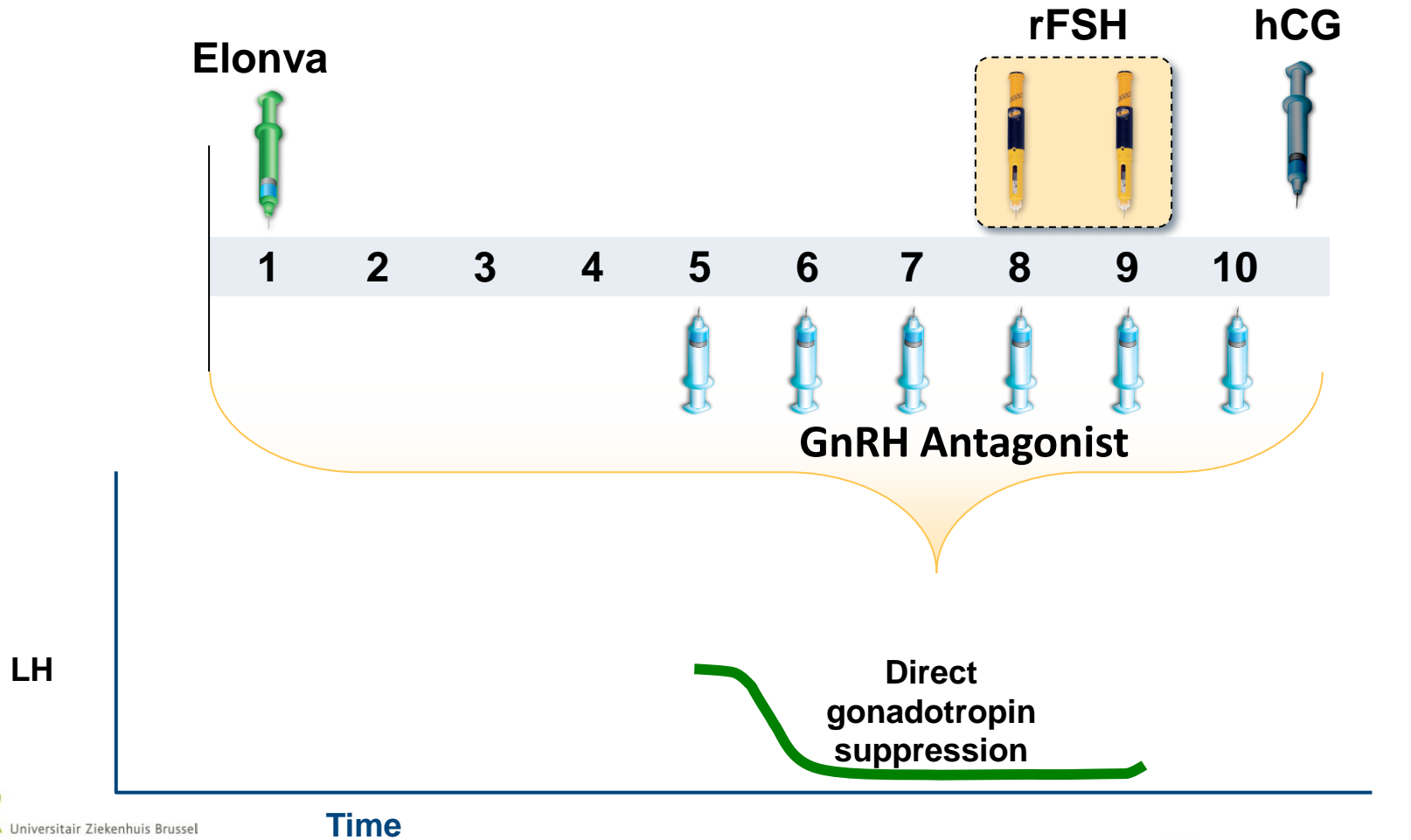


# Unique pharmacokinetic profile



Fauser et al., RBMonline 2010

# Corifollitropin alfa Reduces the Number of Necessary Injections



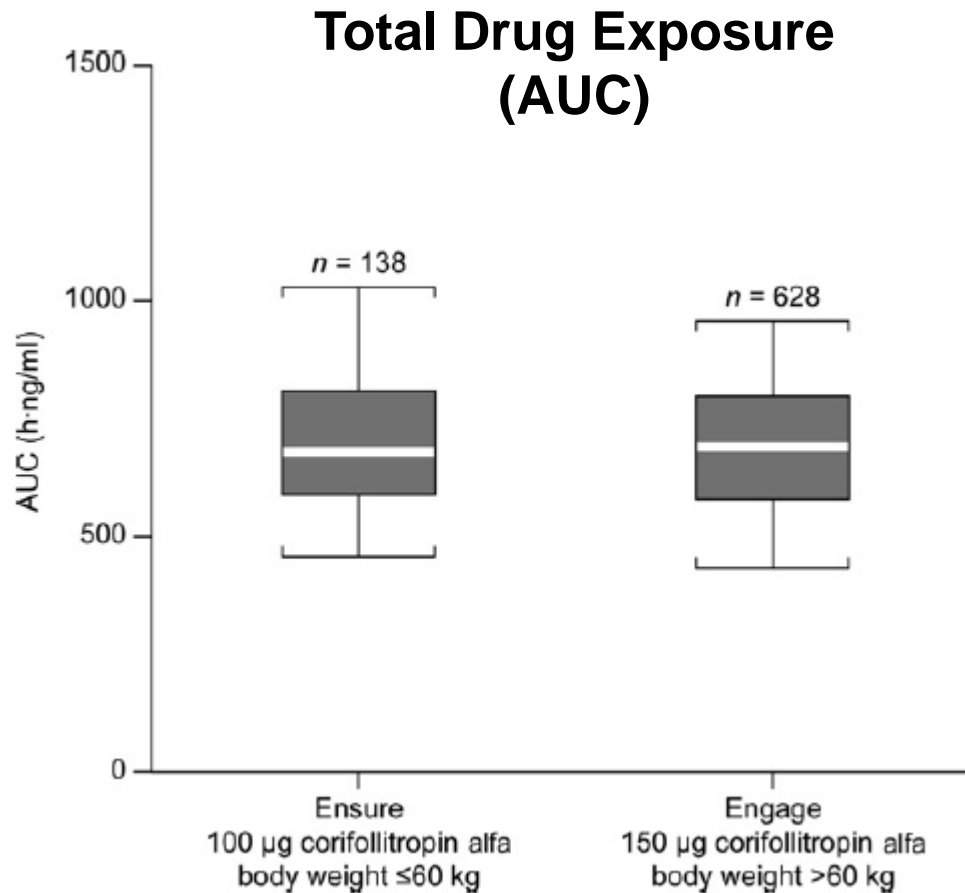
## DOSE OF CORIFOLLITROPIN ALFA

Corifollitropin alfa dose should be selected based on body weight

- $\leq 60$  kg-----100  $\mu\text{g}$  Corifollitropin alfa
- $> 60$  kg-----150  $\mu\text{g}$  Corifollitropin alfa

