R-Recent Advance in Patient Friendly Protocol

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Clinical Director

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Objective of ovarian stimulation

To increase number of eggs (with good quality?)

↓

Increase number of fertilized embryos

↓

Increase number of embryos to select for transfer

↓

Increase cumulative pregnancy chance from FET
Ovarian stimulation protocol

- GnRH agonist + Gonadotropin
  - Ultrashort protocol
  - Short protocol
  - Long protocol
  - Ultralong protocol
- GnRH antagonist + Gonadotropin
- Clomiphene citrate
- Aromatase inhibitor
What can be considered ideal “Patient Friendly” ovarian stimulation?

- No medication
- Oral medication
- Few injection
- Few side-effect
- Easy-to-follow protocol
- High pregnancy rate
- Low cost
Traditional Protocols

- **Long GnRH agonist protocol**

- **GnRH antagonist protocol**
Drop-out rate between antagonist vs long agonist protocol

Mild = antagonist
Standard = long agonist

Verberg MFG; Human Reprod 2008
Novel Protocol

1/3 of patients did not require additional rFSH

Corifollitropin alfa

hCG

GnRH Antagonist

Cycle day 2-3 = Stimulation day 1
Stimulation day 5
Stimulation day 8
hCG as appropriate

1: HK Elonva PL. 2011.
IVF: It Works But Is Burdensome

• Current treatments induce stress
  – Women who had undergone an IVF experience rated their injections as either an extremely stressful or very stressful event

• Discontinuation reduces cumulative pregnancy rates
  – Treatment burden is a major reason for discontinuation

• Need to find ways to reduce stress and make treatment more patient-friendly
  – IVF patients who were presented information about a single-dose protocol felt it would improve convenience and reduce stress

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.

New Class of gonadotropin

Sustained follicular stimulant
Corifollitropin alfa: Recombinant Hormone

α Subunits

β Subunits

Human FSH

92 aa

110 aa

Follitropin beta = 30 h

hCG

92 aa

145 aa

Corifollitropin alfa

92 aa

110 aa

28 aa

t½ corifollitropin alfa = 69 h

FSH = follicle-stimulating hormone; aa = amino acids; t½ = half life.

Molecular Structure of Corifollitropin alfa

Corifollitropin alfa

92 AA

α

β

4 N-linked similar to FSH

4 O-linked similar to hCG

~ 10 fold increase in bio-potency compared to wild type FSH

AA sequence

- No deviation from human sequence
- No additional linkage AA

Carbohydrate side chains

- 4 N-linked similar to FSH
- 4 O-linked similar to hCG

AA = amino acid.
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 wild-type FSH
- Interacts only with the FSH receptor and not with the LH receptor

CTP = carboxy-terminal peptide; LH = luteinizing hormone.
Comparative Pharmacokinetics

Graph showing the pharmacokinetics of Corifollitropin alfa and rFSH.

- Peak level of FSH activity is reached within 2 days for corifollitropin alpha.
- Steady state level of daily rFSH is reached after 4-5 days.

rFSH = recombinant FSH; t1/2 = half-life; Tmax = time to maximum concentration.

Corifollitropin alfa reduces number of Injections

Corifollitropin alfa

Time

1 2 3 4 5 6 7 8 9 10

rFSH = recombinant follicle-stimulating hormone; hCG = human chorionic gonadotropin.
Comparative pharmacokinetics

Van Schanke et al., Pharmacology 2010; 85, 77-87
Duijkers et al., Hum Reprod 2002; 17, 1987-1993
Devroey P, et al. JCEM. 2004;89:2062-2070
Dose-Finding Studies: 60µg is not enough

