Indications de la FSH retard

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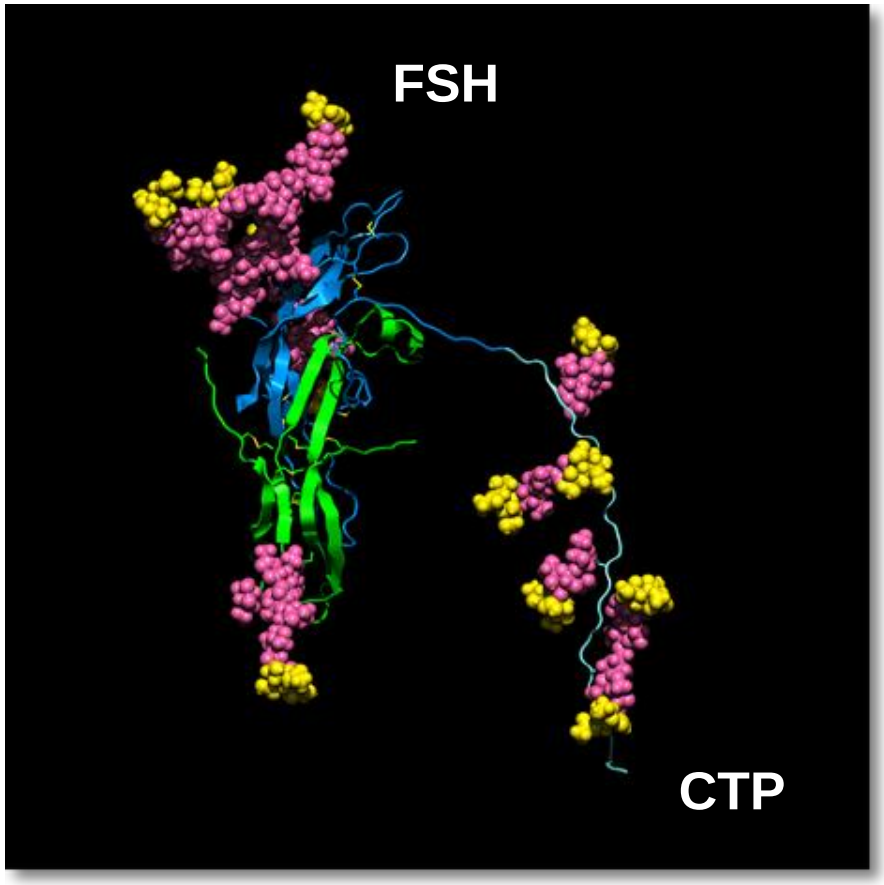
Molecular Structure of Corifollitropin alfa



- A recombinant fusion molecule of FSH and the CTP of the hCGβ-subunit
- The first of a new class of gonadotropins with different pharmacokinetic properties but similar pharmacologic features as rFSH
- Interacts only with the FSH receptor and not with the LH receptor

FSH, follicle-stimulating hormone; CTP, carboxy-terminal peptide; hCG, human chorionic gonadotropin; LH, luteinizing hormone; rFSH, recombinant FSH.

Fares FA, et al. *Proc Natl Acad Sci U S A*. 1992;89:4304-4308.

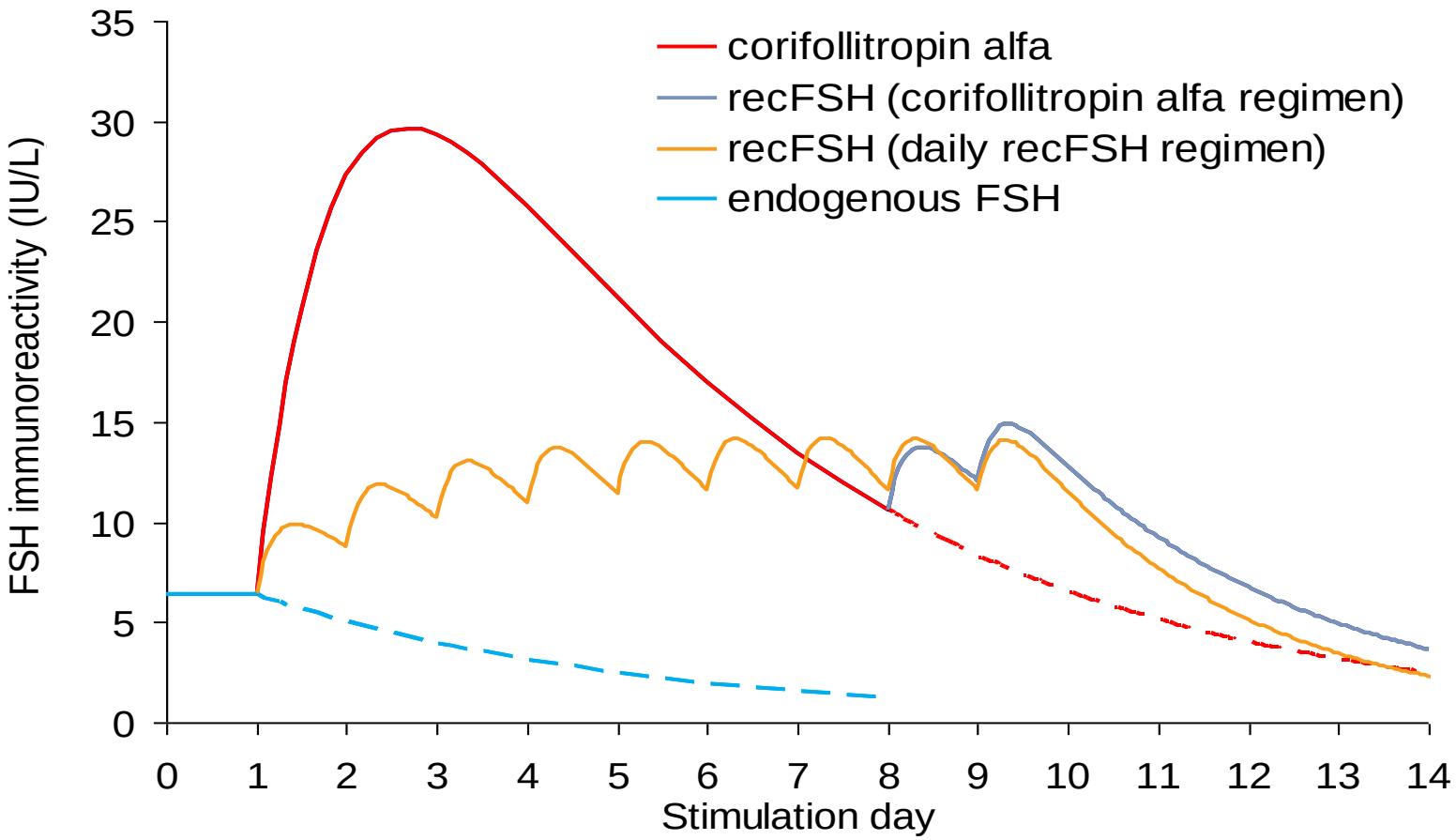
Pharmacokinetics of corifollitropin alfa Females of Reproductive Age

