Product Monograph

elonva®
corifollitropin alfa

Elonva®
(corifollitropin alfa): A simplified, patient-focused approach to controlled ovarian stimulation

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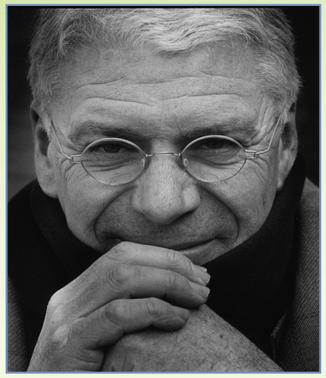

INTRODUCTION

Assisted reproductive techniques (ARTs), in particular in vitro fertilization (IVF), rely on controlled ovarian stimulation (COS) to stimulate the development and maturation of a sufficient number of oocytes to improve the chances for conception.[1,2] Historically, conventional COS treatment regimens require repeated, daily self-injections of follicle-stimulating hormone (FSH)[3] along with the extended use of gonadotropin-releasing hormone (GnRH) agonists, both prior to and during stimulation, to suppress a premature rise in endogenous luteinizing hormone (LH).[1] The availability of GnRH antagonists allowed the development of COS protocols that have several advantages over protocols that employ GnRH agonists, including shorter and less complicated stimulation regimens and reduced patient discomfort.[4] Although improvements in the methods of FSH administration (eg, the introduction of the Puregon Pen® [follitropin beta injection]) have somewhat lessened the burden on patients, daily injections are still necessary.[3]

Since the first IVF baby, many scientific advances have been made in the treatment of infertility: intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis (PGD), cryopreservation, single embryo transfer (SET), etc. Despite all these advances, one area has been largely ignored: the stress that infertility and its treatment cause for patients. Infertility itself is a stressful condition, but the treatment of infertility can also be extremely stressful because of the complexity as well as the physical and emotional demands of the process.[5,6] The ovarian stimulation phase has significant impact, with patients who undergo this treatment reporting high levels of negative emotions resulting in constant worry, stress, and anxiety.[5] This stress and anxiety is generally above and beyond the emotions patients reported in general for the IVF process.[5] In addition, stress has been shown to have a negative impact on oocyte retrieval rates,[7] fertilization rates,[7] and pregnancy rates following IVF,[6] indicating that reducing the physical and psychological burden associated with COS could lead to improvements in treatment outcomes with ART.

In a recent survey of couples who discontinued IVF before achieving pregnancy ("dropout"), the most frequent cause of dropout was the physical or psychological burden of treatment.[8] Patients are far more distressed by daily injections than most physicians realize.[5] This stress is due to not only the physical burden of self-injections, but also concerns about medication errors such as proper injection techniques, achieving the correct dosing and timing of injections, and whether treatment will lead to success.[5] In an interview-based study, 57% of patients reported concern about injection mistakes, and even 47% of the interviewed fertility specialists reported concern about patients injecting themselves properly.[9] Twenty-eight percent of couples that discontinued an IVF program in this survey stated that the physical or psychological toll associated with the program was the primary reason for their treatment discontinuation.[8] Additionally, the treatment burden became more severe with each successive cycle in patients undergoing standard long-agonist COS, and the burden was greater in those patients compared with women undergoing COS with a GnRH antagonist protocol.[10] This treatment burden, along with stress related to medication injection, contributed to discontinuation rates ranging from 39.9% after the first cycle to 62.2% after the fourth cycle among couples participating in ART or IVF programs without achieving a live birth of a child even before completion of all cycles for which costs were covered.[11,12]

Fortunately, the development of new clinical protocols that require fewer injections may help to reduce the treatment burden of patients undergoing COS.[3] As described above, the use of a GnRH antagonist results in a shorter period of physical discomfort for patients than occurs with a long-cycle GnRH agonist protocol, which requires daily injections or a depot formulation injection from the mid-luteal phase of the pretreatment cycle for approximately 2 weeks before COS even begins (Figure 1).[13] In addition to fewer injections, other advantages of a GnRH antagonist protocol include: no initial flare-up, no estrogen deprivation, shorter cycles, lower risk of ovarian hyperstimulation syndrome (OHSS), and reduced gonadotropin use. Since stress may have a negative impact on IVF outcomes,[11,14] treatment strategies that require fewer injections may further reduce the treatment burden and enhance COS acceptability.[3] Specifically, most women participating in a patient-reported outcome study of the impact of COS reported