# Rationale for different doses (1)

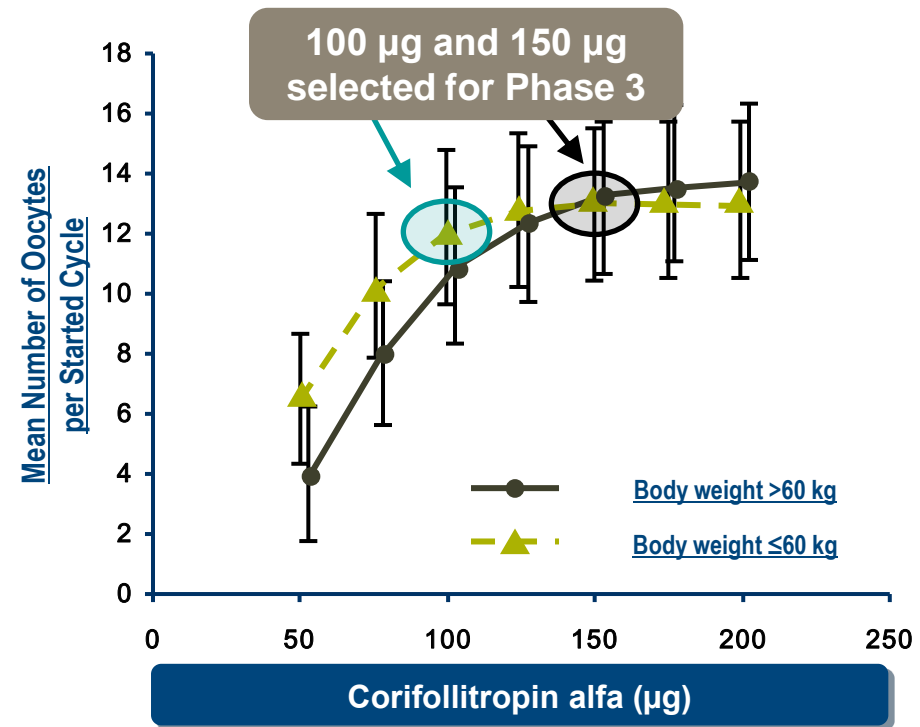
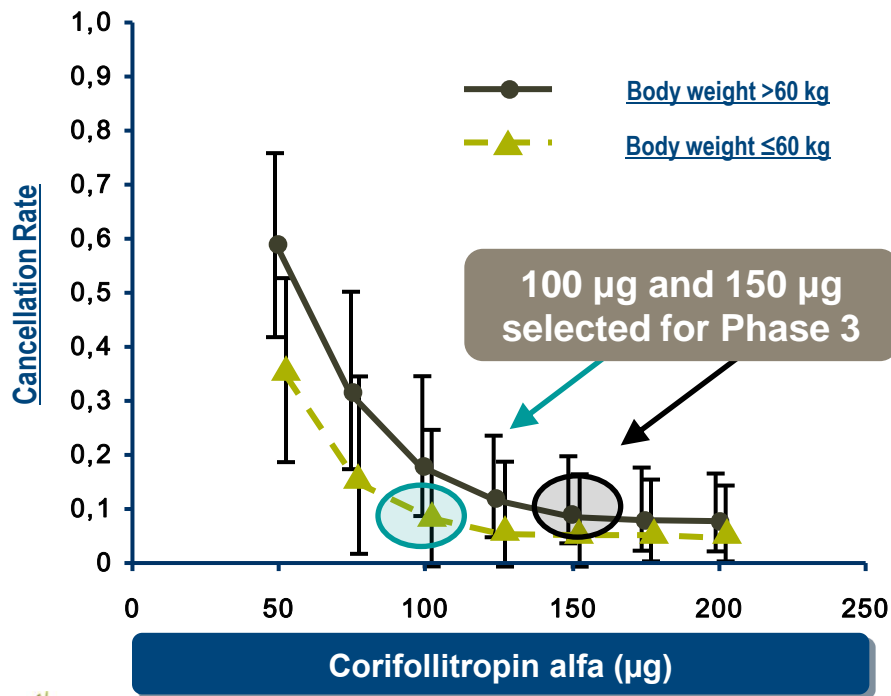
Similar exposure for both body weight groups



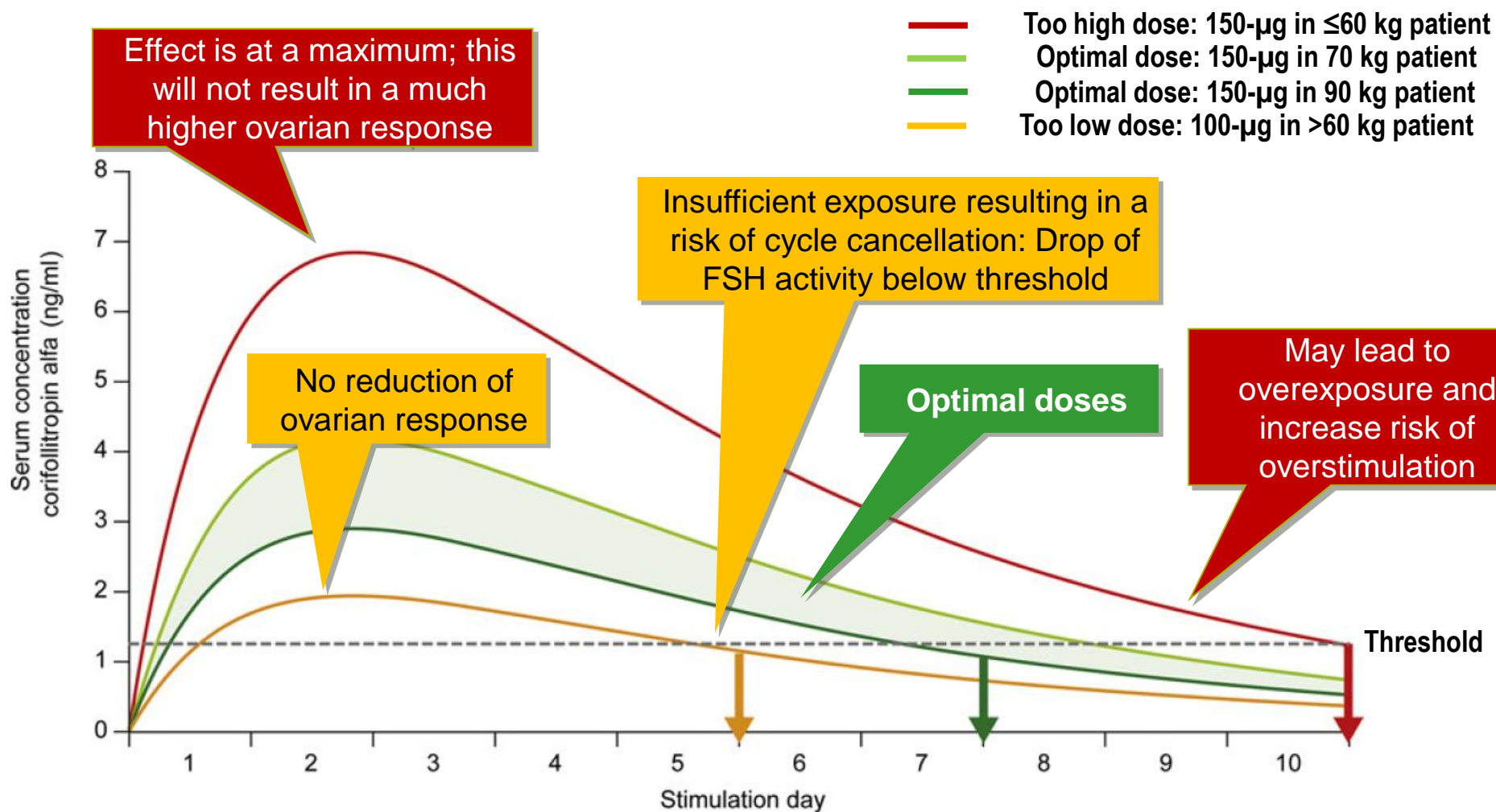
Ledger, et al. *Reprod Biomed Online*. 2011

# Rationale for different doses (2)

The lowest corifollitropin alfa dose for an optimal chance of treatment success is 100  $\mu\text{g}$  for women weighing  $\leq 60$  kg and 150  $\mu\text{g}$  for women weighing  $>60$  kg



# Consequences of Inappropriate Dosing of Corifollitropin Alfa: Risk of Cycle Cancellation or Overstimulation<sup>1</sup>



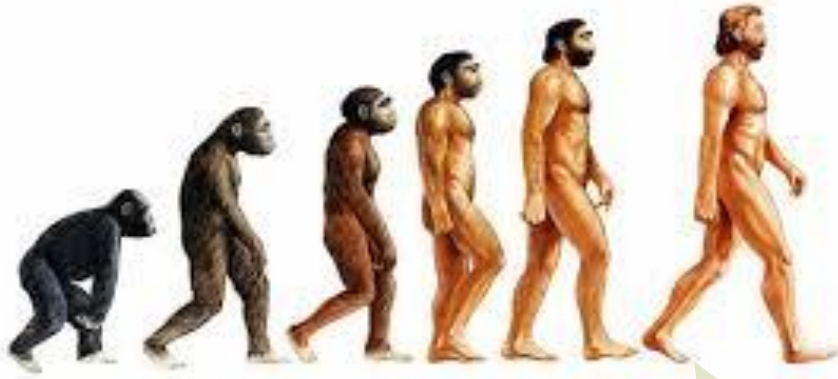
<sup>a</sup>Utilizing the modeling framework described by de Greef R et al. *Clin Pharmacol Ther.* 2010;88:79–87.