<table>
<thead>
<tr>
<th>Corifollitropin alfa Dose-finding Study Group. <em>Hum Reprod.</em> 2008;23:2484–2492.</th>
<th>ELONVA™ (corifollitropin alfa) 60 µg</th>
<th>ELONVA 120 µg</th>
<th>ELONVA 180 µg</th>
<th>rFSH 150 IU daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started stimulation, n</td>
<td>78</td>
<td>77</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Oocyte retrieval, n (%)</td>
<td>50 (64.1)</td>
<td>72 (93.5)</td>
<td>74 (93.7)</td>
<td>73 (90.1)</td>
</tr>
<tr>
<td>ET, n (%)</td>
<td>44 (56.4)</td>
<td>70 (90.9)</td>
<td>70 (88.6)</td>
<td>66 (81.5)</td>
</tr>
<tr>
<td>Cancellation rate %</td>
<td>30.8</td>
<td>2.6</td>
<td>3.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>
What is the lowest dose which can be given without high cancellation rate?

- Simulation performed to select the lowest dosage that would result in a minimal cancellation rate
- 100 μg for women ≤ 60 kg
- 150 μg for women > 60 kg
- Predicated mean number of oocytes was similar in both groups eg. 12.1 and 13.2, respectively

De Greef R; Clin Pharmacol Ther 2010
Why was Body Weight and not BMI important?

- Corifollitropin alfa is distributed within the extracellular fluid space, which increases with body weight.
- Adipose tissue does not substantially increase the volume distribution of corifollitropin alfa.
- Hence, body weight is a stronger determinant of drug exposure than BMI.

Exposure to normalised dose of corifollitropin alfa decreases with greater weight.
# ELONVA Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Engage</th>
<th>Ensure</th>
<th>Trust</th>
<th>Pursue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study arms</strong></td>
<td>Elonva 150 µg vs rFSH 200 IU/d women &gt;60 kg Age 18-36 y</td>
<td>Elonva 100 µg vs rFSH 150 IU/d women ≤60 kg Age 18-36 y</td>
<td>Elonva 150 µg women &gt;60 kg Age 18–39 y</td>
<td>Elonva 150 µg vs rFSH 300 IU/d women &gt;50 kg Age 35–42 y</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Double-blind RCT 1 cycle</td>
<td>Double-blind RCT 1 cycle</td>
<td>Multicenter, open-label, uncontrolled Up to 3 cycles</td>
<td>Double-blind RCT 1 cycle</td>
</tr>
<tr>
<td><strong>Patient n./randomization</strong></td>
<td>1506 (1:1)</td>
<td>397 (2:1)</td>
<td>Cycle 1 682 Cycle 2 375 Cycle 3 198</td>
<td>1390 (1:1)</td>
</tr>
<tr>
<td><strong>1° End point</strong></td>
<td>Ongoing PR/cycle</td>
<td>Nr. of oocytes</td>
<td>- Antibody formation - Serious AE - Moderate/severe OHSS</td>
<td>Vital PR/cycle</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>Europe 20 North America 14</td>
<td>Europe 14 Asia 5</td>
<td>Europe 15 Latin America 10 Australia 5</td>
<td>North America 33</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; PR, pregnancy rate; OHSS, ovarian hyperstimulation syndrome.
## Corifollitropin alfa Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>Study arms</th>
<th>Engage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corifollitropin alfa 150 µg vs rFSH 200 IU/d in women &gt;60 kg</td>
<td>Corifollitropin alfa 100 µg vs rFSH 150 IU/d in women ≤60 kg</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Engage</th>
<th>Ensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1506</td>
<td></td>
<td>396</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary end point (noninferiority)</th>
<th>Engage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing PR/cycle</td>
<td></td>
</tr>
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</table>

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<tr>
<th>Sites</th>
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</tr>
</thead>
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<tr>
<td>(Europe 20, North America 14)</td>
<td></td>
</tr>
</tbody>
</table>

rFSH = recombinant FSH; RCT = randomized controlled trial; PR = pregnancy rate.