	Corifollitropin alfa	Recombinant FSH	Recombinant hCG
Elimination half-life	59-79 h	27-41 h	29-38 h
T_{max}	34-57 h	10-12 h	12-24 h

Tmax = time to maximum concentration.

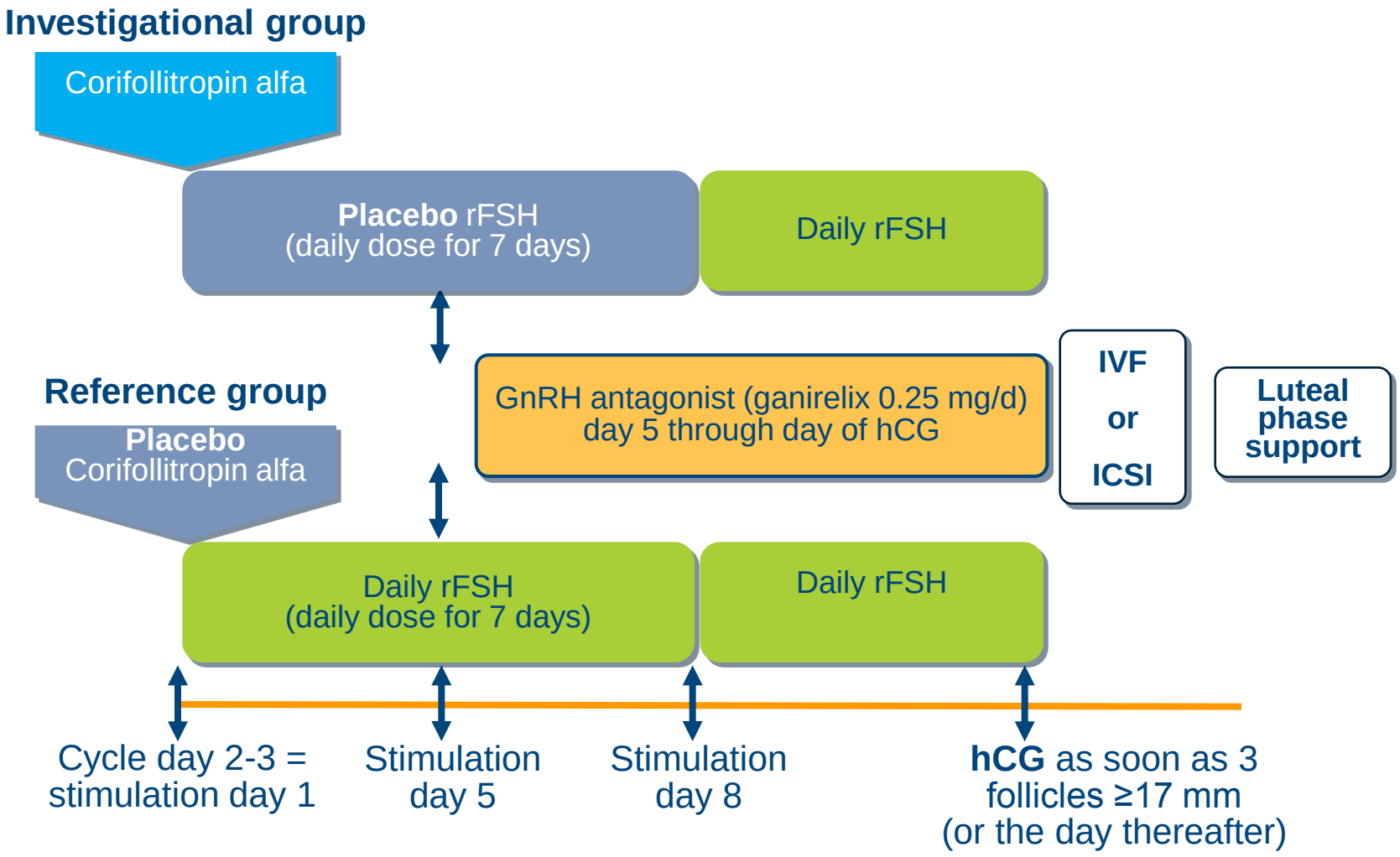
Duijkers et al. *Hum Reprod*. 2002; Devroey et al. *JCEM,* 2004; Voortman et al. *Hum Reprod*. 1999; Mannaerts et al. *Fertil Steril*.1993; Trinchard-Lugan et al. *RBM Online*. 2002

Comparative Pharmacokinetics



Van Schanke et al Pharmacology, 2010; Duijkers et al. *Hum Reprod*. 2002; Devroey et al. *JCEM,* 2004