FSH = follicle-stimulating hormone

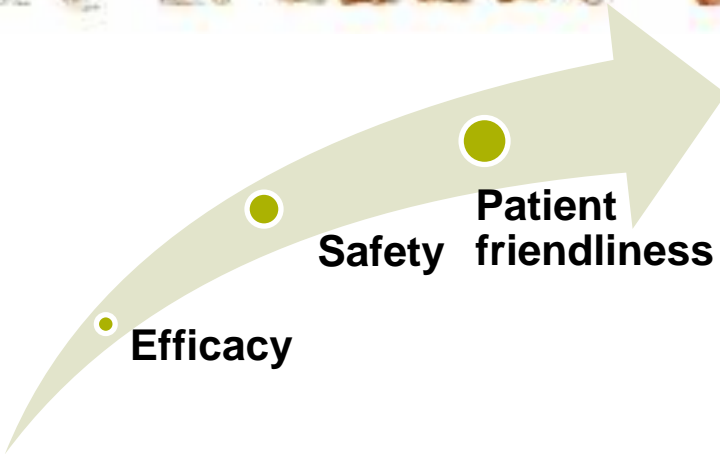
1. Adapted with permission from Ledger WL et al. *Reprod Biomed Online.* 2011;23:150–159.

um voor  
ductieve Geneeskunde

# Corifollitropin alfa. Is it an evolution in ovarian stimulation?



**Efficacy**



# ELONVA

## Phase III Clinical Trials

	ENGAGE <sup>1</sup>	ENSURE <sup>2</sup>	PURSUE <sup>3</sup>
<b>Patients</b>	<ul style="list-style-type: none"> <li>▪ &gt;60 kg</li> <li>▪ 18 to 36 years</li> </ul>	<ul style="list-style-type: none"> <li>▪ ≤60 kg</li> <li>▪ 18 to 36 years</li> </ul>	<ul style="list-style-type: none"> <li>▪ ≥50 kg</li> <li>▪ 35 to 42 years</li> </ul>
<b>Sample Size / Sites</b>	<ul style="list-style-type: none"> <li>▪ 1,509</li> <li>▪ Europe 20, North America 14</li> </ul>	<ul style="list-style-type: none"> <li>▪ 397</li> <li>▪ Europe 14, Asia 5</li> </ul>	<ul style="list-style-type: none"> <li>▪ 1,424</li> <li>▪ United States 33</li> </ul>
<b>Treatment Arms</b>	<ul style="list-style-type: none"> <li>▪ Corifollitropin alfa 150 µg</li> <li>▪ rFSH 200 IU/d</li> </ul>	<ul style="list-style-type: none"> <li>▪ Corifollitropin alfa 100 µg</li> <li>▪ rFSH 150 IU/d</li> </ul>	<ul style="list-style-type: none"> <li>▪ Corifollitropin alfa 150 µg</li> <li>▪ rFSH 300 IU/d</li> </ul>
<b>&gt; 3,000 women randomized</b>			
<b>Design</b>	<ul style="list-style-type: none"> <li>▪ Double-blind RCT</li> <li>▪ 1 cycle</li> </ul>	<ul style="list-style-type: none"> <li>▪ Double-blind RCT</li> <li>▪ 1 cycle</li> </ul>	<ul style="list-style-type: none"> <li>▪ Double-blind RCT</li> <li>▪ 1 cycle</li> </ul>
<b>Primary End Point/Coprimary End Point</b>	<ul style="list-style-type: none"> <li>▪ Ongoing pregnancy rate</li> <li>▪ Number of oocytes</li> </ul>	<ul style="list-style-type: none"> <li>▪ Number of oocytes</li> </ul>	<ul style="list-style-type: none"> <li>▪ Vital pregnancy rate, assessed 5-6 weeks post-ET</li> </ul>



# Phase III RCTs : ALL Similar Regimens

## Investigational group

Corifollitropin alfa  
(150 or 100µg)

Placebo rFSH

Daily rFSH  
(daily dose ≤150 or 200  
or 300 IU)

GnRH antagonist (ganirelix 0.25 mg/d)  
day 5 through day of hCG

IVF  
or  
ICSI

ET  
1-2 good-quality  
embryos  
(day 3-5)  
2 good-quality  
embryos  
(day 3)

Luteal  
phase  
support

## Reference group

Placebo  
Corifollitropin alfa

Daily rFSH  
(daily dose 150, 200 or 300 IU for 7  
days)

Daily rFSH  
(daily dose ≤150 or 200  
or 300 IU)

Stimulation day 1  
=Cycle day 2-3

Stimulation  
day 5

Stimulation  
day 8

hCG as soon as 3  
follicles ≥17 mm  
(or the day thereafter)