Entry Criteria

Inclusion criteria
- Indication for COS and IVF/ICSI using ejaculatory sperm
- Normal menstrual cycle length (24-35 days)
- ≥18 and ≤36 years of age
- Body weight >60 and ≤90 kg, and BMI ≥18 and ≤32 kg/m²

Exclusion criteria
- Endocrine abnormality
- PCOS
- Previous low ovarian response or no ovarian response
- Abnormal blood chemistry, hematology, cervical cytology
- Chronic disease
- Disease relevant to ovary, fallopian tube or uterus which could interfere with treatment (eg. Endometrioma, fibroid ≥ 5 cm)
- History of OHSS, ovarian hyper-response (> 30 follicles ≥ 11 mm) PCOS, AFC > 20
- Baseline FSH or LH > 12 IU/L

BMI = body mass index; PCOS = polycystic ovarian syndrome.
Engage Treatment Regimen

**Investigational group**

- **Corifollitropin alfa (150 µg)**

**Placebo**
- rFSH (daily dose 200 IU for 7 days)

**Reference group**

- **Placebo**
  - Corifollitropin alfa (150 µg)

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

- **Daily rFSH** (daily dose ≤200 IU)

**Cycle day 2-3** = **stimulation day 1**

**Stimulation day 5**

**Stimulation day 8**

**hCG as soon as 3 follicles ≥17 mm**

(or the day thereafter)

Adapted with permission from Devroey P et al. Hum Reprod. 2009;24:3063–3072.
Primary End Point: Ongoing PR*

ITT Group

Corifollitropin alfa 150 µg (n=756)

38.9%
No. of embryos transferred: 1.7

rFSH 200 IU/d (n=750)

38.1%
No. of embryos transferred: 1.7

*Defined as the presence of at least 1 fetus with heart activity at least 10 weeks after embryo transfer as assessed by ultrasound scan or Doppler, or confirmed by live birth.

Live birth rate calculated as the number of patients with an ongoing pregnancy with at least 1 liveborn infant relative to the total number of patients in that arm of the Engage trial (ie, per started COS cycle).

ITT = intent to treat; rFSH = recombinant FSH; COS = controlled ovarian stimulation.

Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package WOMN-1010423–0000.
### Co-Primary End Point: Oocytes

<table>
<thead>
<tr>
<th>Corifollitropin alfa 150 µg (n=756)</th>
<th>rFSH 200 IU/d (n=750)</th>
<th>Estimated Difference, ANOVA (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) number of oocytes retrieved</td>
<td>13.7 (8.2)</td>
<td>12.5 (6.7)</td>
</tr>
<tr>
<td>Mean percentage of MII oocytes</td>
<td>78.9%</td>
<td>77.4%</td>
</tr>
</tbody>
</table>

- Quality of oocytes, by percentage of MII oocytes, was comparable between treatments

*P<0.001.

Predefined equivalence range: -3 to +5 oocytes.

ANOVA = analysis of variance; CI = confidence interval; MII = metaphase II.

**2PN Oocytes**

*Restricted to Patients With IVF/ICSI (ITT Group)*

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<thead>
<tr>
<th></th>
<th>Corifollitropin alfa</th>
<th>rFSH</th>
</tr>
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<tr>
<td></td>
<td>150 µg (n=727)</td>
<td>200 IU/d (n=737)</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>66.0 (23.4)</td>
<td>67.6 (22.9)</td>
</tr>
<tr>
<td>2PN oocytes obtained, mean (SD)</td>
<td>8.3 (5.6)</td>
<td>7.4 (4.8)</td>
</tr>
</tbody>
</table>

PN = pronuclear; ITT = intent to treat.

ENGAGE: Safety

- 16 subjects (2.1%) in corifollitropin alfa group and 3 subjects (0.4%) in rFSH group discontinue due to a serious adverse event.
- 53 subjects (7.0%) in corifollitropin alfa group and 47 subjects (6.3%) in rFSH group develop OHSS.
- Incidence of moderate/severe OHSS were 4.1% and 2.7% for the corifollitropin alfa and rFSH, respectively (p = 0.15).
## Corifollitropin alfa Phase 3 Clinical Trials

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**RCT** = randomized controlled trial; **PR** = pregnancy rate; **rFSH** = recombinant FSH.