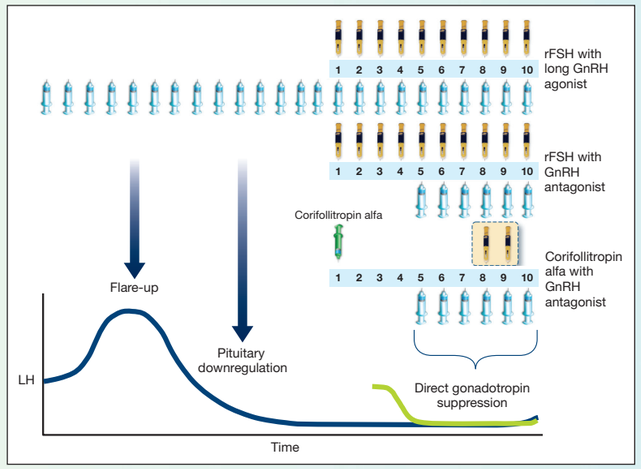

Figure 1. The number of injections COS requires has been reduced with the advent of the GnRH antagonist protocol.

that the injection experience was so negative that even 1 fewer injection would make a meaningful difference to them.[5] This suggests that enhanced COS acceptability and the reduction of the burden of treatment may, in turn, lead to fewer discontinuations and to possible improvements in the outcome of treatment programs.[8,11]

The impact of treatment discontinuations on cumulative pregnancy rates has been observed in a study of 2130 women, where the expected rates were lower than real rates due to the diminishing size of the cohort because of dropouts.[11] Data from 4102 IVF cycles in these women show a difference of nearly 30% between expected and real cumulative pregnancy rates.

Corifollitropin alfa is a novel recombinant fertility hormone that has a half-life approximately twice that of recombinant FSH (rFSH) and is the first and only sustained follicle stimulant.[3] A single injection of corifollitropin alfa can initiate and sustain multiple follicular development for 1 week in women undergoing COS for IVF or ICSI and can safely replace 7 days of conventional gonadotropin administration (Figure 1).[3] The purpose of this monograph is to describe the properties of corifollitropin alfa, which has been shown to be safe and effective in women undergoing COS for IVF and ICSI.[3]

HISTORICAL PERSPECTIVE

Successful extraction of gonadotropins from human sources (eg, human pituitary gonadotropin [hPG] and human menopausal gonadotropins [hMG]) led to the use of human gonadotropin preparations for COS.[2,15] For over 20 years, although refined purification techniques resulted in greater purity of the extracts, batch variation led to inconsistent bioactivity.[16,17] Further refinements produced hMG with reduced amounts of nonactive proteins and eventually resulted in purified urinary FSH (uFSH), which caused fewer hypersensitivity reactions and less painful injections.[2] Several problems existed with the use of gonadotropins from human sources. First, the growing worldwide demand for the limited supplies of hPG and hMG required large-scale production.[2,15] Second, cases of Creutzfeldt-Jakob disease (CJD) were discovered and linked to the use of other pituitary-derived hormones, including human pituitary growth hormone and hPG.[18,19] As a result, hPG was abandoned, and urine-derived hMG became the main source of exogenous gonadotropins for clinical use.[15] Finally, around this time, the development and refinement of recombinant DNA technology offered the potential for pharmacologically active FSH to be produced in unlimited quantities.[15] The efficacy and safety of rFSH in inducing ovulation, (or superovulation for IVF), along with the pregnancies resulting from its use, were first reported in 1992.[20,21] Subsequent large-scale, multicenter studies further demonstrated the efficacy and safety of rFSH.[22]

Current COS treatment regimens require daily injection of conventional gonadotropin because of its relatively short half-life.[15] Recently, Elonva® (corifollitropin alfa), a sustained follicle stimulant, was approved and indicated for COS in combination with a GnRH antagonist for the development of multiple follicles in women participating in an ART program.