# ENGAGE Trial

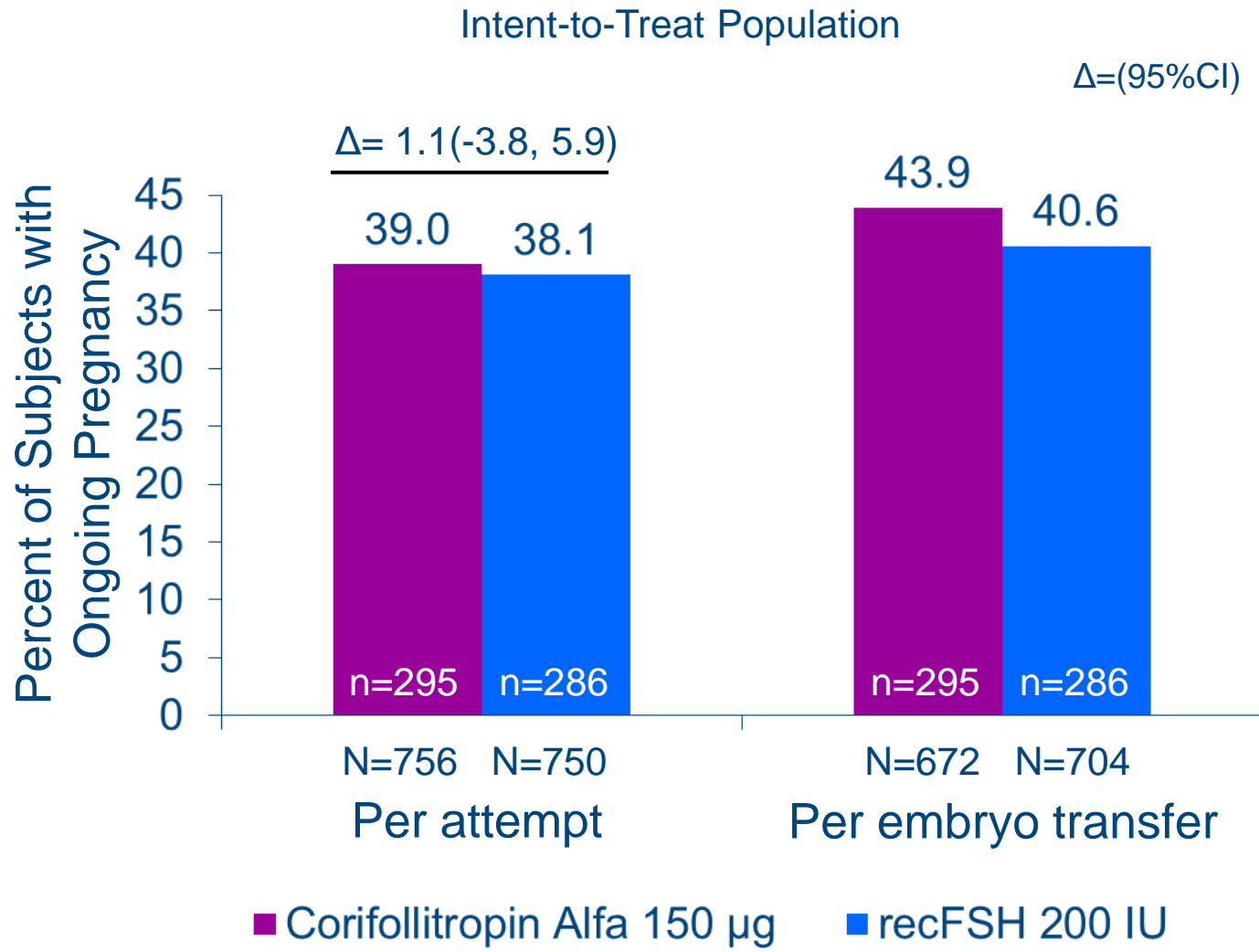
>60 KG

18-36 YEARS OLD

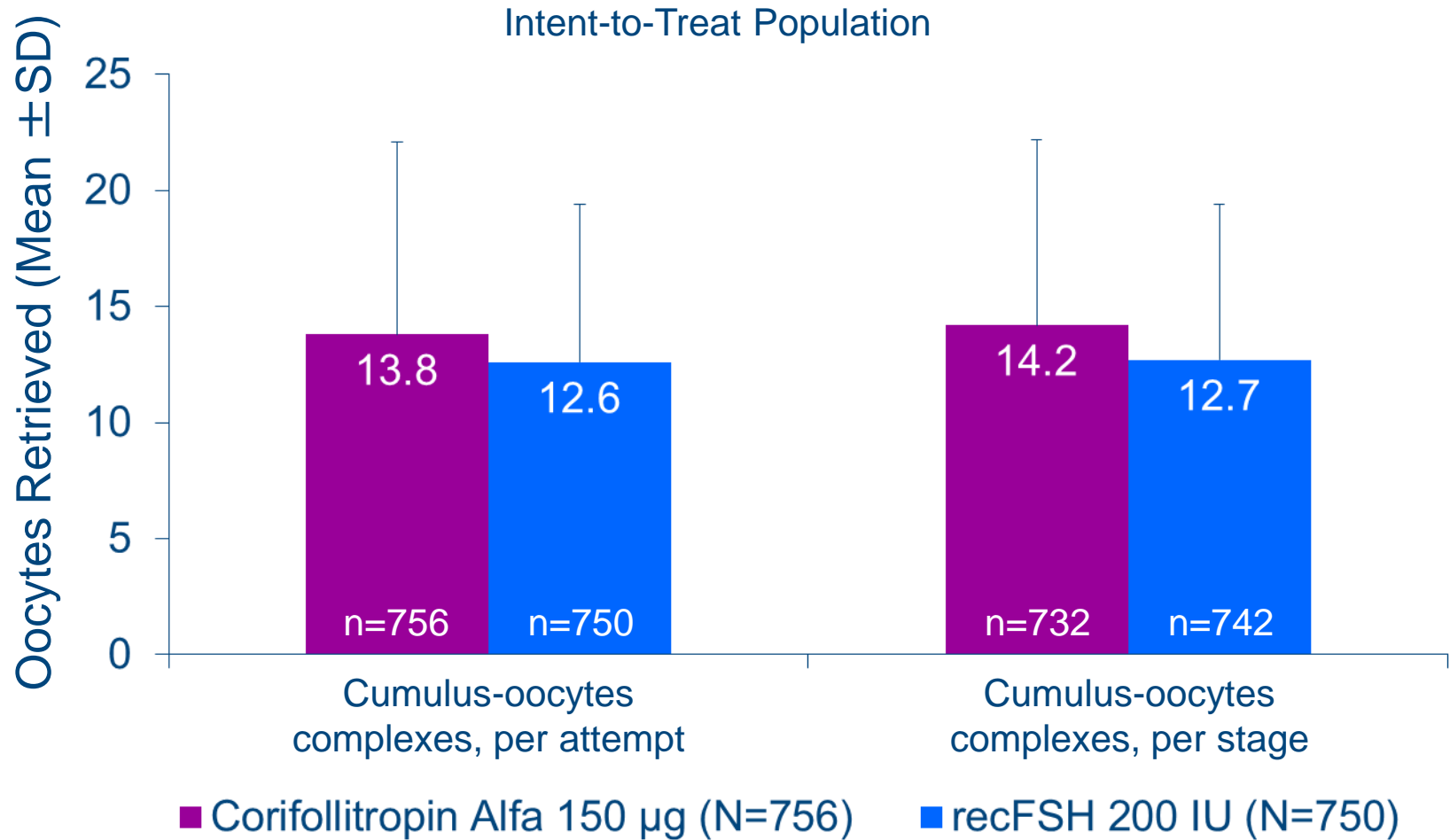
1509 PATIENTS

RCT: CORIFOLLITROPIN ALFA 150 $\mu$ G VS RFSH 200 IU

# Ongoing Pregnancy Rate



# Cumulus-oocyte-complexes



# ENSURE Trial

<60 KG

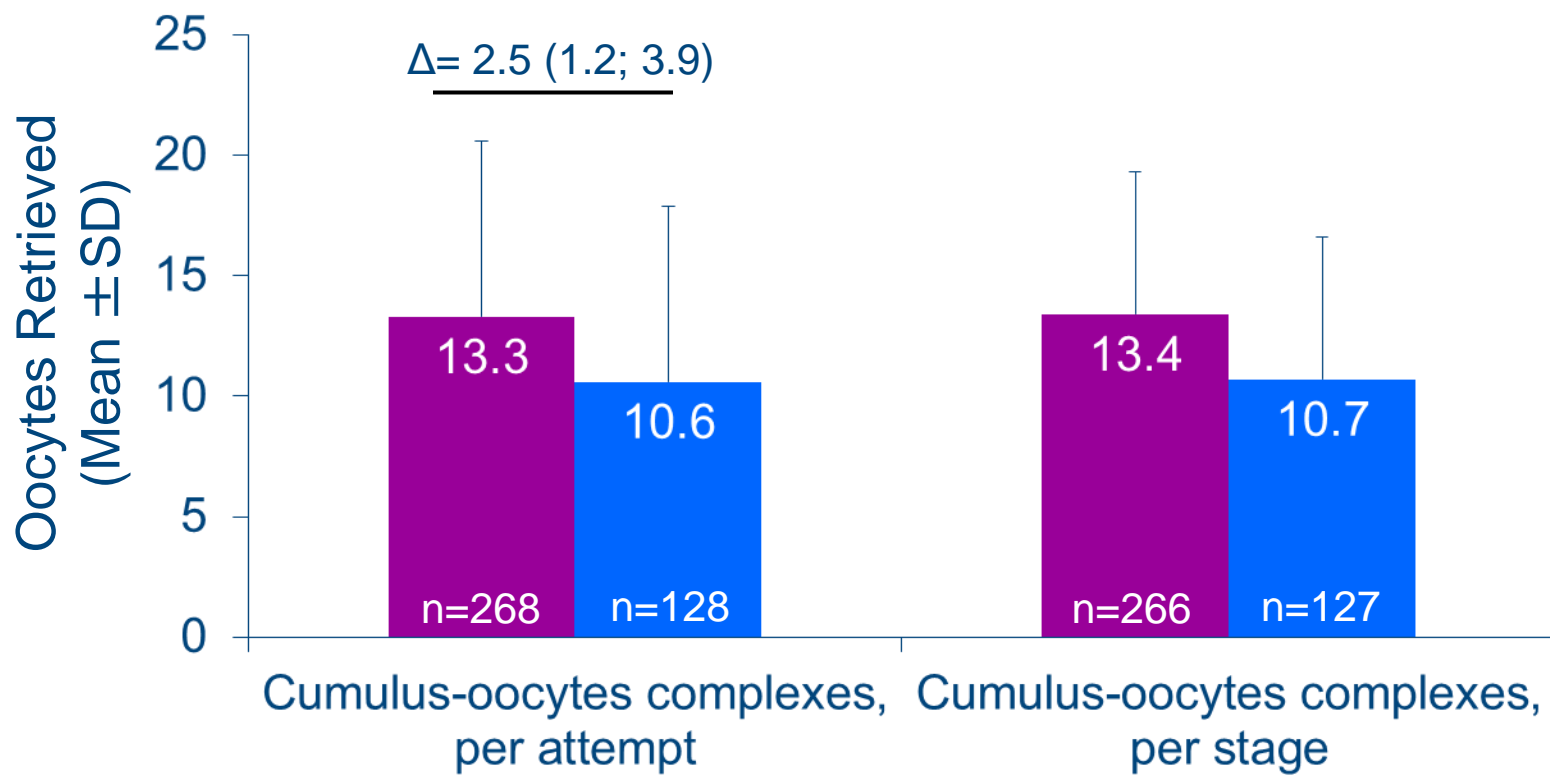
18-36 YEARS OLD

397PATIENTS

RCT: CORIFOLLITROPIN ALFA100 $\mu$ G VS RFSH 150 IU

# Number of Oocytes Retrieved

Intent-to-Treat Population



■ Corifollitropin Alfa 100 µg (N=268) ■ recFSH 150 IU (N=128)