Ensure Treatment Regimen

Investigational group
Corifollitropin alfa (100 µg)

Placebo rFSH (daily dose 150 IU for 7 days)

Daily rFSH (daily dose ≤200 IU)

Reference group
Placebo Corifollitropin alfa (100 µg)

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

Daily rFSH (daily dose 150 IU for 7 days)

Daily rFSH (daily dose ≤200 IU)

IVF or ICSI

Luteal phase support

Cycle day 2-3 = stimulation day 1
Stimulation day 5
Stimulation day 8
hCG as soon as 3 follicles ≥17 mm (or the day thereafter)

Primary End Point: Number of Oocytes\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin alfa</th>
<th>rFSH</th>
<th>Estimated Difference, ANOVA (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 µg (n=268)</td>
<td>150 IU/d (n=128)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) number of oocytes retrieved</td>
<td>13.3 (7.3)</td>
<td>10.6 (5.9)</td>
<td>2.5\textsuperscript{b} (1.2-3.9)</td>
</tr>
</tbody>
</table>

Quality of oocytes, by percentage of MII oocytes, was comparable between treatments (82.5\% for cofifollitropin alfa and 79.1\% for rFSH)

\textsuperscript{a}Primary end point is to show equivalence in number of cumulus-oocyte complexes retrieved. Predefined equivalence range: -3 to +5 oocytes.

\textsuperscript{b}P<0.001.

rFSH = recombinant FSH; ANOVA = analysis of variance; CI = confidence interval; SD = standard deviation; MII = metaphase II.

This trial was not powered to measure a difference in ongoing pregnancy rates

ITT = intent to treat; rFSH = recombinant FSH.

Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package WOMN-1010195-0000.
Number of Oocytes Retrieved and Total Drug Exposure is Comparable Between Patients in the 2 Dosing Groups\textsuperscript{a}

Mean no. of oocytes per attempt (95\% CI) after treatment with ELONVA®

- **Oocytes**
  - >60 kg: Mean=13.7, n=756
  - ≤60 kg: Mean=13.3, n=268

- **Total Drug Exposure**\textsuperscript{1}
  - >60 kg: 1500 h•ng/mL
  - ≤60 kg: 1500 h•ng/mL

\textsuperscript{a}Based on the Engage and Ensure clinical trials.
1. Ledger et al. *RBM Online* 2011; 23 150-159
## Percentage of Patients With OHSS per Grade (Engage + Ensure)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Corifollitropin alfa (n=1023)</th>
<th>rFSH (n=880)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>3.0 (31)</td>
<td>3.5 (31)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.2 (22)</td>
<td>1.3 (11)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.8 (18)</td>
<td>1.3 (11)</td>
</tr>
</tbody>
</table>

*All subjects treated

No significant difference between groups.


<table>
<thead>
<tr>
<th>Cumulative Ongoing Pregnancy Rate, % (n/N)</th>
</tr>
</thead>
</table>
| **ELONVA™**
  (corifollitropin alfa)
  (n=756) | **rFSH**
  (n=750) |
| 47.2 (357/756) | 44.9 (337/750) |

Estimated difference between treatment groups (adjusted for region and age): 2.3% in favour of ELONVA (95% CI, 2.7%–7.2%, NS)

Trust Trial Design

• Design
  – Phase III, uncontrolled, repeated cycle trial

• Primary objective
  – To assess the non-immunogenicity and safety of corifollitropin alfa in repeated COS cycles

• Main endpoints
  – Antibody formation against corifollitropin alfa
  – Occurrence of (S)AEs
  – Occurrence of moderate/severe OHSS

Can we use corifollitropin alfa in repeated (up to 3) cycles? The TRUST trial.