ELONVA® (CORIFOLLITROPIN ALFA) REVIEW

Elonva is a novel recombinant fertility hormone that has been designed as a sustained follicle stimulant with the same pharmacodynamic profile as rFSH, but with a markedly prolonged duration of FSH activity. Due to its ability to initiate and sustain multiple follicular growth for an entire week, a single subcutaneous injection of the recommended dose of Elonva replaces the first 7 injections of any daily rFSH preparation in a COS treatment cycle.

Compared with the half-life of human chorionic gonadotropin (hCG), the half-life of FSH is relatively short.[15] The longer half-life of hCG is associated with the presence of 4 serine O-linked oligosaccharides attached to the extended hydrophilic carboxy-terminal peptide and a high number of proline residues (9 of 30) that confer resistance to proteolytic degradation on the β-subunit of hCG.[23,24] The availability of recombinant DNA techniques such as site-directed mutagenesis and gene transfer enables modifications to recombinant proteins, and it was thought that fusion of a carboxy-terminal peptide extension from the β-subunit of hCG onto the β-subunit of FSH would result in a protein that has FSH bioactivity with a prolonged half-life.[24] The recombinant protein that results from this fusion, corifollitropin alfa, has a longer absorption time, prolonged circulating half-life, and enhanced biological activity compared with wild-type human FSH.[24] Because of the extended absorption and longer half-life of corifollitropin alfa, the frequency of FSH administration may be reduced and result in more injection-free days for patients undergoing COS.[3]

Elonva is available in a prefilled syringe at doses of 100 µg/0.5 mL and 150 µg/0.5 mL and is administered as a single subcutaneous (SC) injection, preferably in the abdominal wall. Appropriate dosage is determined by the body weight of the patient; the recommended dosage for patients weighing ≤60 kg is 100 µg, and 150 µg for patients weighing >60 kg. The prefilled syringe is packaged with a sterile injection needle that is equipped with an automatic safety system to prevent needle stick injuries after use. This dose paradigm has been shown in clinical trials to result in ongoing pregnancy rates comparable with those of Puregon®.

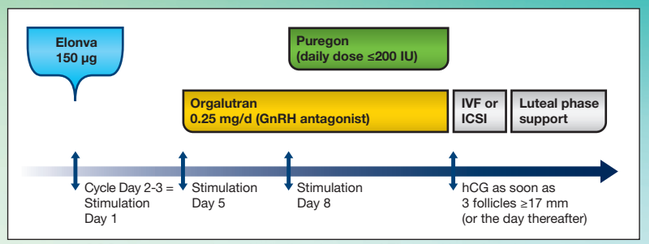

Figure 2. COS treatment regimen including the use of Elonva. Note that the recommended doses of Elonva have only been established in a treatment regimen with a GnRH antagonist.

A recommended COS treatment protocol employing Elonva is presented in Figure 2. Specifically, Elonva is administered on day 2 or 3 of the menstrual cycle. Seven days later (on stimulation day 8), COS may be continued, if necessary, with daily injections of Puregon until the criteria for triggering final egg maturation are present.[25] The dose of Puregon depends on the ovarian response. In normal responders, a daily dose of 150 IU rFSH is advised. To prevent the occurrence of premature LH surges, treatment with a GnRH antagonist should be started on stimulation day 5 or 6 if ovarian response appears to be delayed. The recommended doses of Elonva have only been established in a treatment regimen with a GnRH antagonist.

THE ELONVA (CORIFOLLITROPIN ALFA) CLINICAL TRIAL PROGRAM

The clinical trial program for Elonva is the largest such program for fertility and includes more than 2500 patients in 78 IVF centers in 23 countries. The clinical efficacy and safety of Elonva for initiating and sustaining multiple follicular development in women participating

in an ART program were established in 3 major clinical trials: Engage, Ensure, and Trust. Engage and Ensure are the 2 main randomized controlled trials to be discussed here. Trust is an open-label, single-group safety study conducted to assess the nonimmunogenicity and safety of Elonva in patients undergoing repeated COS with multiple-dose GnRH antagonist protocol. Initial results from Trust appear to corroborate the safety findings from Engage and Ensure.[26]