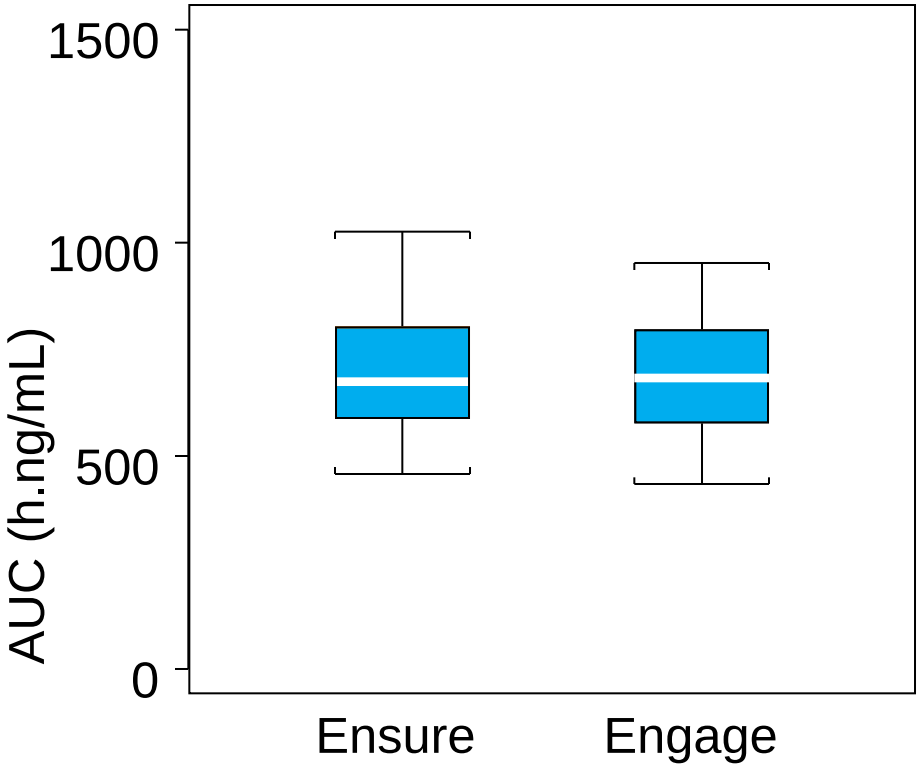
Engage and Ensure Treatment Regimen

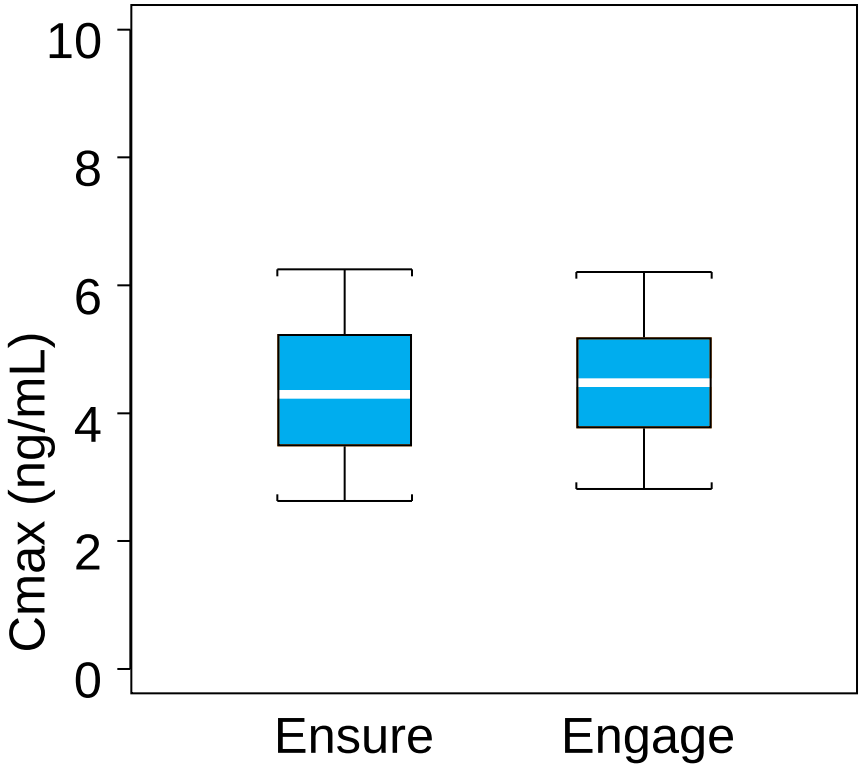


Corifollitropin alfa Phase 3 Clinical Trials

	Engage	Ensure	Trust
Study arms	Corifollitropin alfa 150 µg vs rFSH 200 IU/d in women >60 kg	Corifollitropin alfa 100 µg vs rFSH 150 IU/d in women ≤60 kg	Corifollitropin alfa 150 µg in women > 60 kg
Design	Double-blind RCT 1 cycle	Double-blind RCT 1 cycle	Multicenter, open-label, uncontrolled, up to 3 cycles
Patients (n)	1506	396	Cycle 1 682 Cycle 2 375 Cycle 3 198
Primary end point	Ongoing PR/cycle	Number of oocytes	- Antibody formation - (S)AEs - OHSS
Sites	Europe 20 North America 14	Europe 14 Asia 5	Europe 15 Latin America 10 Australia 5
Publications	Devroey et al 2009 Fauser et al 2010	The corifollitropin alfa Ensure study group, 2010	Norman et al 2011

Similar exposure to corifollitropin alfa using 100 µg and 150 µg doses in Phase 3 Trials