# PURSUE Trial

>50 KG

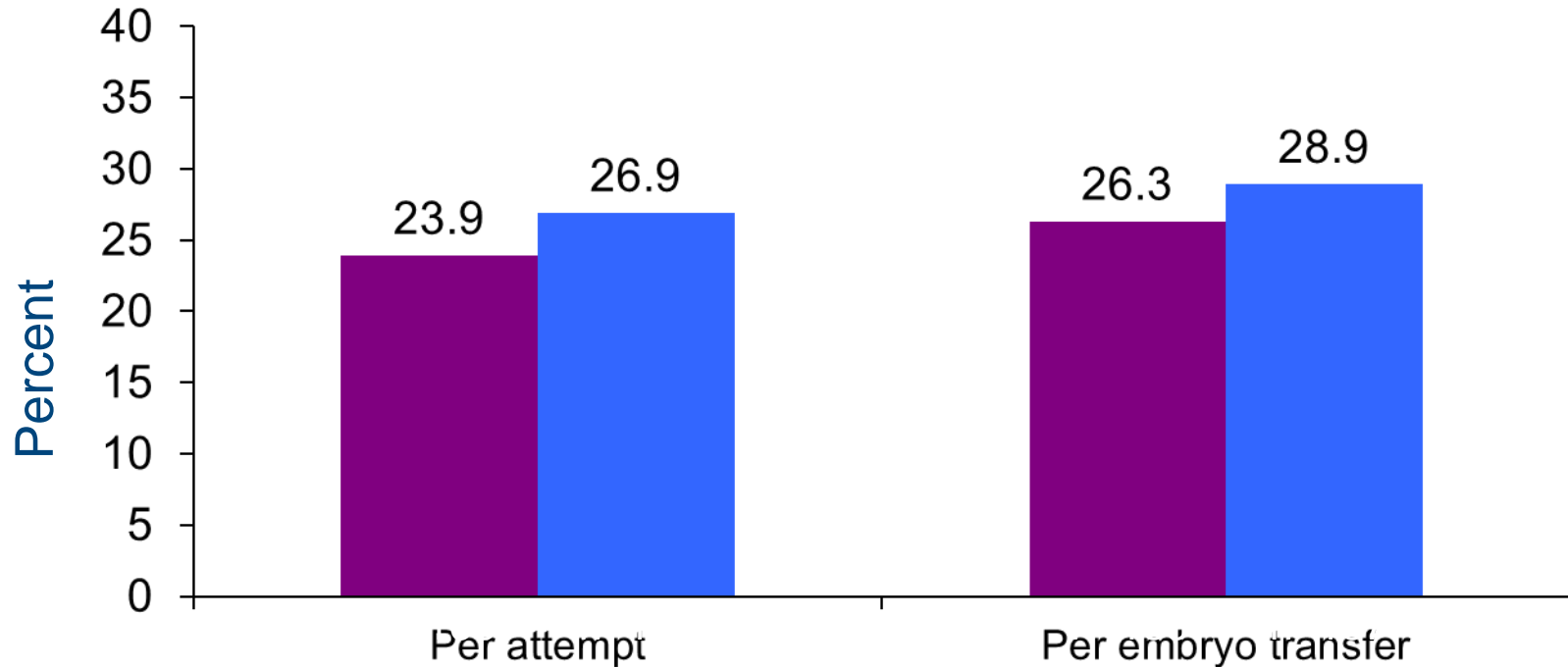
35-42 YEARS OLD

1,424 PATIENTS

RCT: CORIFOLLITROPIN ALFA 150 $\mu$ G VS RFSH 300 IU

# Vital Pregnancy

## Full Analysis Set

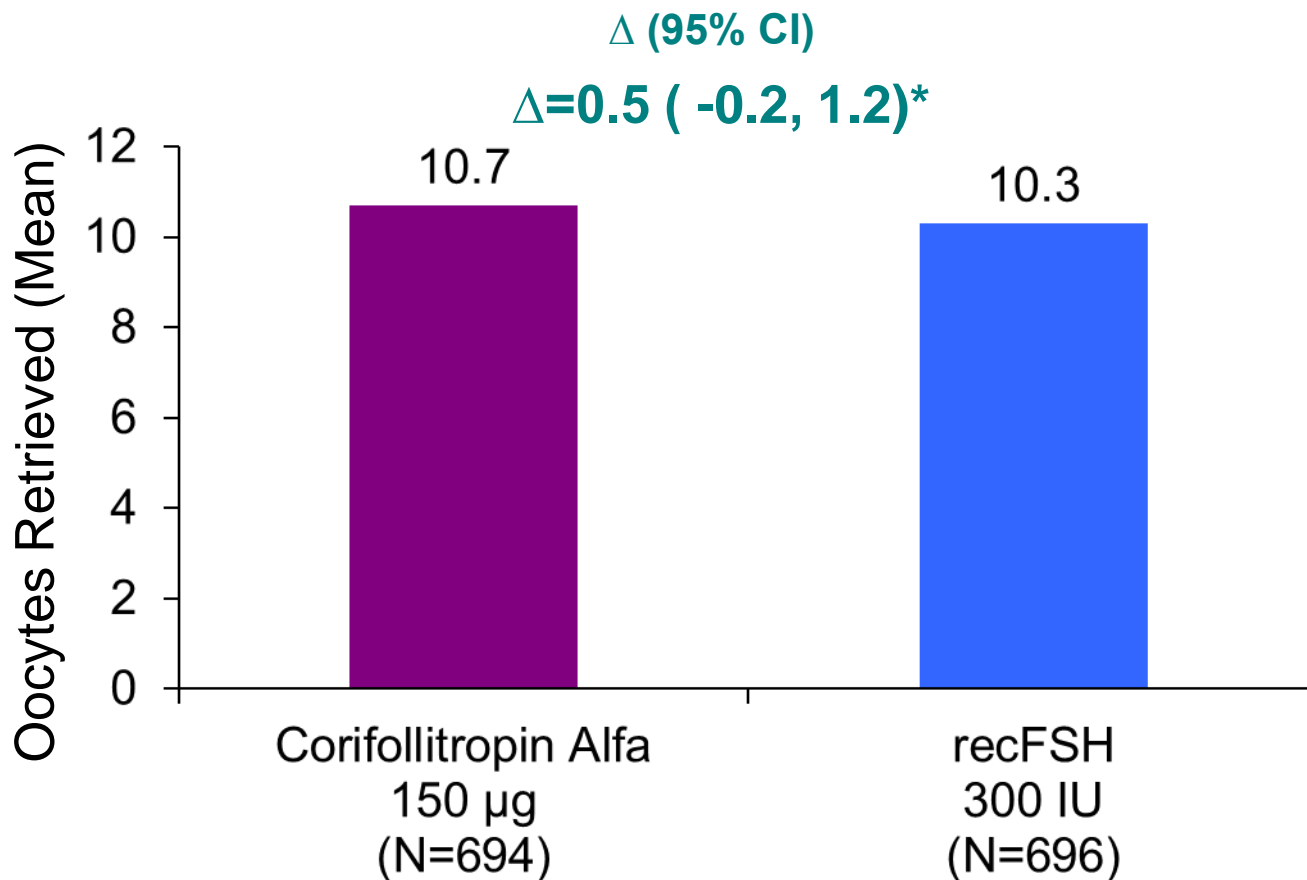


■ Corifollitropin Alfa 150 µg (N=632-694)

■ recFSH 300 IU (N=647-696)



