Corifollitropin alfa: a novel long-acting recombinant follicle stimulating hormone agonist for controlled ovarian stimulation

D Loutradis, A Vlismas† & P Drakakis

The advent of recombinant technology has made possible the production of modified proteins with desired properties. Corifollitropin alfa is a successful example of the first available, long-acting, follicle stimulating hormone. Corifollitropin alfa has prolonged half-life and a slower absorption rate, but has the same receptor binding and biological activity as recombinant FSH (rFSH). Its application is associated with the arrival of a novel simplified approach for controlled ovarian stimulation in IVF patients. Different studies have proven the efficiency of a single corifollitropin alfa dose to initiate and sustain multiple follicular development in a gonadotropin-releasing hormone (GnRH) antagonist protocol. Finally, corifollitropin alfa is well tolerated and is not correlated with serious adverse events, except of the slightly higher incidence of ovarian hyperstimulation syndrome compared with traditional management with rFSH.

Corifollitropin alfa (Elonva®, NV Organon, The Netherlands, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ USA) is the first available long-acting recombinant follicle stimulating hormone (rFSH) preparation, that has recently received approval from the European Commission for controlled ovarian stimulation in a gonadotropin-releasing hormone (GnRH) antagonist protocol in women undergoing assisted reproduction [101,102]. A single subcutaneous injection of Corifollitropin alfa has similar efficacy to a once-daily treatment with rFSH for 7 days in a controlled ovarian stimulation treatment cycle [1]. The clinical Phase III trial for corifollitropin alfa has been completed, and the preparation is ready for clinical use in combination with a GnRH antagonist for the induction of multifolicular development in women participating in assisted reproductive programs. Although it is not well established, it is advisable that corifollitropin alfa should be avoided in patients with a high basal antral follicle count (AFC >20), with a previous hyper-response or a history of ovarian hyperstimulation syndrome [102].

Follicle stimulating hormone administration is considered the cornerstone of contemporary infertility treatment. Currently several commercially available preparations with FSH activity are on market, either extracted and purified from urine or produced recombinantly. However, the limitation of the FSH preparations is their relatively short half-life and rapid metabolic clearance, thus requiring daily subcutaneous or intramuscular administration to induce follicle development. Prolonged daily-treatment regimens raise concerns regarding high drop-out rates and may also be associated with poor patient compliance [2,3].

Breakthroughs in recombinant technology aim to overcome these limitations. Synthesis of modified glycoprotein molecules with desired optimal pharmacokinetic profiles without alterations in receptor binding activity or hormone efficiency. The most widely used approach is the production of hyperglycosylated, long-acting FSH analogues that modify the structure and carbohydrate moieties of the wild FSH molecule. Modifications in oligosaccharide chains of glycoprotein hormones have been proven to be associated with changes in intracellular stability, subunit assembly and secretion and signal transduction, but can also influence the metabolic clearance and in vivo bioactivity of the hormone [4,5]. Different approaches have been proposed with the introduction of one or more additional O- or N-linked glycosylation sites along the polypeptide backbone of FSH-α and β-subunits, in distant positions from the presumed receptor-binding area. These modifications alter the sialic content, reducing the hormone elimination via glomerular filtration, and consequently extend its circulating half-life [5–7]. Examples of successful effort for enhancing the FSH biopotency have been the addition of an extra glycosylation site at the N-terminus of the α-polypeptide chain of FSH [7], the construction of a single-chain fusion hormone analogue, containing variable numbers of additional N-linked glycosylation sites [8–10].

Corifollitropin alfa (Elonva®, NV Organon, The Netherlands, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ USA) is the first available long-acting recombinant follicle stimulating hormone (rFSH) preparation, that has recently received approval from the European Commission for controlled ovarian stimulation in a gonadotropin-releasing hormone (GnRH) antagonist protocol in women undergoing assisted reproduction [101,102]. A single subcutaneous injection of Corifollitropin alfa has similar efficacy to a once-daily treatment with rFSH for 7 days in a controlled ovarian stimulation treatment cycle [1]. The clinical Phase III trial for corifollitropin alfa has been completed, and the preparation is ready for clinical use in combination with a GnRH antagonist for the induction of multifolicular development in women participating in assisted reproductive programs. Although it is not well established, it is advisable that corifollitropin alfa should be avoided in patients with a high basal antral follicle count (AFC >20), with a previous hyper-response or a history of ovarian hyperstimulation syndrome [102].

Follicle stimulating hormone administration is considered the cornerstone of contemporary infertility treatment. Currently several commercially available preparations with FSH activity are on market, either extracted and purified from urine or produced recombinantly. However, the limitation of the FSH preparations is their relatively short half-life and rapid metabolic clearance, thus requiring daily subcutaneous or intramuscular administration to induce follicle development. Prolonged daily-treatment regimens raise concerns regarding high drop-out rates and may also be associated with poor patient compliance [2,3].