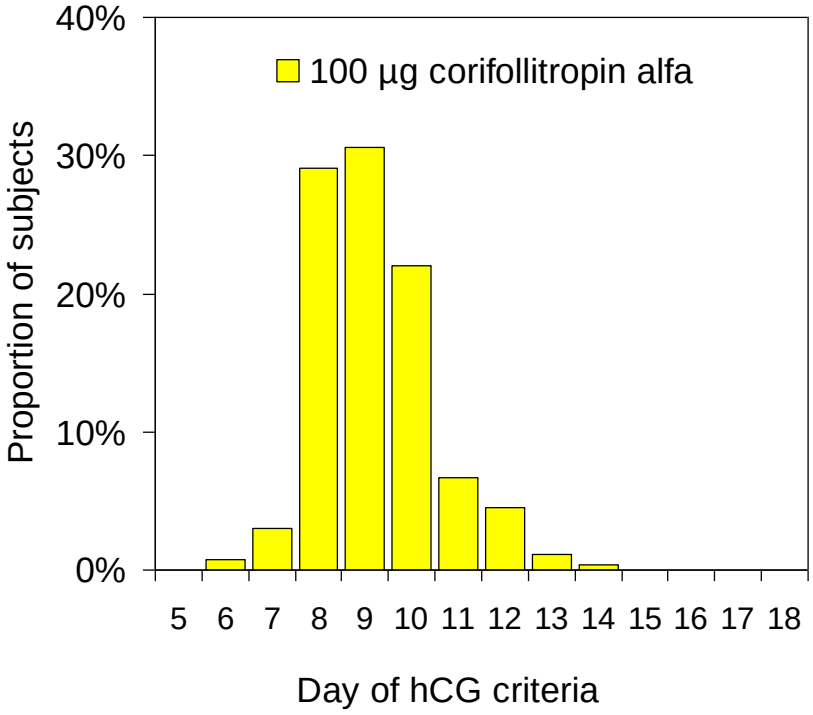


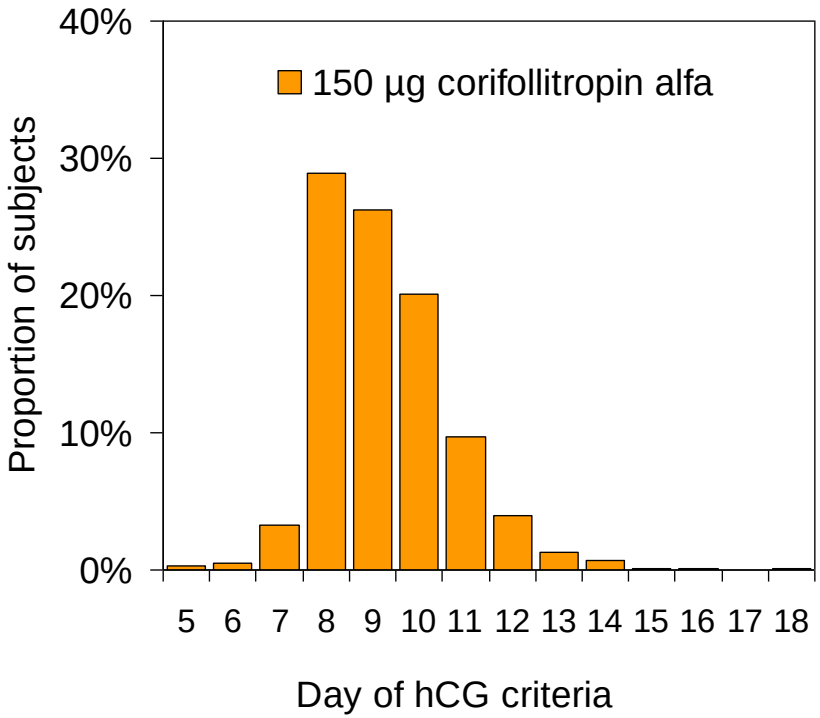
Data shown for non-Asian subjects, All-Subjects-Pharmacokinetically-Evaluable

AUC = area under the curve; Cmax = maximum concentration

De Greef et al. 2010 Clin Pharmacol Ther 2010;888:79-87

Similar time interval to reach criteria for hCG for 100 µg (≤ 60 kg) and 150 µg (> 60 kg)





Note: Median duration of stimulation was 9 days both in the Engage and Ensure and in each trial one third of the patients reached the criteria for hCG before or on Stimulation Day 8.

Ledger et al Accepted RBMonline

Mean (SD) number of oocytes per started cycle

	Corifollitropin alfa	recFSH	Estimated difference* ANOVA (95% CI)
Engage	150 µg **n = 756** **13.7 (8.2)**	200 IU **n = 750** **12.5 (6.7)**	**1.2 (0.5, 1.9)**
Ensure	100 µg **n = 268** **13.3 (7.3)**	150 IU **n = 128** **10.6 (5.9)**	**2.5 (1.2, 3.9)**

*Adjusted for age group (<32 vs ≥32 yrs) and center

(Cumulative) Ongoing Pregnancy Rates & Live Birth Rates in Engage trial

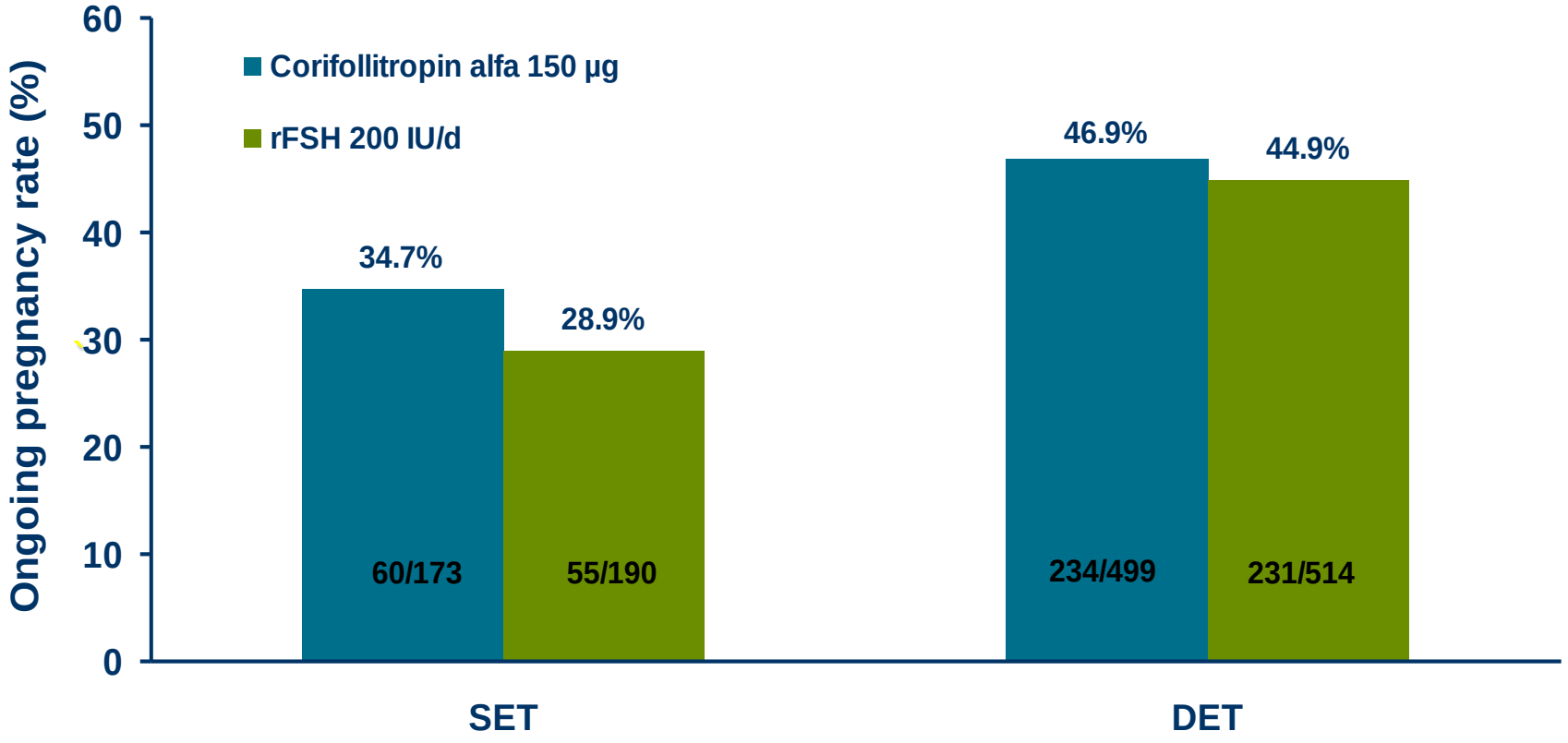
	Corifollitropin alfa 150 µg n = 756	Puregon® 200 IU/day n = 750	Estimated difference[a] (95% CI)
Ongoing PR per started cycle	**38.9%** 294/756	**38.1%** 286/750	**0.9% (–3.9 to 5.7)**
per transfer	**43.8%**	**40.6%**	**3.1% (–2.0 to 8.2)**
Live birth rates/ started cycle	**35.6%** 275 in FU	**34.4%** 266 in FU	
Cumulative ongoing PR/ started cycle	**47.2%** 148 ≥1 FTET	**44.9%** 147 ≥1 FTET	