Preclinical Data

As described above, corifollitropin alfa is a novel recombinant fertility hormone that was created as a sustained follicle stimulant with a prolonged duration of action. This sustained bioactivity was first demonstrated in immature, estrogen-primed rats.[24] Biopotency, as determined by increased ovarian weight and estrogen production, was significantly higher in animals treated with the fusion protein compared with animals treated with wild-type FSH.[24] Corifollitropin alfa bioactivity was confirmed via estrogen production by cultured granulosa cells.[24] Bioactivity was similar to that of wild-type FSH.[24] The presence of the hybrid β subunit does not interfere with the folding of the FSH β-subunit, does not affect the ability of corifollitropin alfa to bind to the FSH receptor, and does not result in LH or hCG bioactivity.[24]

Pharmacokinetics and Pharmacodynamics

As expected, the fusion of the carboxy-terminal peptide from hCG onto the β-subunit of FSH results in corifollitropin alfa having a half-life that is approximately 2- to 3-fold longer than that of rFSH.[27] The elimination half-life ($t_{1/2}$) of corifollitropin alfa in hypogonadotropic hypogonadal men is 94.7 ± 26.2 hours and ranges from 60 to 75 hours in healthy, pituitary-suppressed women, whereas the elimination half-life of wild-type rFSH is approximately 34 hours in healthy, pituitary-suppressed women.[27-29] This extended $t_{1/2}$ of corifollitropin alfa is independent of dose within the range of doses tested,[28] suggesting that the duration of FSH activity, too, will be consistent within that range.

Maximal serum concentrations of corifollitropin alfa increases with the dose injected, but dose-normalization of the pharmacokinetic parameters results in no significant differences in any pharmacokinetic parameters measured.[28] The time to the maximal concentration (t_{max}) is consistent and comparable among doses; corifollitropin alfa concentrations peak between 36 and 48 hours following injection and are dose-independent.[28] The overall pharmacokinetic parameters for corifollitropin alfa are summarized in Table 1.

The pharmacodynamic properties of corifollitropin alfa have been assessed with serum hormone concentrations in hypogonadotropic hypogonadal men[27] and with follicular response and hormone concentrations in healthy, pituitary-suppressed women[28] as well as in female patients presenting with oligomenorrhea or amenorrhea.[30] Injection of corifollitropin alfa resulted in significant increases in serum inhibin B.[27,28,30] In healthy, pituitary-suppressed women, a single injection of corifollitropin alfa stimulated multiple follicular development, and the number and diameter of follicles increased with the dose of corifollitropin alfa.[28]

Table 1. Summary of Overall Pharmacokinetic Parameters for Corifollitropin Alfa[27]

	C_{max} (ng/mL) n=18	t_{max} (h) n=18	$t_{1/2}$ (h) n=14	$AUC_{0-\infty}$ (ng·h/mL) n=14	Cl_{app} (L/h/kg) n=14
Mean (SD)	0.426 (0.116)	45.9 (18.0)	94.7 (26.2)	81.5 (18.8)	0.00245 (0.00046)

C_{max} = maximal concentration at any time; t_{max} = time at which the maximal concentration is reached; $t_{1/2}$ = half-life; $AUC_{0-\infty}$ = area under the concentration-time curve from t=0 h extrapolated to infinity; Cl_{app} = apparent clearance defined by clearance divided by absolute bioavailability.

Clinical Data

Early Studies

An initial study was conducted in which a single injection of corifollitropin alfa (at a dose of 7.5, 15, 30, or 60 µg) was administered to 55 patients presenting with oligomenorrhea or amenorrhea.[30] The aim of the study was to determine if the administration of a single, low dose of corifollitropin alfa was sufficient to induce monofollicular ovulation in anovulatory women and reverse anovulatory status. Therefore, additional exogenous gonadotropins were not used to sustain follicular development or to induce ovulation. In case of risk of ovarian hyperstimulation, endogenous gonadotropins were suppressed and spontaneous ovulation was prevented by daily injections of 2 mg of a GnRH antagonist (Orgalutran®).[30] In the absence of additional FSH or hCG, corifollitropin alfa initiated and sustained multiple follicular development to preovulatory sizes, but the incidence of spontaneous ovulation was low within the dose range tested and in this patient population.[30] It was concluded that corifollitropin alfa may be useful in the induction of ovulation if followed by daily rFSH injections to support the leading follicle(s) up to ovulation, but a single low dose for all patients to maintain monofollicular growth may not be feasible.[30]