Breakthroughs in recombinant technology aim to overcome these limitations. Synthesis of modified glycoprotein molecules with desired optimal pharmacokinetic profiles without alterations in receptor binding activity or hormone efficiency. The most widely used approach is the production of hyperglycosylated, long-acting FSH analogues that modify the structure and carbohydrate moieties of the wild FSH molecule. Modifications in oligosaccharide chains of glycoprotein hormones have been proven to be associated with changes in intracellular stability, subunit assembly and secretion and signal transduction, but can also influence the metabolic clearance and in vivo bioactivity of the hormone [4,5]. Different approaches have been proposed with the introduction of one or more additional O- or N-linked glycosylation sites along the polypeptide backbone of FSH-α and β-subunits, in distant positions from the presumed receptor-binding area. These modifications alter the sialic content, reducing the hormone elimination via glomerular filtration, and consequently extend its circulating half-life [5–7]. Examples of successful effort for enhancing the FSH biopotency have been the addition of an extra glycosylation site at the N-terminus of the α-polypeptide chain of FSH [7], the construction of a single-chain fusion hormone analogue, containing variable numbers of additional N-linked glycosylation sites [8–10].

Corifollitropin alfa (Elonva®, NV Organon, The Netherlands, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ USA) is the first available long-acting recombinant follicle stimulating hormone (rFSH) preparation, that has recently received approval from the European Commission for controlled ovarian stimulation in a gonadotropin-releasing hormone (GnRH) antagonist protocol in women undergoing assisted reproduction [101,102]. A single subcutaneous injection of Corifollitropin alfa has similar efficacy to a once-daily treatment with rFSH for 7 days in a controlled ovarian stimulation treatment cycle [1]. The clinical Phase III trial for corifollitropin alfa has been completed, and the preparation is ready for clinical use in combination with a GnRH antagonist for the induction of multifolicular development in women participating in assisted reproductive programs. Although it is not well established, it is advisable that corifollitropin alfa should be avoided in patients with a high basal antral follicle count (AFC >20), with a previous hyper-response or a history of ovarian hyperstimulation syndrome [102].

Follicle stimulating hormone administration is considered the cornerstone of contemporary infertility treatment. Currently several commercially available preparations with FSH activity are on market, either extracted and purified from urine or produced recombinantly. However, the limitation of the FSH preparations is their relatively short half-life and rapid metabolic clearance, thus requiring daily subcutaneous or intramuscular administration to induce follicle development. Prolonged daily-treatment regimens raise concerns regarding high drop-out rates and may also be associated with poor patient compliance [2,3].

Breakthroughs in recombinant technology aim to overcome these limitations. Synthesis of modified glycoprotein molecules with desired optimal pharmacokinetic profiles without alterations in receptor binding activity or hormone efficiency. The most widely used approach is the production of hyperglycosylated, long-acting FSH analogues that modify the structure and carbohydrate moieties of the wild FSH molecule. Modifications in oligosaccharide chains of glycoprotein hormones have been proven to be associated with changes in intracellular stability, subunit assembly and secretion and signal transduction, but can also influence the metabolic clearance and in vivo bioactivity of the hormone [4,5]. Different approaches have been proposed with the introduction of one or more additional O- or N-linked glycosylation sites along the polypeptide backbone of FSH-α and β-subunits, in distant positions from the presumed receptor-binding area. These modifications alter the sialic content, reducing the hormone elimination via glomerular filtration, and consequently extend its circulating half-life [5–7]. Examples of successful effort for enhancing the FSH biopotency have been the addition of an extra glycosylation site at the N-terminus of the α-polypeptide chain of FSH [7], the construction of a single-chain fusion hormone analogue, containing variable numbers of additional N-linked glycosylation sites [8–10].
The ultimate goal for the pharmaceutical industry is to employ infertility agents that demonstrate maximum efficacy and enhanced safety, with minimal adverse effects and reduced cost. The contemporary trend is directed towards simplified approaches, but without significant reduction in pregnancy rate [17]. Corifollitropin alfa was developed in order to provide a simple, more convenient and patient friendly treatment regimen in women undergoing IVF [18].

The compound & its chemistry
Corifollitropin alfa is a heterodimer that consists of two non-covalently linked subunits: an α-subunit that is identical to that of the other glycoprotein hormones (FSH, LH, hCG, TSH), and a hybrid β-subunit that arises from the fusion of the β-subunit of FSH with the CTP of hCG β-subunit. The addition of CTP to the β-subunit of FSH using site directed mutagenesis and gene transfer techniques lead to the production of a novel class of gonadotrophins, with prolonged duration of FSH activity described as sustained follicular stimulant.

Overview of the market
Infertility represents the most important reproductive health issue worldwide, with serious social and psychological implications not only for the couple, but also for the entire society [15]. It is estimated that 72.4 million people are currently infertile and 40.5 million of these individuals are seeking infertility medical care [16]. The prevalence of infertility lasting for over 12 months in women aged 20–44 years old appears to be similar in developed and developing nations with an estimated overall median prevalence of 9%, ranging from 3.5–16% [16]. The majority of the infertile population wish to have a child at some point in their life, however, only half will seek medical care.