[a]Adjusted for age group and region. CI, confidence interval; FTET, frozen-thawed embryo transfer.

Boostanfar R, et al. *Hum Reprod.* 2010;25(supple 1):i47 [O-119].

Results: Single vs Double Embryo Transfer— Ongoing Pregnancy Rates per Started Cycle

Engage



SET = single embryo transfer; DET = double embryo transfer.

Devroey et al. Hum Reprod. 2009;24:3036.

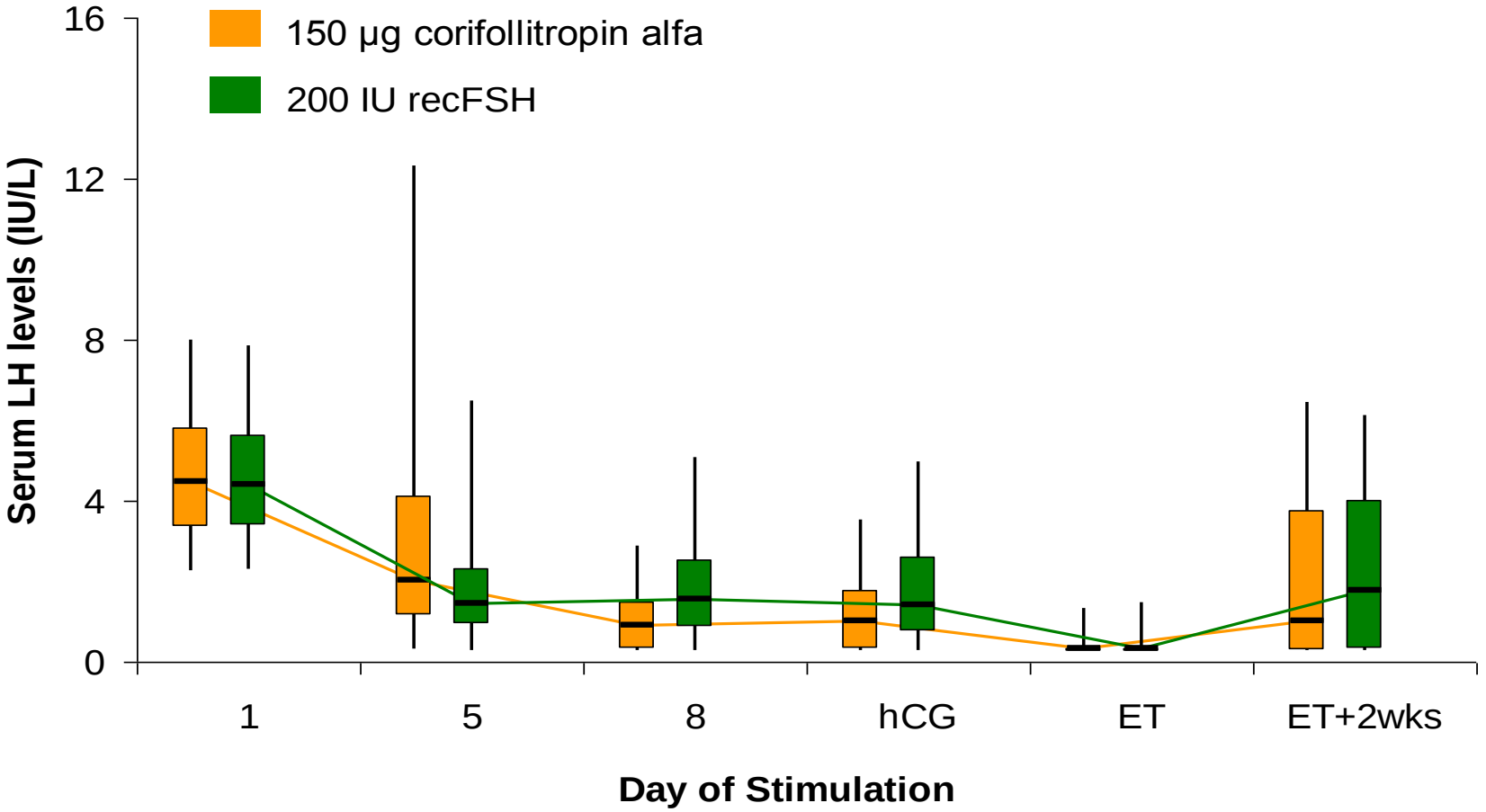
Incidence of OHSS during phase III trials