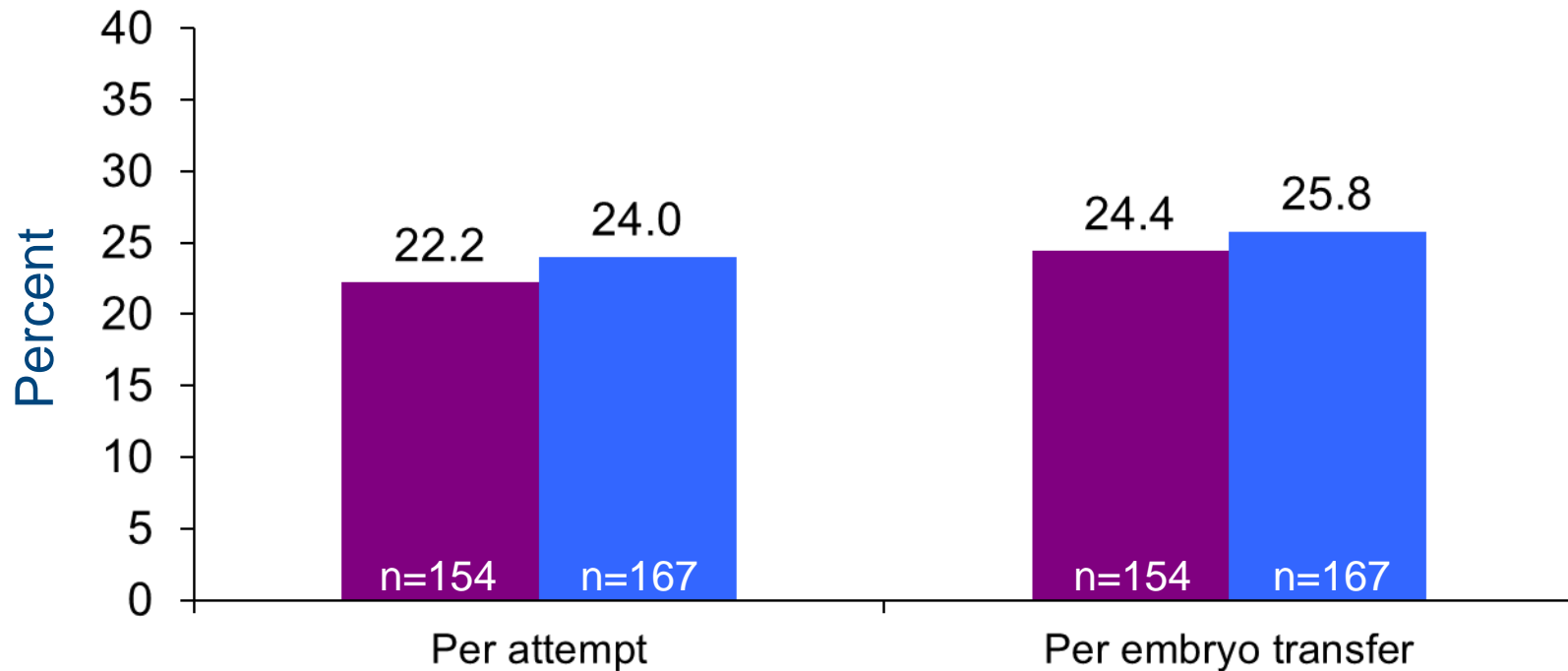
# Number of Oocytes Retrieved



\*Non-inferiority margin: Lower bound of the 95% CI of -3 oocytes

# Ongoing Pregnancy

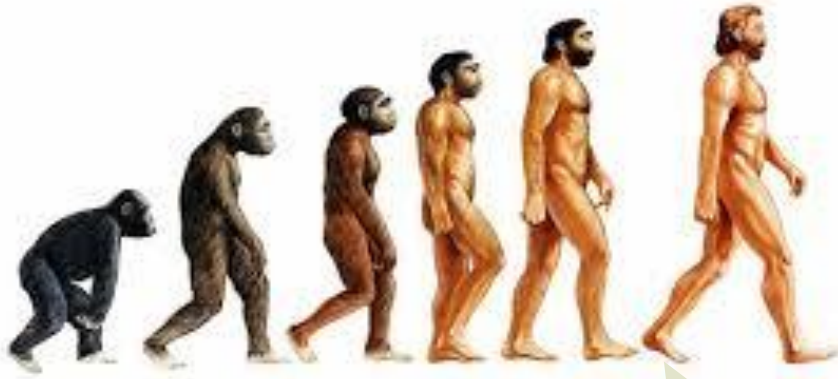
## Full Analysis Set



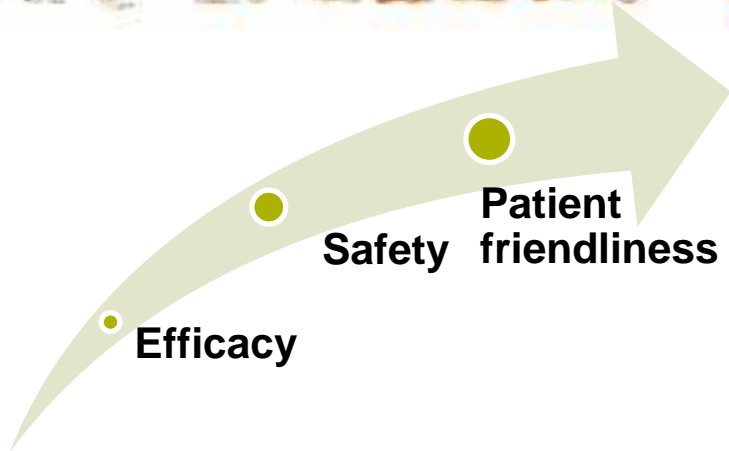
■ Corifollitropin Alfa 150 µg (N=632-694)

■ recFSH 300 IU (N=647-696)

# Corifollitropin alfa. Is it an evolution in ovarian stimulation



Safety



## In which patients categories should be used?

### ➤ Normal responders

Very good pregnancy rates comparable with rFSH and similar OHSS risk (ENSURE, ENGAGE, PURSUE)

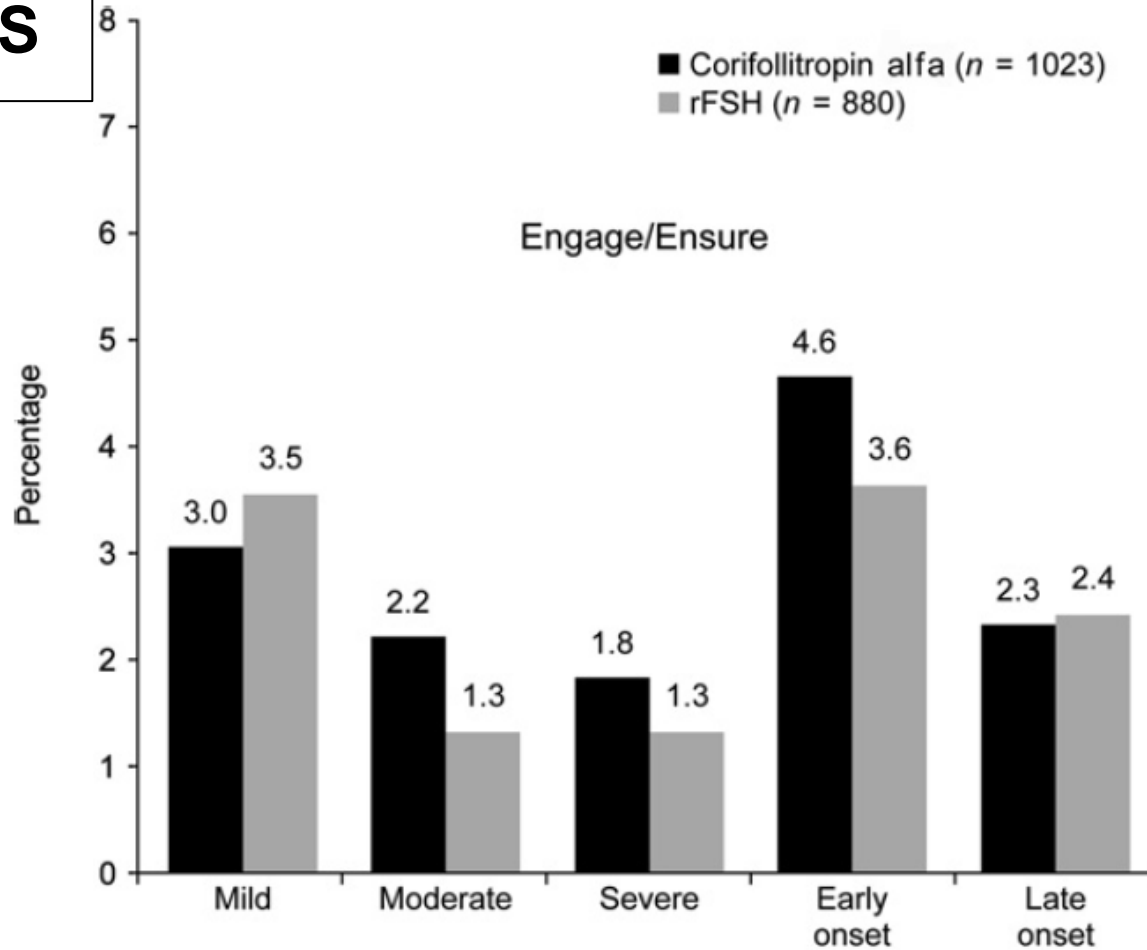
### ➤ Low responders

Comparable pregnancy rates with short agonist protocol

	Corifollitropin alfa antagonist	Short flare-up agonist
Positive hCG/ ET	21.7%	20.6%
Ongoing pregnancy/ET	13%	12%

# Safety

## OHSS



Comparative incidence of ovarian hyperstimulation syndrome following ovarian stimulation with corifollitropin alfa or recombinant FSH

## Hyper- responders

Follow the Summary product characteristics!!!!