During the last three decades, significant progress has been made in the field of assisted reproduction, and due to developments in biotechnology new highly-purified pharmaceutical agents have been introduced that give promise for improved results. Controlled ovarian stimulation with the exogenous administration of gonadotrophins is essential in assisted reproduction and has enabled conception to many infertile couples. However, despite all the advances in drug production and improvement of ovarian stimulation protocols, the implantation rates continue to remain relatively low.
Corifollitropin a FSH agonist for controlled ovarian stimulation – DRUG EVALUATION

a model of immature female rats occurred much slower than that of the rFSH [14]. The differences in serum plasma concentrations of FSH-CTP and rFSH determined by radioimmunoassay became notable even within the first 4 h. The chimera levels were still present in serum after 24 h, while rFSH levels had been reduced to basal level after 8–24 h [14].

The pharmacokinetic parameters of corifollitropin alfa were evaluated in the first human study conducted in hypogonadotrophic hypogonadal males as part of a Phase I clinical trial [21]. A total of 13 hypogonadotrophic hypogonadal males were included in the study and they received four subcutaneous injections of 15 µg corifollitropin alfa with an interval ranging from 27 to 39 days. The elimination half-life (t½) of corifollitropin alfa (94.7 ± 26.2 h) was 2–3 fold longer than that of rFSH (Puregon) (33.4 ± 4.2 h) [22]. The absorption rate was also slower with a mean maximum serum concentration (Cmax) being 0.426 ± 0.116 ng/ml that was reached on 46 ± 18 h after administration, while the time to reach maximum serum concentration (Tmax) for rFSH was 12.6 ± 6.2 h.

In a further Phase I study, the pharmacokinetic profile of corifollitropin alfa was determined in healthy female volunteers whose pituitary glands were suppressed by oral contraceptives [23]. Following single subcutaneous injections of 15, 30, 60 and 120 µg corifollitropin alfa, dose proportional correlation was observed for mean AUC (area under the curve from time zero to infinity) and Cmax ratios, whereas tmax (ranged from 36–48 h) and t½ (60–75 h) was dose independent. The mean dose normalized peak plasma level (dn-Cmax) was between 0.022 and 0.028, with a dose normalized corresponding area under the curve (dn-AUC) varied from 2.67 to 4.11 ng.h/ml/µg (Table I) [23].

In women undergoing controlled ovarian stimulation for IVF or Intracytoplasmic Sperm Injection (ICSI), the pharmacokinetic data of corifollitropin alfa (120, 180 and 240 µg) were in accordance with the values obtained in previous Phase I studies [24]. The mean elimination half time (t½) and tmax were 65 h and 24.7 h respectively, while the AUC and Cmax ratios showed dose proportionality (Table I).

The pharmacokinetic profile after administration of a single dose of 7.5–60 µg corifollitropin alfa in anovulatory women was consistent with the data observed in previous studies with AUC and Cmax being strongly correlated to the dose. The Tmax and t½ values were between 26–28 h and 77–86 h independent of the dose administered [25]. The only exception was the t½ value in the lowest-dose group (7.5 µg) (Table I).

Body weight inversely affects corifollitropin alfa exposure, as expressed with Cmax and

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>n</th>
<th>Tmax (h)</th>
<th>T½ (h)</th>
<th>Cmax (ng/ml)</th>
<th>Dn Cmax (ng/ml)/µg</th>
<th>AUC0–∞ (ng.h/ml)</th>
<th>Dn-AUC0–∞ (ng.h/ml)/µg</th>
<th>CL/F (l/h)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>13</td>
<td>28.6</td>
<td>110</td>
<td>0.203</td>
<td>0.027</td>
<td>35.8</td>
<td>4.77</td>
<td>0.22</td>
<td>[25]</td>
</tr>
<tr>
<td>15</td>
<td>9</td>
<td>26.9</td>
<td>86.0</td>
<td>0.334</td>
<td>0.0223</td>
<td>50.2</td>
<td>3.35</td>
<td>0.31</td>
<td>[25]</td>
</tr>
<tr>
<td>15</td>
<td>8</td>
<td>36</td>
<td>68.4</td>
<td>0.416</td>
<td>0.0278</td>
<td>61.7</td>
<td>4.11</td>
<td>0.243</td>
<td>[23]</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>47.7</td>
<td>89.0</td>
<td>0.412</td>
<td>0.0278</td>
<td>76.0</td>
<td>7.69</td>
<td>0.31</td>
<td>[21]</td>
</tr>
<tr>
<td>30</td>
<td>11</td>
<td>26.0</td>
<td>77.4</td>
<td>0.761</td>
<td>0.0254</td>
<td>105</td>
<td>3.49</td>
<td>0.30</td>
<td>[25]</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td>48</td>
<td>59.5</td>
<td>0.661</td>
<td>0.0220</td>
<td>80.1</td>
<td>2.67</td>
<td>0.375</td>
<td>[23]</td>
</tr>
<tr>
<td>60</td>
<td>8</td>
<td>26.5</td>
<td>83.9</td>
<td>1.3</td>
<td>0.0216</td>
<td>189</td>
<td>3.15</td>
<td>0.35</td>
<td>[25]</td>
</tr>
<tr>
<td>60</td>
<td>7</td>
<td>36</td>
<td>64.8</td>
<td>1.49</td>
<td>0.0249</td>
<td>187</td>
<td>3.11</td>
<td>0.321</td>
<td>[23]</td>
</tr>
<tr>
<td>60</td>
<td>75</td>
<td>41.9</td>
<td>65.7</td>
<td>1.9</td>
<td>0.0317</td>
<td>275</td>
<td>4.58</td>
<td>0.37</td>
<td>[26]</td>
</tr>
<tr>
<td>120</td>
<td>6</td>
<td>36</td>
<td>74.5</td>
<td>3.27</td>
<td>0.0272</td>
<td>385</td>
<td>3.21</td>
<td>0.311</td>
<td>[23]</td>
</tr>
<tr>
<td>120</td>
<td>25</td>
<td>24.6</td>
<td>64.1</td>
<td>4.3</td>
<td>0.0355</td>
<td>511.7</td>
<td>4.3</td>
<td>0.35</td>
<td>[24]</td>
</tr>
<tr>
<td>120</td>
<td>75</td>
<td>41.2</td>
<td>65.3</td>
<td>3.71</td>
<td>0.0309</td>
<td>534</td>
<td>4.45</td>
<td>0.46</td>
<td>[26]</td>
</tr>
<tr>
<td>180</td>
<td>24</td>
<td>24.8</td>
<td>65.6</td>
<td>6.6</td>
<td>0.0367</td>
<td>815.2</td>
<td>4.5</td>
<td>0.54</td>
<td>[26]</td>
</tr>
<tr>
<td>180</td>
<td>76</td>
<td>44.1</td>
<td>66.0</td>
<td>5.53</td>
<td>0.0307</td>
<td>827</td>
<td>4.59</td>
<td>0.54</td>
<td>[26]</td>
</tr>
<tr>
<td>240</td>
<td>25</td>
<td>24.7</td>
<td>64.9</td>
<td>8.9</td>
<td>0.0369</td>
<td>1080.0</td>
<td>4.5</td>
<td>0.54</td>
<td>[26]</td>
</tr>
</tbody>
</table>