		Corifollitropin alfa	recFSH
		N=1033	N=880
Engage + Ensure	Mild	3.0%	3.5%
	Moderate	2.2%	1.3%
	Severe	1.8%	1.3%
		N=682	
Trust	Mild	1.8%	
1e cycles	Moderate	0.9%	
	Severe	0.9%	

Incidence of Congenital Malformations: Live-born Infants

		Corifollitropin alfa	recFSH
Combined phase 3 RCTs[1] Engage and Ensure	Major	4.0% (17/424)	5.4% (20/370)
	Minor	12.3% (52/424)	11.6% (42/370)
	Any	16.3% (69/424)	17.0% (63/370)
All phase 2 and 3 trials	Major	4.5% (36/806)	
	Minor	10.0% (81/806)	
	Any	14.5% (117/806)	

Serum LH Levels During Stimulation Engage Trial



Fauser et al Hum Reprod 2010

Ongoing PR Per Started Cycle Engage
Serum LH on Day 8

Treatment group	Serum LH level	Ongoing pregnancy rate			
	IU/L	N	n	%	95% CI
Corifollitropin alfa					
P25≤0.62	<P25	216*	77	35.6	[29.3; 42.4]
P50=0.96	P25-P75	316	125	39.6	[34.1; 45.2]
P75=1.58	>P75	176	68	38.6	[31.4; 46.3]
recFSH					
P25=0.91	<P25	169	60	35.5	[28.3; 43.2]
P50=1.57	P25-P75	340	125	36.8	[31.6; 42.1]
P75=2.66	>P75	169	65	38.5	[31.1; 46.2]

*more than 25% of patients had a value below the LLOQ and were all included in the <P25 group

Ongoing Pregnancy Rate by <P25 and ≥ P25 LH Categories
Stimulation Day 8, recFSH Group Including 1664 Subjects

Ongoing pregnancy rate

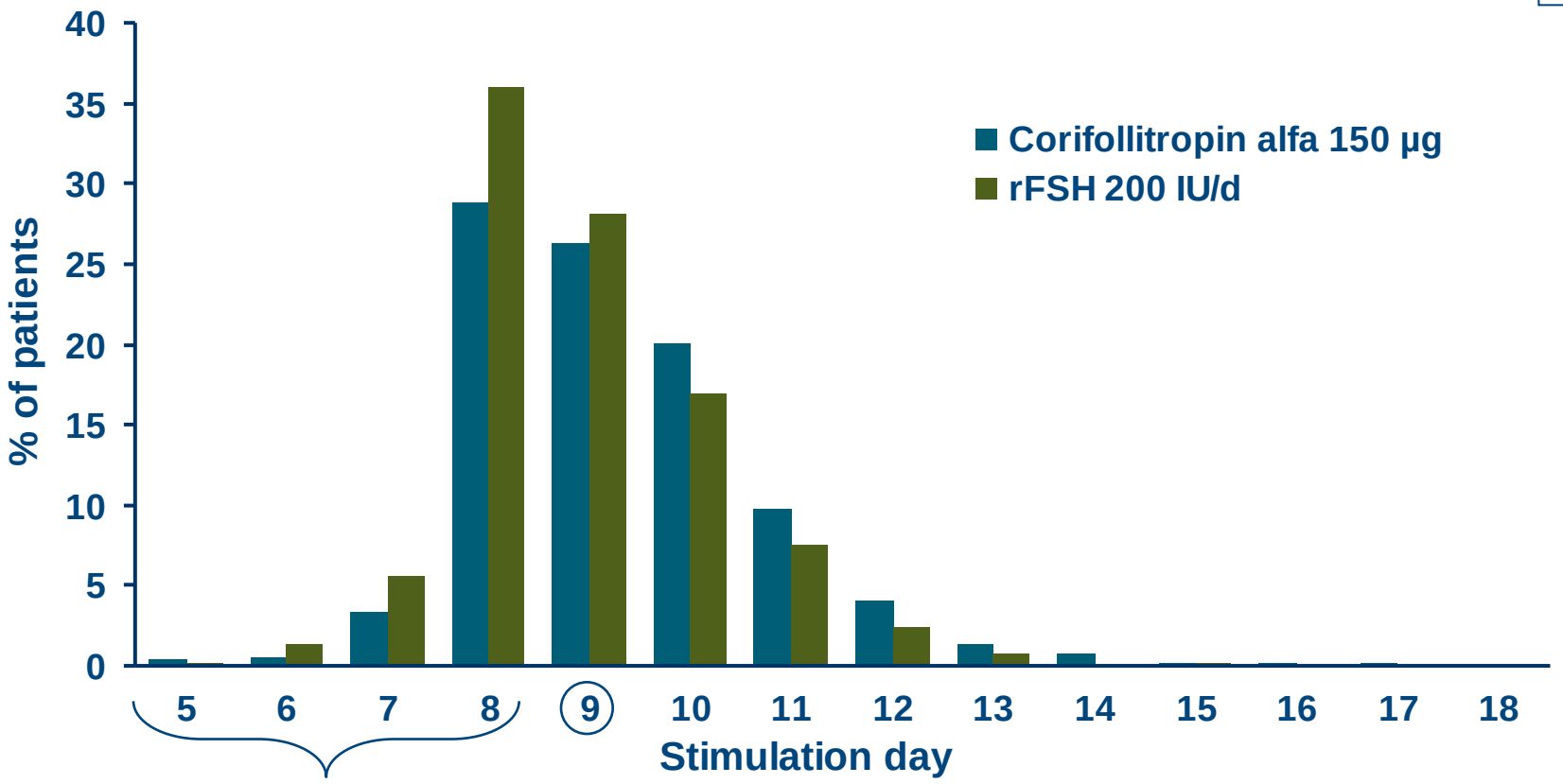
Trial	<P25 n N (%)	≥P25 n N (%)	<*P*25 versus ≥P25 Odds ratio
NA ganirelix	15 41 (36.6)	39 132 (29.5)	1.32 (0.62-2.78)
EU ganirelix	20 105 (19.0)	67 315 (21.3)	0.86 (0.49-1.52)
EU-ME ganirelix	19 49 (38.8)	42 153 (27.5)	1.71 (0.86-3.40)
Xpect	17 42 (40.5)	46 128 (35.9)	1.28 (0.61-2.65)
Ensure	12 30 (40.0)	30 91 (33.0)	1.35 (0.57 -3.21)
Engage	60 169 (35.5)	190 509 (37.3)	0.91 (0.63 -1.32)
Estimated overall odds ratio:			**1.07 [0.85-1.36]*** **0.96 [0.85-1.36]****

* Adjusted for trial

** Adjusted for age, oocytes and serum P on day 8

What was the clinical outcome in the early responders?