Corifollitropin alfa 150 µg/0.5 mL

7 days

(rec)FSH daily ≤ 225 IU

GnRH antagonist (0.25 mg/daily) Day 5 or 6 through day hCG

(rec)hCG

Oocyte retrieval
IVF ICSI
ET (max 3)

Luteal phase support (vaginal P)

As soon as 3 follicles ≥ 17 mm

Cycle Day 2-3 = Stimulation Day 1

Stimulation Day 5 or 6

Stimulation Day 8

# Immunogenicity Testing

## All-subjects-treated group

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Number of subjects treated with corifollitropin alfa</th>
<th>Number of subjects tested for antibodies</th>
<th>Observed clinically relevant immunogenicity incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>682</td>
<td>681</td>
<td>0.0</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>375</td>
<td>372</td>
<td>0.0</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>198</td>
<td>192</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Conclusion:** No immunogenicity found

### Number of Subjects with OHSS per Grade

**All-subjects-treated group**

<table>
<thead>
<tr>
<th>OHSS incidences (WHO criteria)</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I (mild)</td>
<td>1.8%</td>
<td>0.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Grade II (moderate)</td>
<td>0.9%</td>
<td>0.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Grade III (severe)</td>
<td>0.9%</td>
<td>0.5%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Trust

Conclusions

• Repeated exposure to a single injection of 150 µg corifollitropin alfa over 3 COS cycles resulted in:
  – No concerns related to immunogenicity
  – A similar ovarian response in each of the 3 COS cycles
  – A low incidence of OHSS

Pursue Treatment Regimen

Investigational arm

Placebo rFSH (daily dose for 7 days 300 IU)  
rFSH (follitropin beta) (daily dose ≤ 300 IU)

Corifollitropin alfa 150 µg

Reference arm

Placebo  
Corifollitropin alfa

GnRH antagonist (ganirelix, 0.25 mg/d)  
Day 5 up to day of hCG

rFSH (follitropin beta) (daily dose for 7 days 300 IU)  
rFSH (follitropin beta) (daily dose ≤ 300 IU)

Cycle day 2–3 = Stimulation day 1  
Stimulation day 5  
Stimulation day 8  
rhCG (Ovidrel 250 µg) as soon as 3 follicles ≥ 17 mm (or 1-day later)

Oocyte retrieval  
IVF ICSI

Luteal phase support  
Crinone 8%, 90 mg/d

ET 2 good-quality embryos on day 3

GnRH, gonadotropin-releasing hormone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; ET, embryo transfer; rhCG, recombinant hCG.
Crinone 8% (progesterone gel), Columbia Laboratories, Inc.
Ovidrel PreFilled Syringe (choriogonadotropin alfa injection), Merck Serono SA.
Most Important Entry Criteria

• **Inclusion criteria**
  – Women with an indication for controlled ovarian stimulation and IVF/ICSI
  – Age ≥ 35 and ≤ 42 years
  – Body weight ≥ 50 kg, and body mass index ≥ 18 and ≤ 32 kg/m²
  – Regular spontaneous menstrual cycle (cycle length 24–35 days)
  – Availability of ejaculatory sperm

• **Exclusion criteria**
  – Recent history of/or current endocrine abnormality
  – History of/or current polycystic ovary syndrome (PCOS)
  – > 20 basal antral follicles < 11 mm (both ovaries combined)
  – Previous hyper-response or ovarian hyperstimulation syndrome (OHSS)
  – Previous low ovarian response or no ovarian response to FSH/human menopausal gonadotropins (hMG)
  – FSH > 15.0 IU/L or luteinizing hormone (LH) > 12.0 IU/L
  – Smoking or recently stopped smoking
# Number of Oocytes Retrieved