\( AUC_{∞}: \) Area under the curve from time zero to infinity; CL/F: total serum clearance; Cmax: Maximum serum concentration; Dn-AUC: = Dose-normalized area under the curve from zero to infinity; Dn Cmax: Dose-normalized maximum serum concentration; t½: Elimination half-life; Tmax: Time to maximum serum concentration.
AUC and is an additional factor that should be addressed to determine the corifollitropin alfa dose in controlled ovarian stimulation protocols [26].

Briefly, following a single subcutaneous dose of corifollitropin alfa, the absorption rate is slow and the elimination half-life time is 2–3 fold longer than that of rFSH. The AUC and Cmax are dose related, while the tmax and t½ remain steady in different dose regimens. The values of all these parameters are similar in both healthy volunteers and IVF patients suggesting that the endocrine status of women have no impact on the pharmacokinetic profile. Finally, the body weight should be taken into consideration before deciding on the optimal dose regimen in a controlled ovarian stimulation treatment cycle.

Clinical efficacy

**Phase I**

In a clinical Phase I non-randomized clinical trial (NCT00647933) in healthy pituitary-suppressed women of reproductive age, the effects of a single dose of 15, 30, 60 and 120-µg corifollitropin alfa on follicular development and serum hormones levels were assessed [23]. Follicles above 8 mm were developed only in the two highest dose groups, whereas follicles between 12.0 and 15.9 mm were present only in the 120 µg group. The maximum number of follicles above 5 mm was measured on day 5, 6, 7 and 9 (median) in the 15, 30, 60 and 120-µg dose group, respectively. Follicular growth was observed in almost all of the women with establishment of a dose-related increase in both the number and diameter of follicles. A single injection of 120 µg corifollitropin alfa is able to sustain multifollicular growth with a pattern of growth that is slightly reduced compared with that of daily administration of 150 or 225 IU of rFSH for 7 days. Maximum serum levels of inhibin-B were observed 2–3 days earlier than the day of the peak follicular development in different study groups [23].

Another clinical Phase I study in hypogonadotrophic hypogonadal males, administration of corifollitropin alfa is associated with an increase in inhibin-B levels [21].

**Phase II**

In a Phase II randomized clinical trial (NCT00702806), the efficacy of single dose regimens of corifollitropin alfa (120, 180 and 240 µg) to stimulate multifollicular development was determined in IVF patients undergoing controlled ovarian stimulation and was compared with daily 150 IU rFSH administration [24]. The differences in duration of stimulation, the number of rFSH ampoules administered from day 8 onwards, the number of follicles above 11 mm that developed or the numbers of follicles retrieved were not statistically significant between the four study groups. On day 8, the number of follicles above 17 mm increased in a dose-related manner, whereas on the day of hCG administration, a dose-dependent relationship was observed only for the number of follicles above 15 mm. There were no significant differences in the number of viable embryos available for embryo transfer or in pregnancy rates. The mean number of retrieved oocytes was higher in the three corifollitropin alfa groups compared with the rFSH treated group. This study showed for the first time that a single