During the pharmacokinetic study conducted in healthy, pituitary-suppressed women, 7 patients were administered a single, 120-µg injection of corifollitropin alfa, which initiated and sustained multiple follicular development that was comparable to COS with daily rFSH (150 IU) for 7 days.[28] The results from that study suggested that corifollitropin alfa would support 7 days of multiple follicular development, and therefore a study was conducted to determine the efficacy and safety of corifollitropin alfa as part of a new treatment regimen for COS.[31]

COS Feasibility Study

The first study conducted to determine the feasibility of corifollitropin alfa for COS to initiate and sustain 7 days of multiple follicular development was an open-label, randomized, 4-arm trial in which patients (N=99) undergoing COS for IVF or ICSI were administered a single injection of corifollitropin alfa (120, 180, or 240 µg) or daily Puregon (150 IU; control) beginning on cycle day 3.[31] In patients receiving corifollitropin alfa, the initiation of multiple follicle growth was followed by daily SC injection of 150 IU Puregon beginning 7 days after the initial injection (stimulation day 8), whereas control patients continued to receive daily Puregon injections.[31] Cotreatment with the GnRH antagonist ganirelix (Orgalutran, 0.25 mg/d SC) was flexible and started when the largest follicle exceeded 14 mm, in order to prevent premature LH surges.[31] Final oocyte maturation was induced with a single SC injection of 10,000 IU hCG (Pregnyl®) when 3 follicles ≥17 mm were observed by transvaginal sonography.[31]

Study end points included total Puregon dose, clinical outcome parameters, the number and size of follicles, and hormonal responses.[31] The duration of stimulation and the total amount of Puregon administered from treatment day 8 onwards were similar, with no statistical differences among the 4 treatment groups.[31] The median starting day for GnRH antagonist was stimulation day 7.0 in all treatment arms.[31] An average of 3 days of Puregon were required in patients who had received corifollitropin alfa, regardless of initial corifollitropin alfa dose.[31] The average total amount of Puregon in corifollitropin alfa–treated patients was 450 IU compared with an average total Puregon dose of 1350 IU in control patients.[31] As shown in Table 2, the mean number of oocytes recovered was similar across doses of corifollitropin alfa (mean range, 11.0-12.0) and tended to be less

among patients treated with Puregon (mean, 7.9).[31] The 3 doses of corifollitropin alfa resulted in similar follicular development and clinical outcomes across treatments, and no differences in clinical outcomes were found compared with daily Puregon treatment. The first pregnancy and live birth using this treatment regimen was reported in 2003.[32] As a result of this first successful pregnancy and demonstration of the feasibility of corifollitropin alfa as part of an ART program, further studies have been conducted to determine the optimal regimen of corifollitropin alfa administration for COS.

Dose-Finding Study

The total dose of Puregon needed to reach the hCG criteria was similar among the 3 doses of corifollitropin alfa in the feasibility study, indicating that the corifollitropin alfa doses tested were too high to demonstrate a significant dose-response relationship.[31] As a result, a larger multicenter, open-label, randomized study was conducted to investigate the dose-response relationship for the number of oocytes retrieved following a single injection of corifollitropin alfa over a lower dose range of 60 to 180 µg.[3] Similar to the earlier study, 3 doses of corifollitropin alfa (60, 120, or 180 µg) were administered as a single injection on cycle day 2 or 3 followed by a fixed daily dose of Puregon beginning 1 week later.[3] The daily Puregon treatment regimen and hCG dose to induce final oocyte maturation were similar to those described above, but treatment with the GnRH antagonist ganirelix began on treatment day 5 rather than using a flexible schedule.[3] A group of patients treated with daily Puregon (150 IU) was used as a positive control.[3] The primary end point of this study was the number of cumulus-oocyte complexes retrieved.[3] Other end points included the total dose of Puregon required, number and size of follicles, serum hormone concentrations, normal fertilization rate, number and quality of embryos obtained and transferred, and pregnancy rates.[3]