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin Alfa 150 µg</th>
<th>rFSH 300 IU/day</th>
<th>Estimated Difference ANOVA (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per attempt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 694</td>
<td>n = 696</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.7 (7.2)</td>
<td>10.3 (6.8)</td>
<td>0.5 (−0.2 to 1.2)</td>
</tr>
<tr>
<td><strong>Per oocyte pick-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 675</td>
<td>n = 671</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.0 (7.0)</td>
<td>10.6 (6.7)</td>
<td>0.4 (−0.3 to 1.1)</td>
</tr>
</tbody>
</table>
## Number and Quality of Embryos Transferred

*(ITT Group\(^a\))*

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin Alfa 150 µg N=632</th>
<th>rFSH 300 IU/day N=647</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Embryos transferred</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All embryos, mean (SD)</td>
<td>1.9 (0.3)</td>
<td>1.9 (0.2)</td>
</tr>
<tr>
<td>Grade 1 and 2 embryos, mean (SD)</td>
<td>1.4 (0.8)</td>
<td>1.4 (0.8)</td>
</tr>
<tr>
<td><strong>% subjects with:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 embryo transferred</td>
<td>6.5</td>
<td>5.6</td>
</tr>
<tr>
<td>2 embryos transferred</td>
<td>93.4</td>
<td>94.3</td>
</tr>
<tr>
<td>3 embryos transferred</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\(^a\)Restricted to subjects with embryo transfer.
## Vital Pregnancy Rates

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin Alfa 150 µg</th>
<th>rFSH 300 IU/day</th>
<th>Estimated Difference(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per started cycle, % (n/N)</td>
<td>23.9 (166/694)</td>
<td>26.9 (187/696)</td>
<td>−3.0 (−7.4 to 1.4)</td>
</tr>
<tr>
<td>≤ 38 years</td>
<td>30.4 (122/401)</td>
<td>33.2 (134/404)</td>
<td></td>
</tr>
<tr>
<td>&gt; 38 years</td>
<td>15.0 (44/293)</td>
<td>18.2 (53/292)</td>
<td></td>
</tr>
<tr>
<td>Per embryo transfer, % (n/N)</td>
<td>26.3 (166/632)</td>
<td>28.9 (187/647)</td>
<td>−2.7 (−7.4 to 2.0)</td>
</tr>
</tbody>
</table>

\(^a\)Linear model including treatment group and age class (≤ 38 years vs >38 years as randomized) as independent factors.
## Ongoing Pregnancy Rates

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin Alfa 150 µg</th>
<th>rFSH 300 IU/day</th>
<th>Estimated Difference&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per started cycle, % (n/N)</td>
<td>22.2 (154/694)</td>
<td>24.0 (167/696)</td>
<td>–1.9 (–6.1 to 2.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Linear model including treatment group and age class (≤ 38 years vs > 38 years as randomized) as independent factors.
• Down regulation with 0.1 mg triptorelin in the mid-luteal phase
• Single dose of 150 μg or 100 μg corifollitropin alpha followed by daily dose of rFSH (follitropin beta) from day 8 of stimulation
• No statistical analysis
<table>
<thead>
<tr>
<th>Clinical outcome after treatment with corifollitropin alfa in a long GnRH agonist protocol.</th>
<th>100 μg corifollitropin alfa (n = 25)</th>
<th>150 μg corifollitropin alfa (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles (≥ 11 mm) on day 8</td>
<td>10.7 (5.7)</td>
<td>11.9 (5.0)</td>
</tr>
<tr>
<td>Median serum E₂ on day 8 (pmol/L)</td>
<td>3,780</td>
<td>3,712</td>
</tr>
<tr>
<td>Follicles (≥ 11 mm) on day of hCG</td>
<td>17.5 (5.5)</td>
<td>18.3 (6.4)</td>
</tr>
<tr>
<td>Median serum E₂ on day of hCG (pmol/L)</td>
<td>10,019</td>
<td>10,221</td>
</tr>
<tr>
<td>Number of oocytes, per started cycle</td>
<td>15.4 (6.7)</td>
<td>17.8 (5.1)</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>71.6</td>
<td>69.6</td>
</tr>
<tr>
<td>Number of embryos on day 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10.0 (5.1)</td>
<td>10.8 (4.9)</td>
</tr>
<tr>
<td>Good quality embryos</td>
<td>4.8 (4.8)</td>
<td>4.8 (4.5)</td>
</tr>
<tr>
<td>Number of embryos on day 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.9 (4.4)</td>
<td>8.0 (5.1)</td>
</tr>
<tr>
<td>Good quality embryos</td>
<td>1.9 (2.0)</td>
<td>1.4 (1.4)</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>1.1 (0.3)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td>Subjects with SET, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with elective SET, n (%)</td>
<td>20 (90.9)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Subjects with DET, n (%)</td>
<td>9 (40.9)</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>Number of embryos cryopreserved</td>
<td>2 (9.1)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Pregnancy rate per started cycle, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td>10 (40.0)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Clinical&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (32.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Vital&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (32.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Ongoing&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7 (28.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Pregnancy rate per embryo transfer, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td>10 (45.5)</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>Clinical&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (36.4)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Vital&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (36.4)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Ongoing&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7 (31.8)</td>
<td>8 (44.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Clinical pregnancy