### Table 2. Clinical outcome after treatment with corifollitropin alfa.

<table>
<thead>
<tr>
<th>Dose of corifollitropin alfa (µg)</th>
<th>60 (n = 78)</th>
<th>120 (n = 25)</th>
<th>120 (n = 77)</th>
<th>180 (n = 24)</th>
<th>180 (n = 79)</th>
<th>240 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of ovarian stimulation from day 8 (days)</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total dose of rFSH from day 8 (IU)</td>
<td>600</td>
<td>450</td>
<td>450</td>
<td>450</td>
<td>300</td>
<td>450</td>
</tr>
<tr>
<td>Follicles ≥11 mm on day 8 (n)</td>
<td>6.8 ± 4.4</td>
<td>8.8 ± 5.6</td>
<td>10.1 ± 6.1</td>
<td>9.3 ± 5.7</td>
<td>12.8 ± 7.5</td>
<td>10.3 ± 6.6</td>
</tr>
<tr>
<td>Follicles ≥11 mm on day of hCG (n)</td>
<td>11.4 ± 5.3</td>
<td>12.7 ± 6.8</td>
<td>13.5 ± 6.5</td>
<td>13.5 ± 7.1</td>
<td>16.4 ± 7.2</td>
<td>15.5 ± 8.3</td>
</tr>
<tr>
<td>Oocytes retrieved per cycle (n)</td>
<td>5.2 ± 5.5</td>
<td>11.0 ± 7.1</td>
<td>10.3 ± 6.3</td>
<td>11.1 ± 7.5</td>
<td>12.5 ± 8.0</td>
<td>12.0 ± 7.3</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>60.5 ± 27.1</td>
<td>73 ± 27</td>
<td>65.2 ± 23.9</td>
<td>68 ± 31</td>
<td>59.8 ± 22.7</td>
<td>67 ± 31</td>
</tr>
<tr>
<td>No. of embryos (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Total</td>
<td>4.9 ± 3.3</td>
<td>8.5 ± 5.5</td>
<td>7.1 ± 4.1</td>
<td>6.6 ± 4.9</td>
<td>8.2 ± 6.5</td>
<td>7.3 ± 5.9</td>
</tr>
<tr>
<td>– Good quality</td>
<td>2.2 ± 2.0</td>
<td>4.8 ± 5.0</td>
<td>3.5 ± 2.7</td>
<td>3.8 ± 3.3</td>
<td>3.5 ± 3.4</td>
<td>3.9 ± 4.1</td>
</tr>
<tr>
<td>– Transferred</td>
<td>1.3 ± 0.7</td>
<td>2.0 ± 0.2</td>
<td>1.4 ± 0.7</td>
<td>2.0 ± 0.5</td>
<td>1.3 ± 0.7</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Ongoing pregnancy rate per cycle</td>
<td>12 (15%)</td>
<td>4 (16%)</td>
<td>12 (16%)</td>
<td>5 (21%)</td>
<td>11 (14%)</td>
<td>6 (24%)</td>
</tr>
</tbody>
</table>

Data taken from [24,26].
dose of corifollitropin alfa was able to initiate and sustain multiple follicular growth that lasts for 7 days. Thereafter, all patients received rFSH 7 days after the corifollitropin injection. Sufficient multifollicular ovarian response was observed in all study groups, suggesting that the smallest effective dose of corifollitropin alfa could be lower [Table 2] [24].

Another Phase II double-blind, placebo-controlled, randomized clinical trial (NCT00702585), evaluates the follicular response and ovulation rate in women with WHO group II anovulatory infertility following administration of single low doses corifollitropin alfa (7.5, 15, 30 and 60 µg) or placebo [25]. The mean number and the size of follicles were increased in a dose-related manner, while the time interval to reach the maximal number of follicles was not significantly elongated. Serum levels of inhibin B and estrogen were significantly increased and in correlation with the number of follicles in the groups received 30 and 60 µg corifollitropin alfa. The ovulation rate was low (16.4%) in all groups, and a possible explanation for it this the heterogeneity of anovulatory patients included in the study [25].

A third Phase II multicentre randomized clinical trial (NCT00598208), randomized 325 IVF patients to receive a single dose of 60, 120 or 180 µg corifollitropin alfa or daily administration of 150 IU rFSH [26]. There was a dose-dependent increase in the number of follicles greater than 11 mm on day 8 or on the day of hCG administration. A statistically significant dose-related increase in the number of oocytes retrieved and the cancellation rate was also observed. The oocytes retrieved in the study group treated with 60 µg corifollitropin alfa was significantly lower when compared with daily rFSH administration, while the cancellation rate was too high (44%). The overall pregnancy rate was relatively low, albeit slightly higher in groups with 120 and 180 µg corifollitropin alfa without reaching significance. These findings imply that the dose of 60 µg corifollitropin alfa is insufficient to sustain ovarian stimulation for a week and higher dose regimens are required. Median serum levels of inhibin-B and estradiol increased with an increasing corifollitropin alfa dose. On day 8 the increase in estradiol levels reached statistical significance [Table 2] [26].