Engage



One-third of the patients did not require any rFSH

Characteristics of early responders reaching the criteria for hCG ≤ day 8 vs > day 8 (Engage)

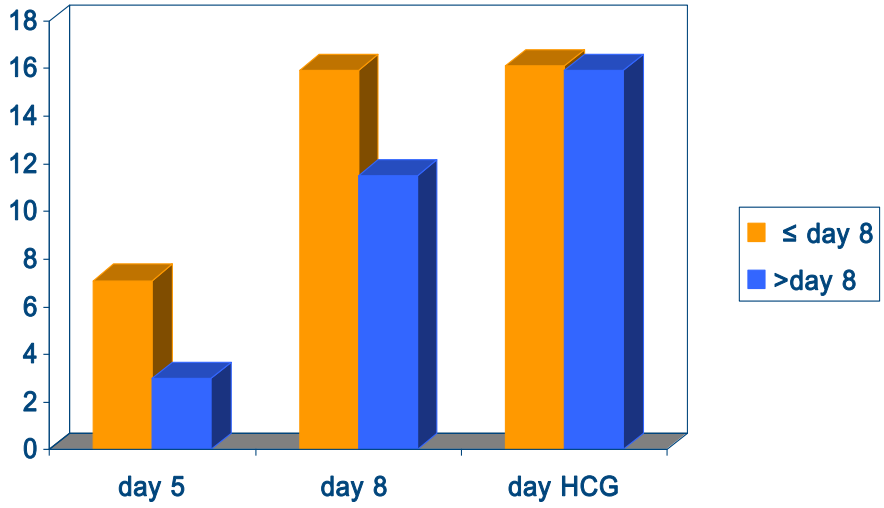
	corifollitropin alfa		recFSH	
	≤ day 8 N=249 (35%)	>day 8 N=472	≤ day 8 N=322 (44%)	>day 8 N=417
Age (years)	31.5 (3.3)	31.5 (3.4)	31.4 (3.2)	31.6 (3.3)
BMI (kg/m2)	24.7 (2.7)	24.9 (2.8)	24.7 (2.7)	24.9 (2.7)
Primary infertility, %	54.6%	52.8%	57.8%	48.7%
Duration of infertility (yrs)	3.3 (2.5)	3.4 (2.4)	3.1 (2.1)	3.3 (2.3)
Median FSH, day 1 (IU/L)	6.2	6.5	6.0	6.6
AFC, day 1	12.5 (4.4)	12.4 (4.6)	13.3* (4.4)	11.8 (4.3)

•P<0.001

Values are mean (SD) unless otherwise stated.

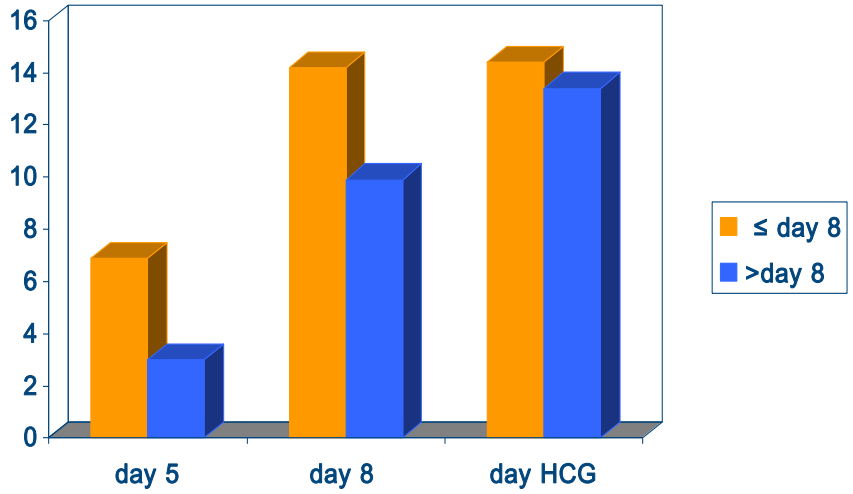
Number of follicles ≥ 11 mm in subjects who reached the criteria of hCG ≤ day 8 vs > day 8