<sup>b</sup> Vital pregnancy

<sup>c</sup> Ongoing pregnancy
# Summary of Phase III ELONVA study

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial aim</th>
<th>Type</th>
<th>GnRH</th>
<th>n</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engage¹</td>
<td>Non-inferiority for ongoing preg</td>
<td>RCT</td>
<td>Antag</td>
<td>1506</td>
<td>Equivalent preg rates +1.2 oocytes with corifollitropin alfa</td>
</tr>
<tr>
<td>Ensure²</td>
<td>Equivalency for no. of oocytes</td>
<td>RCT</td>
<td>Antag</td>
<td>396</td>
<td>+2.5 oocytes with corifollitropin alfa</td>
</tr>
<tr>
<td>Trust³</td>
<td>Non-immunogenicity of corifollitropin alfa</td>
<td>Uncontrolled, repetitive administration</td>
<td>Antag</td>
<td>682</td>
<td>no immunogenicity</td>
</tr>
<tr>
<td>Pursue⁴</td>
<td>Non-inferiority for clinical preg in patients 35-42 yrs</td>
<td>RCT</td>
<td>Antag</td>
<td>1391</td>
<td>Equivalent Preg Rates Equivalent Oocyte no.</td>
</tr>
<tr>
<td>Pilot Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Realize⁵</td>
<td>No. of oocytes and OHSS</td>
<td>Uncontrolled, pilot</td>
<td>Long agonist</td>
<td>49</td>
<td>High number of oocytes (~15-18 oocytes)</td>
</tr>
</tbody>
</table>

Similar Treatment Duration for 100 μg (≤60 kg) and 150 μg (>60 kg)

One-third of the patients, regardless of the corifollitropin alfa dose, met the criteria for hCG injection before or on stimulation day 8

Ongoing Pregnancy Rates for Patients Meeting hCG Criteria on or Before Day 8 vs After Day 8

ELONVA® (corifollitropin alfa)

- n=249, 43.8%
- n=472, 37.3%

rFSH

- n=322, 40.1%
- n=417, 37.4%

ELONVA is a registered trademark of Merck & Co., Inc.

rFSH = recombinant FSH.

Ongoing Pregnancy Rates: hCG Delay of 1 Day

p = 0.29

<table>
<thead>
<tr>
<th>Group</th>
<th>No delay in hCG</th>
<th>1-day delay in hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELONVA® (corifollitropin alfa)</td>
<td>40.0%</td>
<td>38.9%</td>
</tr>
<tr>
<td>rFSH</td>
<td>37.8%</td>
<td>41.8%</td>
</tr>
</tbody>
</table>

n=503 n=193
n=524 n=201

ELONVA is a registered trademark of Merck & Co., Inc.
rFSH = recombinant FSH.
Considerations for Patients >90 kg

- A dose of 150 µg ELONVA® is sufficient to initiate and sustain ovarian response, even in subjects >90 kg

- Patients >90 kg are generally overweight and have a high percentage of fat tissue

- Distribution of ELONVA® is limited to the extracellular fluids. Fat tissue has a low fluid content and is not expected to significantly increase the volume of distribution of ELONVA®

- For patients weighing >90 kg, the relationship between drug exposure and body weight seems to plateau

---

What if: 100-µg Dose in Patients >60 kg?