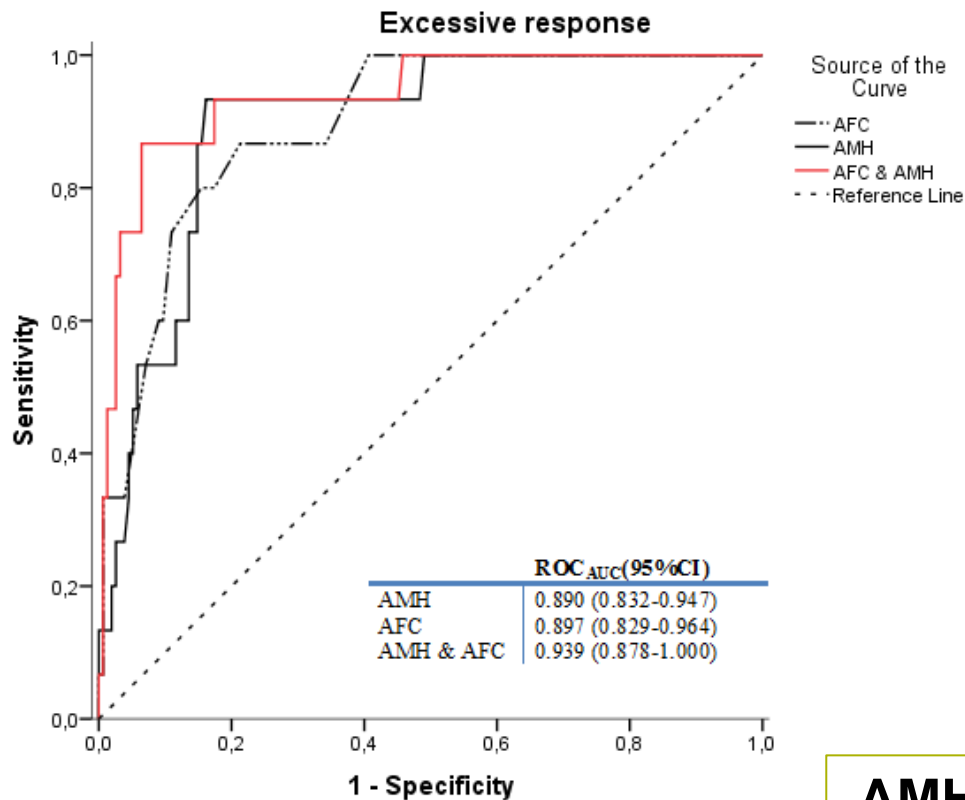
### Do not use Elonva if you

- ❑ have had OHSS
- ❑ have previously had a treatment cycle of controlled stimulation with >30 follicles of >11mm
- ❑ AFC>20

Can we predict excessive response prior to starting a cycle with corifollitropin?

YES

# Excessive ovarian response after corifollitropin alfa



Diagonal segments are produced by ties.

**Predictors of ovarian response in women treated with corifollitropin alfa for in vitro fertilization/ intracytoplasmic sperm injection**

Nikolaos P. Polyzos, M.D., Ph.D.,

Fertil Steril. 2013

**AMH: 3.52 ng/ml**  
**AFC: 16**



# Unexpected hyper-response.... do not pull the trigger..

## GnRH agonist triggering

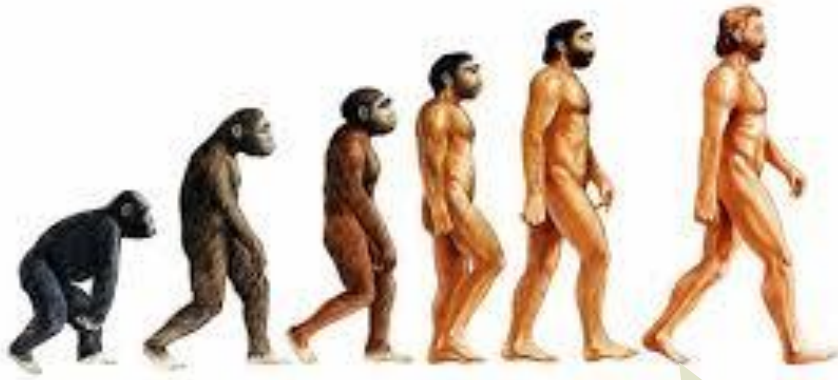
1500 IU hCG 1 hour after oocyte  
retrieval and fresh embryo transfer

***Humaidan, Polyzos et al.  
Hum Reprod 2013***

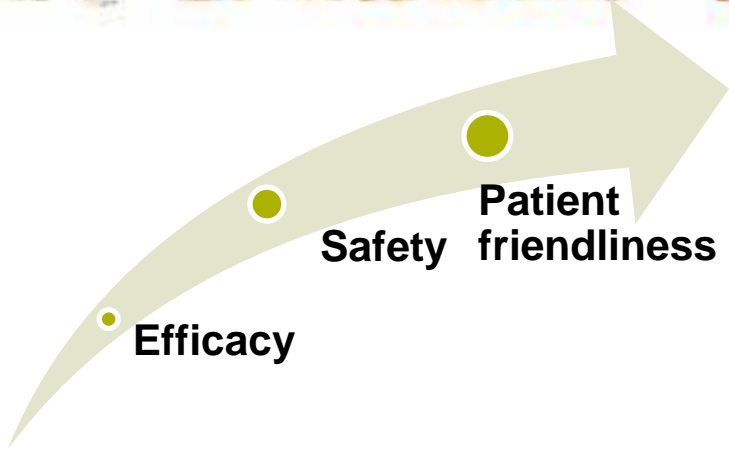
Freeze all embryos

***Devroey, Polyzos et al.  
Hum Reprod 2011***

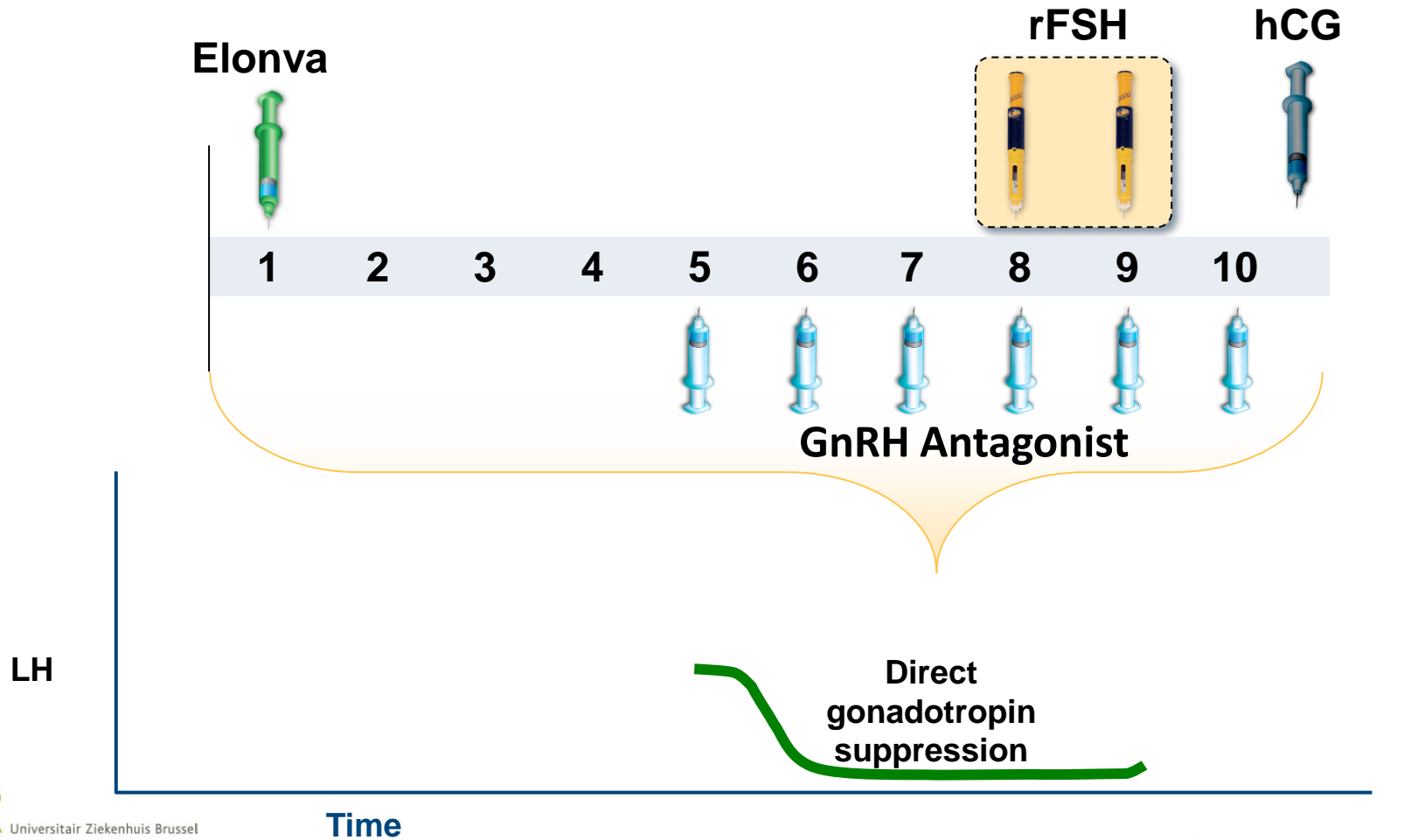
# Corifollitropin alfa. Is it an evolution in ovarian stimulation