150 µg corifollitropin alfa



On day 8 the mean number of follicles ≥ 17 mm was 5.4 vs 0.6

200 IU recFSH



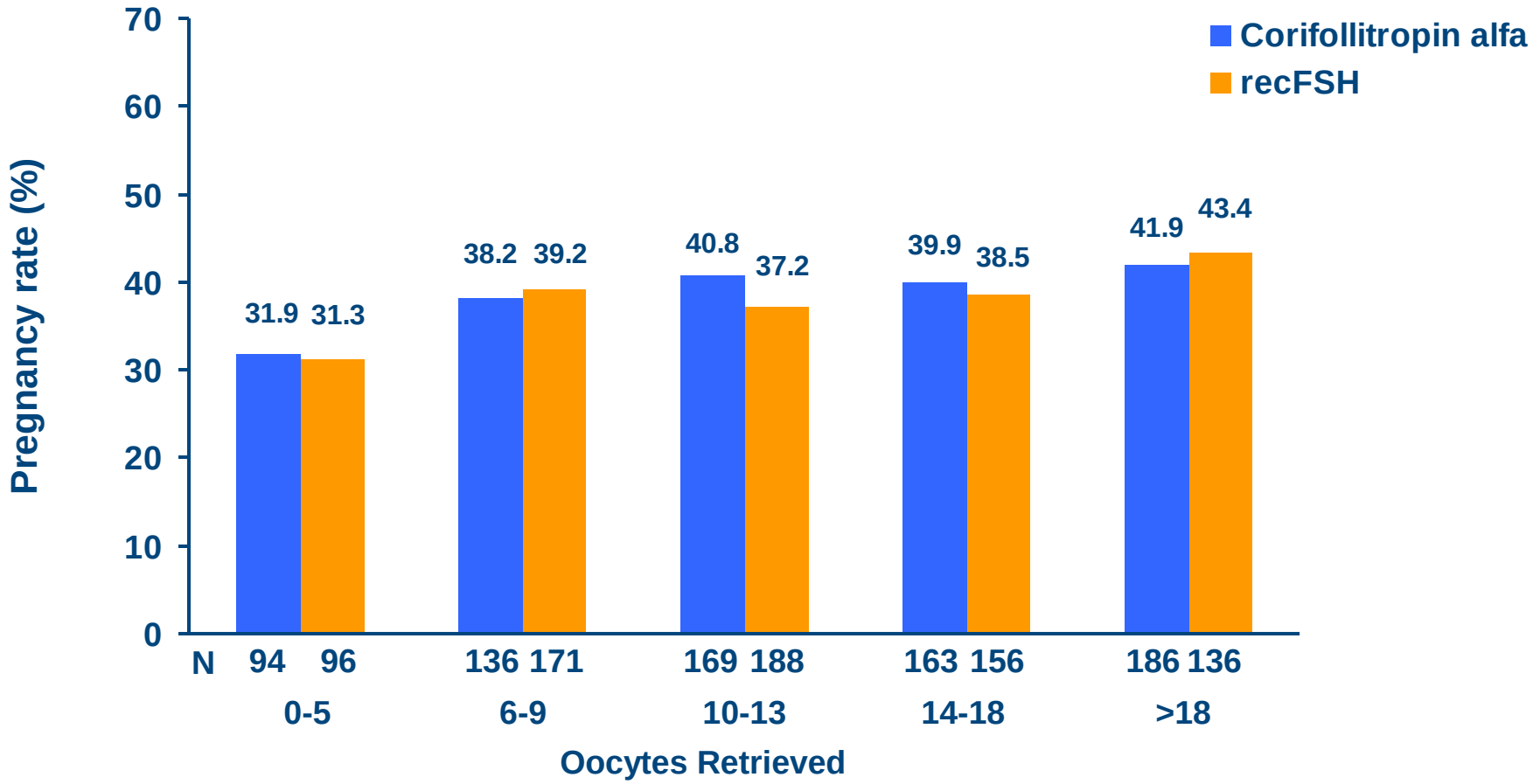
On day 8 the mean number of follicles ≥ 17 mm was 5.2 vs 0.7

Clinical outcome of early responders reaching the criteria for hCG at ≤ day 8 vs > day 8 (Engage)

	Corifollitropin alfa		recFSH	
	≤ day 8 N=249	>day 8 N=472	≤ day 8 N=322	>day 8 N=417
Duration of stimulation (days)	8.3 (0.7)	10.2 (1.3)	8.2 (0.7)	10.0 (1.0)
Follicles ≥ 11 mm, day 8	15.9 (7.0)	11.5 (5.6)	14.2 (6.1)	9.9 (5.2)
Follicles ≥ 11 mm, day hCG	16.1 (7.0)	15.9 (7.0)	14.4 (6.2)	13.4 (6.1)
Number of oocytes	13.9 (7.2)	14.2 (8.3)	13.3 (6.7)	12.2 (6.7)
Number of GQE, day 3	4.5 (3.7)	4.7 (4.6)	4.5 (3.8)	4.3 (4.0)
Number of embryos transferred	1.7 (0.6)	1.5 (0.7)	1.7 (0.6)	1.6 (0.6)
Ongoing PR	43.8%	37.3%	40.1%	37.4%

Values are mean (SD) unless otherwise stated.

Engage: ongoing pregnancy rates vs. oocytes



hCG administration, immediately vs 1-day delay Engage trial

	Corifollitropin alfa		recFSH	
	No delay N=503	1-day delay N=211	No delay N=524	1-day delay N=209
Oocytes	14.1 ±8.2	14.4 ±7.0	12.5 ±6.7	13.3 ±6.5
GQ Embryos day 3	4.4 ±4.4	5.4 ±4.1	4.3 ±3.8	4.8 ±4.2
Ongoing PRs	40.0%	38.9%	37.8%	41.8%

P value of the estimated difference in ongoing PR is 0.29 when taking treatment and region into account

Indication

Indication:

Controlled Ovarian Stimulation in combination with a GnRH antagonist for development of multiple follicles in women participating in an ART program

Indications

Pas d’indication en induction monofolliculaire

Pas d’AMM en protocole agoniste

Indications

- Contre-indiqué :

.CFA > 20

.recueil de plus de 30 ovocytes

- SOPK

Indications

- Posologies établies selon le poids (pas le BMI) :

.100 microgrammes : <=60 kgs

.150 microgrammes : >60 kgs

Indications

Etudes chez les mauvaises répondeuses attendues

Bénéfices attendus

-1 injection à la place de 7

-simplification du traitement

-meilleure acceptabilité attendue

-diminution du nombre d’erreurs de traitement

Enquête Européenne

445 femmes interrogées par TNS

108 en France

18 à 44 ans

3 groupes : *- en cours traitement*

- ayant eu un traitement dans les 2 dernières années

- infertiles, pas encore traités

Barrière P et al COGI 2010

Enquête Européenne

- 91 % auraient souhaité commencer plus tôt

- Freins aux traitements :

72 % : crainte de l'échec

46 % : crainte des effets secondaires

52 % : anxiété liée aux injections, au respect et au coût du protocole

- Moins d'injections :

26 % : meilleure compliance

19 % : diminution du stress

Barrière P et al COGI 2010

Bénéfices attendus

-Cmax obtenue plus rapidement

-Plus physiologique

-Potentiellement favorable au recrutement folliculaire

UTILISATION

Utilisation actuelle dans les pays disposant de la molécule :

Évolution de 2 à 5% des prescriptions de gonadotrophines

CONCLUSION

-PHARMACOLOGIE INNOVANTE

-CONTRIBUTION à L'EVOLUTION DES PROTOCOLES