No reduction of ovarian response

Insufficient exposure resulting in a risk of cycle cancellation: Drop of FSH activity below threshold

FSH Activity

Stimulation day

Threshold

DEGREE

ELONVA®

What if: 150-µg Dose in Patients ≤60 kg?

Effect is at a maximum; this will not result in a much higher ovarian response.

May lead to overexposure and increase risk of overstimulation.

Threshold

Maximum response

FSH activity

Stimulation day

Long-acting FSH versus daily FSH for women undergoing assisted reproduction

Annefloor W Pouwer¹, Cindy Farquhar², Jan AM Kremer³

Main results

We included four RCTs with a total of 2335 participants. A comparison of long-acting FSH versus daily FSH did not show evidence of difference in effect on overall live birth rate (Peto OR 0.92; 95% CI 0.76 to 1.10, 4 RCTs, 2335 women) or OHSS (Peto OR 1.12; 95% CI 0.79 to 1.60, 4 RCTs, 2335 women). We compared subgroups by dose of long-acting FSH. There was evidence of reduced live birth rate in women who received lower doses (60 to 120 μg) of long-acting FSH compared to daily FSH (Peto OR 0.60; 95% CI 0.40 to 0.91, 3 RCTs, 645 women). There was no evidence of effect on live births in the medium dose subgroup (Peto OR 1.03; 95% CI 0.84 to 1.27) and no evidence of effect on clinical pregnancy rate, ongoing pregnancy rate, multiple pregnancy rate, miscarriage rate or ectopic pregnancy rate.

Authors’ conclusions

The use of a medium dose of long-acting FSH is a safe treatment option and equally effective compared to daily FSH. Further research is needed to determine if long-acting FSH is safe and effective for use in hyper- or poor responders and in women with all causes of subfertility.
Corifollitropin α followed by menotropin for poor ovarian responders’ trial (COMPORT): a protocol of a multicentre randomised trial

Nikolaos P Polyzos,¹ Michel Camus,¹ Joaquin Llacer,² Konstantinos Pantos,³ Herman Tournaye¹
COMPORT study

- Multicenter, open-label, phase III RCT
- Belgium, Spain and Greece
- Computer generated central randomization
- 150 patients (1:1 allocation)
- < 40 years old
- Poor ovarian response “Bologna criteria”
- Primary outcome: ongoing pregnancy rate
- Secondary outcome: clinical and biochemical pregnancy, number of oocytes retrieved
Now Corifollitropin alfa
What is the future?
Neonatal Fc receptor (FcRn) candidate transport partway

FcRn responsible for the transport of IgG from maternal milk into newborn bloodstream

FcRn detect in epithelial cells of adult human lung and intestine

α and β subunit of FSH can fuse with Fc domain of IgG
Oral and pulmonary delivery of FSH–Fc fusion proteins via neonatal Fc receptor-mediated transcytosis


Figure 2. Ovarian weight in 21 day old female rats treated with a single s.c. dose of 1 nmol/kg recombinant FSH, single chain FSH–Fc or heterodimer FSH–Fc. Ovarian weight was measured 72 h after dosing. Data are presented as average ovarian weight ± SD. n = 10/group.
Half-life of heterodimer FSH-Fc in cynomolgus monkeys is 182 – 219 hours (significantly longer than half-life of rFSH of 24 hours)

FSH-Fc fusion proteins is a potential way for oral and intranasal FSH delivery system with reduced dosing frequency
THANK YOU