In a pilot Phase II open-label, dose comparison, non-randomized clinical trial (REALIZE trial; NCT702351), 50 women undergoing controlled ovarian stimulation for IVF or ICSI were recruited to receive a long GnRH agonist protocol [27]. Ovarian stimulation was initiated with varying corifollitropin alfa doses (100 µg in women ≤60 kg and 150 µg in women >60 kg) followed by 150 or 200 IU daily rFSH respectively from day 8 onwards to the day of hCG administration. Both dose regimes of corifollitropin alfa were found to be sufficient to initiate and sustain multifollicular growth in a long GnRH agonist protocol assessed by the median inhibin-B and estradiol serum levels or the number and size of recruited follicles. They were also associated with relatively higher rFSH consumption and longer treatment duration from day 8 onward in order to reach the criteria of hCG administration. The overall duration of stimulation was 10.5 days in the group treated with 150 µg corifollitropin alfa and 11 days in the 100 µg dose group, while the total rFSH addition was 700 and 600 IU, respectively. The extent of ovarian response following either treatment arm was found to be comparable or higher when compared with the findings of previous studies of women treated with 225 IU rFSH in a long GnRH agonist protocol [27].

Phase III

In a Phase III double-blind, randomized clinical trial (ENGAGE trial; NCT00696800), a total of 1506 IVF patients with a body weight of 60 kg or more were enrolled and randomized to receive either a single dose of 150 µg corifollitropin alfa or daily injections of 200 IU rFSH for 7 days in a GnRH antagonist protocol [1]. From 8 days onward all women received rFSH until the day of hCG administration. The ongoing pregnancy rate was high and comparable in both groups (38.9% for corifollitropin alfa vs 38.1% for rFSH). The mean duration of stimulation was similar in both groups at 9 days. A total of 32.9% of women who received corifollitropin alfa met the criteria of hCG administration before or on day 8 and in this subgroup of ‘good responders’ the ongoing pregnancy rate was higher at 44%. The number of oocytes retrieved was slightly higher in the corifollitropin group (13.7 vs 12.5). Significant differences were not found in: the mean number of follicles greater than 11 mm, fertilization rate, embryo transfer, number and quality of embryos obtained, pregnancy rates or hormone levels in both treatment groups. Multiple pregnancy rates were higher in the corifollitropin alfa group (28.2 vs 23.1%), which was not significant.

Another Phase III double-blind, randomized clinical trial (ENSURE, NCT00702845), enrolled 396 IVF patients weighing less than...
60 kg, they were randomized into a single dose of 100 µg corifollitropin alfa or 7 administration of 150 IU rFSH group for seven days in a GnRH antagonist protocol [28]. From 8 days onward all women received rFSH until the day of hCG administration. The difference in the mean number of oocytes retrieved was significant (+2.5; CI: 1.2–3.9) in favor of corifollitropin alfa. The mean duration of stimulation was 9 days (6–15) in both groups while 32.8% of women in the corifollitropin alfa group reached the criteria of hCG administration without receiving additional rFSH injections.

A third Phase III clinical trial (TRUST; NCT00696878) focuses on the safety of corifollitropin alfa administered in 681 IVF patients weighing more than 60 kg undergoing repeated controlled ovarian stimulation cycles in an GnRH antagonist protocol. From 8 days onward all women received rFSH until the day of hCG administration. The primary end points of the trial are the main safety parameters, including: induction of ovarian hyperstimulation syndrome, tolerance, antibody production and adverse effects. Secondary end points include: pregnancy rates, number and size of follicles, number of fertilized oocytes, implantation rate, and number and quality of embryos. This trial has been completed at the time of publication, however, no results have been reported [103].

Post-marketing surveillance
Corifollitropin-α is the first long-acting FSH agonist that has recently received approval from European Commission [101]. No post-marketing information is currently available.

Safety & tolerability
Several concerns have been raised regarding the safety and tolerability of corifollitropin alfa due to its prolonged circulating life-time and increased biopotency. Once the initial dose of corifollitropin alfa has been given, it is not possible to take action for at least a week in order to prevent the development of ovarian hyperstimulation syndrome (OHSS) when the first signs of the syndrome appear, as is the case for all high responder patients irrespective of treatment. The data on the safety of corifollitropin alfa are reassuring according to studies conducted to date, however, the conclusions of the completed TRUST trial have not yet been published.

The first reports on corifollitropin alfa safety came from Phase I studies. Following repeated doses of corifollitropin alfa on hypogonadotrophic hypogonadal males, no serious adverse events were related to the drug and no changes in hematological or biochemical parameters were reported, administration was found to be well tolerated [23]. The incidence of local reactions at the site of injection was also not found to increase after repeated doses [23]. Similar findings regarding adverse events, trial discontinuations and alterations to laboratory parameters were reported in a Phase I study on healthy pituitary suppressed volunteers [23].

The overall incidence of serious adverse events for both corifollitropin alfa and rFSH treatment groups in the ENGAGE trial was comparable [1]. Among the most frequent adverse events were headache (10.5 vs 15.2%), pelvic pain (12.1 vs 12.3%) or discomfort (11.5 vs 11.6%), procedural pain (22.3 vs 20.1%), pregnancy-related complications (13.8 vs 11.2%), severe OHSS (1.9 vs 1.2%) and ruptured ectopic pregnancy (0.9 vs 1.2%). Similar results were found in all Phase II studies with headaches being the most frequent adverse event [24–26].