Patient  
friendliness

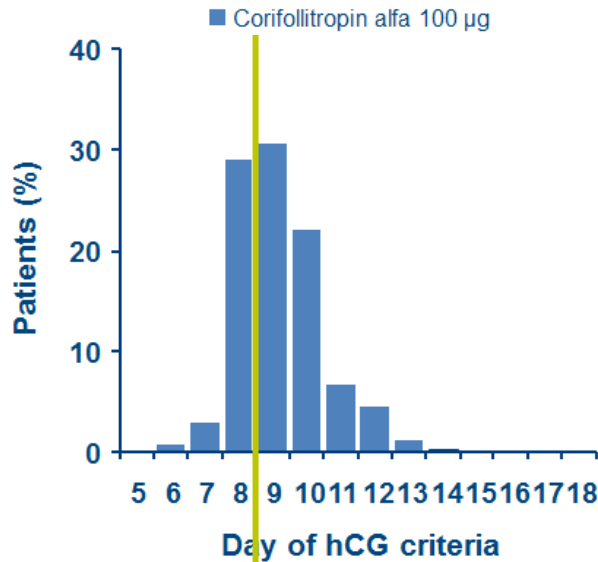


# Corifollitropin alfa Reduces the Number of Necessary Injections

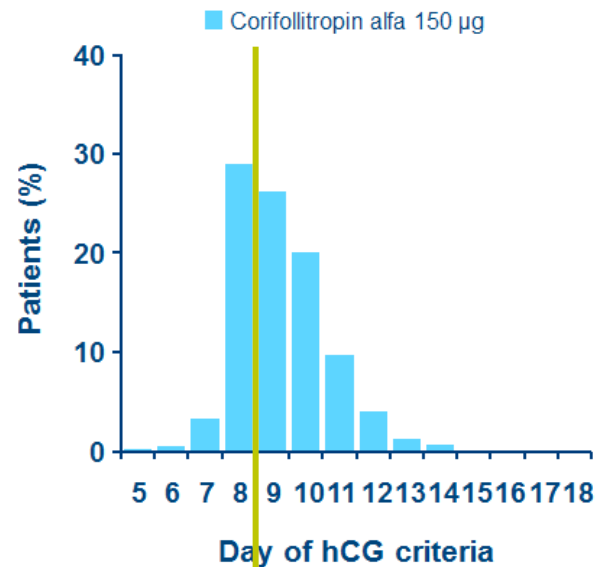


# Patients needing additional rFSH

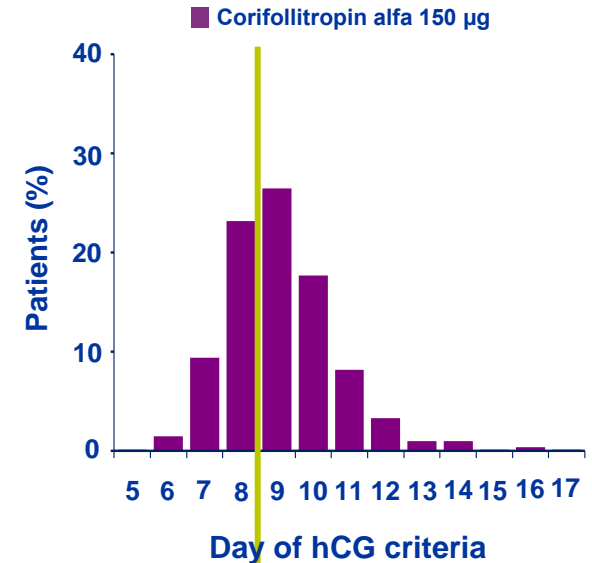
## ENSURE<sup>1</sup>



## ENGAGE<sup>2</sup>



## PURSUE<sup>3</sup>



**1/3 of patients met the criteria for hCG injection  
before or on stimulation day 8**

# Does early response compromise pregnancy rates?

	Criteria for hCG reached....	
	Early responders* N=166	Normal responders** N=549
Duration of stimulation (days)	7.9 ± 0.3	10.1 ± 1.2
Number of oocytes	13.6 ± 7.2	14.5 ± 8.1
Number of GQE, day 3	4.3 ± 3.6	4.8 ± 4.5
Number of embryos transferred	1.7 ± 0.6	1.6 ± 0.6
Ongoing PR	43.4	38.8

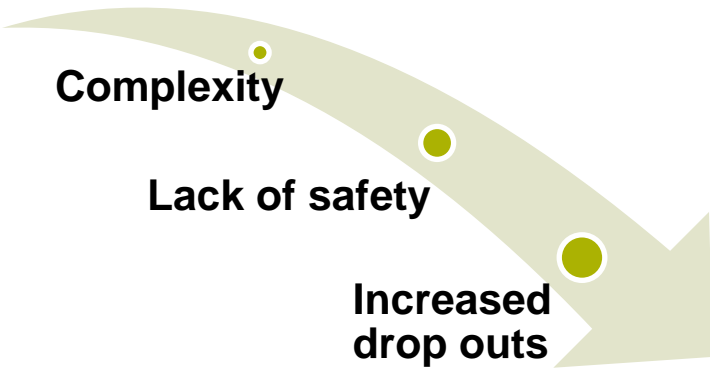
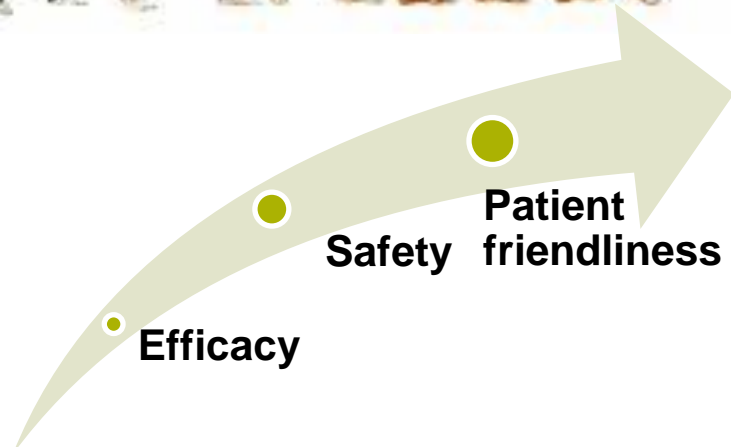
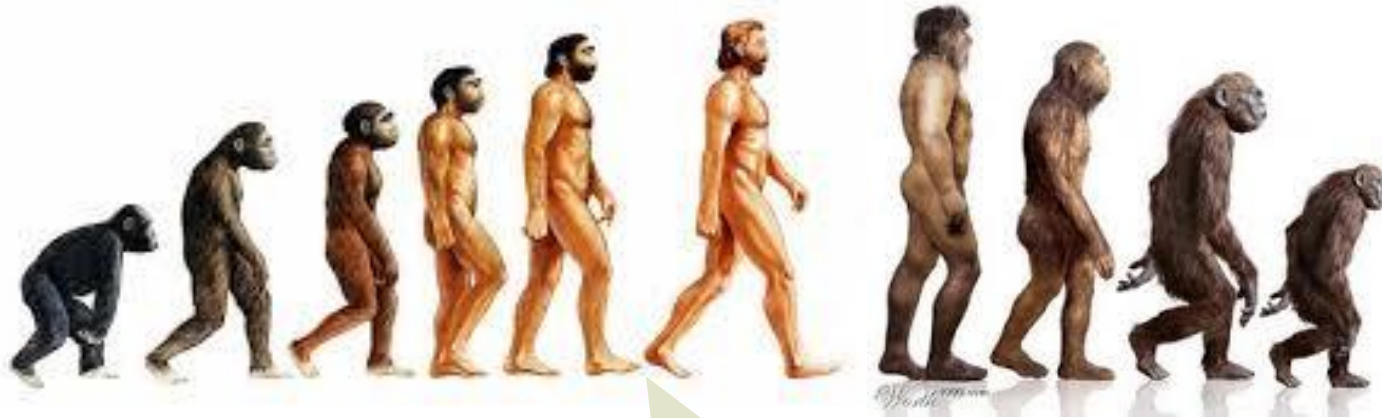
\*early responders: reaching the criterion for HCG administration on or prior to stimulation day 8

\*\* normal responders: reaching the criterion after stimulation day 8

# Summary

- Corifollitropin alfa is a key molecule towards a patient-friendly ovarian stimulation
- Very good pregnancy rates in all age categories
- Very good pregnancy rates for normal and poor responders
- Proven safety in terms of OHSS risk
- Patients and physicians may reduce the burden and complexity of IVF treatment
  - 1/3 of women may reach oocyte retrieval with one injection of corifollitropin alfa

# What is eventually our perception for the evolution in ovarian stimulation?



# Thank you