A single dose of corifollitropin alfa was able to induce and sustain multiple follicular development for 1 week. As shown in Table 3, the number of oocytes retrieved showed a dose-response relationship and was statistically significantly greater with the higher doses of corifollitropin alfa compared with 60 µg of corifollitropin alfa and daily Puregon.[3] Dose-related increases in the mean number of follicles ≥11 mm were seen on treatment day 8 before daily Puregon treatment was started, as well as on the day of hCG administration.[3] Although the total amount of Puregon required was lower and fewer injections were required following a single injection of corifollitropin alfa, corifollitropin alfa did not alter or accelerate COS dynamics, since the median duration of stimulation was similar across treatments (10 to 11 days in corifollitropin alfa–treated patients and 10 days in patients treated with daily Puregon).[3]

A higher mean number of good-quality embryos was achieved with 120 and 180 µg of corifollitropin alfa.[3] The incidence of single embryo transfer of a good-quality embryo, as well as implantation rates, was comparable across treatments.[3] The incidence and percentage of ongoing pregnancies also were comparable across treatments, but the cumulative pregnancy rate was slightly higher in patients treated with 120 or 180 µg of corifollitropin alfa, possibly because of the higher number of good-quality embryos available in these treatment groups.[3]

The results of the dose-finding study indicated that the optimal dose of corifollitropin alfa to induce and sustain multiple follicular growth for 7 days is higher than 60 µg and lower than 180 µg.[3] As a result, subsequent modeling and simulation were employed to identify the optimal dose of corifollitropin alfa for use in a 1-week program for COS.[33] Using 5 parameters—inhibin B levels, follicular volume on stimulation day 8, cancellation rate, number of oocytes, and the pharmacokinetics of corifollitropin alfa (based on data from more than 3000 patients)[33]—a statistical model was developed to simulate ovarian responses after various single doses of corifollitropin alfa. The lowest dose of corifollitropin alfa resulting in a minimal cancellation rate was selected as the optimal dose for the phase 3 clinical trials.

Table 2. Follicle Dynamics and Clinical Outcomes in Patients Treated With a Single Injection of Corifollitropin Alfa (120, 180, or 240 µg) or Daily rFSH (150 IU) in the Feasibility Study[31]

	Corifollitropin alfa, 120 µg (n=25)	Corifollitropin alfa, 180 µg (n=24)	Corifollitropin alfa, 240 µg (n=25)	Daily rFSH, 150 IU (n=24)
Day 8, mean (SD) ≥11 mm ≥15 mm ≥17 mm	 8.8 (5.6) 2.5 (2.0; *P*=0.05) 0.8 (1.1; *P*=0.02)	 9.3 (5.7) 2.5 (2.0; *P*=0.06) 0.9 (1.1; *P*=0.04)	 10.3 (6.6) 3.8 (3.1; *P*=0.93) 1.4 (1.5; *P*=0.51)	 9.4 (6.9) 4.2 (2.4) 1.9 (1.7)
Day of hCG, mean (SD) ≥11 mm ≥15 mm ≥17 mm	 12.7 (6.8) 5.9 (2.5) 3.3 (0.9)	 13.5 (7.1) 6.6 (3.1) 3.5 (1.2)	 15.5 (8.3) 7.8 (3.1) 4.0 (2.0)	 12.3 (7.3) 6.3 (2.4) 3.7 (1.3)
Number of oocytes per started cycle, mean (SD)	11.0 (7.1)	11.1 (7.5)	12.0 (7.3)	7.9 (4.1)
Metaphase II oocytes in ICSI	10.9 (6.9; n=11)	8.5 (6.3; n=14)	9.1 (5.5; n=15)	8.6 (3.0; n=11)
Fertilization rate, mean (SD)	73 (27%)	68 (31%)	67 (31%)	74 (15%)
Number of embryos obtained Total, mean (SD) Good quality, mean (SD) Transferred, mean (SD)	 8.5 (5.5) 4.8 (5.0) 2.0 (0.2)	 6.6 (4.9) 3.8 (3.3) 2.0 (0.5)	 7.3 (5.9) 3.9 (4.1) 1.9 (0.5)	 5.3 (3.2) 3.8 (3.4) 2.0 (0.3)
Ongoing pregnancies per started cycle	4/25	5/24	6/25	10/24

Treatment group comparison was performed using ANOVA, and when $P<0.05$, Dunnett's t test was performed to compare the 3 corifollitropin alfa groups.