The overall incidence of OHSS has been found to be slightly higher in the group of 150 or 100 µg corifollitropin alfa compared with that of 150 or 200 IU of rFSH without reaching statistical significance [1,28]. The incidence of severe or moderate OHSS was also found to be slightly increased in the corifollitropin alfa-treated group in both trials (4.1 vs 2.7% for ENGAGE trial and 3.4 vs 1.6% in ENSURE trial). Furthermore, the discontinuation rate due to a serious adverse event was higher after corifollitropin alfa compared with rFSH administration (2.1 vs 0.4%) [1].

Finally, the use of corifollitropin alfa is safe and there were no reports suggesting antibody formation against corifollitropin alfa.

Regulatory affairs
Corifollitropin alfa has been approved by the European Commission and is available for use in European countries for controlled ovarian stimulation in assisted reproductive technology (ART) programs. Corifollitropin alfa is recommended for use in a GnRH antagonist protocol.

Conclusion
Corifollitropin alfa is the first available recombinant long-acting, FSH that has completed three clinical phases of drug development successfully and has recently been approved for clinical use. The benefit of this novel molecule is its improved pharmacokinetic properties without, however, apparent conformational changes in the receptor
binding area or modifications in the folding of the hormone. Its properties are mainly attributed to the addition of CTP on the FSH-β, an oligosaccharide extension in the terminus of β-chain of hCG that consists of four O-linked glycosylation sites. The enhanced biopotency of corifollitropin alfa is due to increased sialic acid content that influences the glomerular filtration rate [14].

A range of dose regimens for corifollitropin alfa have been tested in view of kinetic characteristic, clinical efficacy and safety in different studies. The optimal dose in a one-week regimen of corifollitropin alfa for stimulation of multiple follicular growth in IVF patient has been determined by a specialized pharmacokinetic and dynamic model that relied on parameters such as the initial follicular response, the number of oocytes retrieved and serum Inhibin-B levels [29]. According to this model, it was found that the patient body weight is a contributing factor that should be taken into account when determining the optimal corifollitropin alfa dose. The dose regimens of the clinical Phase III studies were based on this model. The dose of 150 µg was selected for women more than 60 kg and 100 µg for women less than 60 kg to ensure comparable corifollitropin alfa exposure [30].

A single dose of corifollitropin alfa seems to be adequate for ovulation induction in IVF and can replace the first seven daily rFSH injections with similar efficiency in a GnRH antagonist protocol. From day 8 onward, corifollitropin alfa is reduced to a critical threshold level and the stimulation protocol should be completed with the addition of different daily doses of rFSH in order to reach the conditions required for hCG administration. This approach enables the coordinated use of the rFSH and corifollitropin alfa, in which the rFSH could play the role of ‘fine-tuner’ of the ovarian response [19].

The privileged one-week regimen of corifollitropin alfa compared with daily administration of rFSH for 7 days seems to be an attractive, patient-friendly alternative. Such reduction in injection number is considered to be associated with reduced discomfort and stress and could potentially increase patient compliance. Local reactions and discomfort at injection site are also reduced.

Corifollitropin alfa has also been tested in a long GnRH agonist protocol and the results of this trial have recently been announced [27]. In a long protocol the total gonadotropin dose and the duration of stimulation was higher in order to reach the criteria of hCG administration. The main issue to be answered in this trial was the extent of corifollitropin alfa efficiency after profound pituitary suppression with the prior use of GnRH agonist. It was revealed that a single dose of corifollitropin alfa is able to initiate and sustain follicular growth for 7 days and can recruit large a number of follicles. More studies are required to prove and compare corifollitropin alfa efficiency and safety in a long GnRH agonist protocol with that of rFSH before extending corifollitropin alfa use.

Regarding corifollitropin alfa safety concerns, the increased frequency of OHSS development have been raised due to its longer elimination half-life and enhanced bioavailability. Once corifollitropin alfa is administered, it is not possible to intervene for at least 1 week. However, the rate of OHSS, especially severe forms of the syndrome are only slightly higher when compared with the classical treatment with rFSH. The validity of the safety data is somewhat due to the selection criteria of patients in different studies. Women with a higher risk for ovarian stimulation syndrome were excluded from the clinical Phase III studies. It is noteworthy, however, to mention that 74% of patients included in the ENGAGE trial were involved in an IVF treatment cycle for the first time.

In assisted reproduction protocols, patient’s response to exogenous FSH is variable. This remains a serious issue for IVF treatment, factors that have been implicated as responsible for the variability in ovarian response in women, in many cases, are unpredictable. Close surveillance, monitoring and dose adjustment depending on the degree of response appears to be the best solution in preventing a response that is too low (resulting in cycle cancellation) or a high response (leading to the potentially life-threatening ovarian hyperstimulation syndrome). However, due to the prolonged circulation life-time of corifollitropin alfa it is impossible to adjust the extent of response for at least a week if excessive ovarian stimulation occurs. Thus, corifollitropin alfa is better to be initially reserved for patients who have already tried several cycles of IVF therapy and whose response to therapy can be reasonably predicted [19].

In summary, with the advent of recombinant DNA technology using site-directed mutagenesis and gene transfer techniques, the field of infertility drug research has been directed to the synthesis of new genetically modified gonadotropins with improved properties that can be applied in practice. The use of corifollitropin alfa is believed to rise above its expectations and become an essential agent in the marketplace.
RUG EVALUATION – Loutradis, Vlismas & Drakakis1

of infertility. The extent to which corifollitropin alfa will achieve this goal is dependent on the confirmation of its efficacy regarding ovulation induction, the associated pregnancy rates, the confirmation of the low rate of adverse events and finally the cost of the drug.

Executive summary

**Background**
- Follicle Stimulating Hormone (FSH) is the mainstay of infertility treatment.
- FSH has a relatively short half-life and rapid metabolic clearance.
- Corifollitropin alfa has been developed in order to simplify infertility treatment and increase patient compliance.

**Overview of the market**
- 72.4 million people are currently infertile worldwide and 40.5 million of these are seeking infertility medical care.
- The prevalence of infertility lasting for over 12 months in women aged 20-44 years old ranged from 3.5–16%.
- Significant progress has been made in the pharmacology of assisted reproduction due to developments in biotechnology.

**The compound & its chemistry**
- Corifollitropin alfa is a heterodimer consisting of two of the same α-subunits as the other glycoprotein hormones (FSH, LH, hCG, TSH) and a hybrid β-subunit.
- The hybrid β chain arises from the fusion of the β-subunit of FSH with the carboxyl-terminal peptide (CTP) of hCG β-subunit.
- The chimeric gene was then transfected together with the FSHα-subunit gene into Chinese hamster ovary cells.
- Corifollitropin alfa did not significantly affect the assembly of α and β-FSH-subunits or the hormone secretion.
- Its in vivo biopotency in animal studies was found to be 10-fold higher compared with rFSH.
- It is totally devoid of LH bioactivity and interacts only with FSH receptors.

**Pharmacokinetics & metabolism**
- The absorption rate is slow and the elimination half-life time is 2-3 fold longer than that of rFSH.
- The AUC and Cmax are dose related.
- Body weight has an impact on corifollitropin alfa exposure.

**Clinical efficacy**
- Multiple follicular growth was observed following different single doses of corifollitropin.
- A dose-related increase in both the number and diameter of follicles was reported.
- A single dose of corifollitropin alfa was able to initiate and sustain multiple follicular growth that lasts for 7 days. Additional rFSH injections are required from day 8 onward to reach the criteria of hCG administration.
- The mean duration of stimulation was 9 days.
- A dose-related increase in the number of oocytes retrieved and the cancellation rate was found.
- Compared with daily rFSH administration there was no observed significant differences in the mean number of follicles more than 11 mm, fertilization rate, embryo transfer, number and quality of embryos obtained, pregnancy rates or hormone levels.

**Safety & tolerability**
- No serious adverse events related to the drug or changes in hematological and biochemical parameters were reported following repeated doses of corifollitropin alfa.
- Its use was well tolerated.
- The most frequent adverse events were headache, pelvic pain or discomfort, procedural pain and pregnancy-related complications (abortions).
- The overall incidence of OHSS was slightly higher following corifollitropin alfa.
- Severe or moderate OHSS was also found to be slightly increased.
- There were no reports suggesting antibody formation against corifollitropin alfa.

**Regulatory affairs**
- Corifollitropin alfa has been approved by the European Commission and is available for use in European countries for controlled ovarian stimulation in a GnRH antagonist protocol.

**Conclusions**
- The first available recombinant long-acting FSH.
- The optimal dose in a 1 week regimen of corifollitropin alfa has been determined by a specialized pharmacokinetic and dynamic model.
- Corifollitropin alfa can replace the first 7 daily rFSH injections with similar efficiency in a GnRH antagonist protocol.
- Its use is well tolerated and is associated with less discomfort and stress and could potentially increase patient compliance.
- In a long GnRH agonist protocol a single dose of corifollitropin alfa is able to initiate and sustain follicular growth for 7 days and can recruit a large number of follicles.
Future perspective
Corifollitropin alfa is the first sustained follicular stimulant that has received approval for clinical use in GnRH antagonist protocol. It is expected to take a part in the marketplace of infertility as a reliable and attractive alternative for controlled ovarian stimulation in IVF patient. It remains to be tested in clinical practice in order to prove its efficiency and be included as an option in the therapeutic arsenal of infertility.

Information resources
Corifollitropin alfa has been described in several Phase I, II and III clinical trials. The most important information concerning its use and dose selection is retained from the ENGAGE and ENSURE clinical trials.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received, or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography
Papers of special note have been highlighted as:
• of interest
** of considerable interest

** Clinical Phase III study describing corifollitropin alfa clinical outcomes.
** The first study that describes the role of carboxyl-terminal peptide (CTP) of human chorionic gonadotrophin (hCG).
** The first human exposure to corifollitropin alfa.


Websites