Table 3. Follicle Dynamics and Clinical Outcomes in Patients Treated With a Single Injection of Corifollitropin Alfa (60, 120, or 180 µg) or Daily rFSH (150 IU) in the Dose-Finding Study[3]

	Corifollitropin alfa, 60 µg (n=78)	Corifollitropin alfa, 120 µg (n=77)	Corifollitropin alfa, 180 µg (n=79)	Daily rFSH, 150 IU (n=81)
Number of cumulus-oocyte complexes retrieved, mean (SD) per started cycle	5.2 (5.5)	10.3 (6.3)[a]	12.5 (8.0)[b]	7.7 (6.3)[c]
Number of metaphase II oocytes, mean (SD) for patients with oocyte retrieval and ICSI only	7.7 (5.5)	10.1 (6.0)	11.6 (6.6)	5.9 (3.0)
Fertilization rate,[d] mean (SD)	60.5 (27.1)	65.2 (23.9)	59.8 (22.7)	61.7 (27.9)
Number of embryos obtained, mean ± SD: Total[d] Good-quality (grade I and II)[d] Good-quality transferred[e]	 4.9 (3.3) 2.2 (2.0) 1.3 (0.7)	 7.1 (4.1) 3.5 (2.7) 1.4 (0.7)	 8.2 (6.5) 3.5 (3.4) 1.3 (0.7)	 5.1 (4.2) 2.4 (2.3) 1.2 (0.7)
Implantation rate,[e] mean (SD)	20.5 (34.6)	19.8 (38.3)	17.1 (37.0)	18.2 (35.8)
Vital pregnancy[f] Per started cycle, number (%) Per transfer, number (%)	 12 (15%) 12 (27%)	 14 (18%) 14 (20%)	 12 (15%) 12 (17%)	 14 (17%) 14 (21%)
Ongoing pregnancy[g] Per started cycle Per transfer	 12 (15%) 12 (27%)	 12 (16%) 12 (17%)	 11 (14%) 11 (16%)	 11 (14%) 11 (17%)
Ongoing pregnancy including 1 year cryocycles,[h] number (%)	14 (18%)	21 (27%)	19 (24%)	16 (20%)
Number of cryocycles (patients, cryocycles)	8, 11	18, 25	23, 34	16, 22

SD = standard deviation.
[a]120 vs 60 µg: $P<0.0001$; [b]180 vs 60 µg: $P<0.0001$ and 180 vs 120 µg: $P=0.028$; [c]rFSH vs 60 µg: $P=0.009$, rFSH vs 120 µg: $P=0.020$; rFSH vs 180 µg: $P<0.001$;
[d]Restricted to patients with IVF or ICSI; [e]Restricted to patients with embryo transfer; [f]Intrauterine pregnancy with ≥1 vital fetus confirmed by ultrasound scan;
[g]≥1 vital fetus with heart activity by ultrasound scan after 12 weeks of gestation; [h]Ongoing pregnancy including fresh and cryoreplacement cycles.

Serum inhibin B levels were included in the model because in the dose-response trial, the time profile of serum inhibin B levels was shown to be a sensitive marker of insufficient ovarian response. After a single injection of 60 µg, insufficient follicular stimulation was reflected by a premature decline in inhibin B levels from day 6 onwards, as well as a high cycle cancellation rate.[3] This finding corroborates several other studies that have found insufficient follicular stimulation associated with the value of inhibin B.[34,35]

Because body weight turned out to be a major determinant of exposure to corifollitropin alfa and treatment outcome,[33] 2 doses of Elonva were selected for patients for the clinical trials: 100 µg for patients with a body weight ≤60 kg, and 150 µg for those weighing >60 kg. These doses in the respective patient populations provide an FSH activity profile that is very similar to a natural step-down protocol (Figure 3[28,31]), in which FSH activity levels, while remaining above a certain threshold, slowly decrease as follicular development occurs.

Phase 3 Efficacy and Safety Studies With Elonva (corifollitropin alfa)

Engage

The Engage trial was a randomized, double-blind, active-controlled, noninferiority clinical trial conducted to investigate the efficacy and safety of a single 150-µg injection of Elonva followed by daily treatment with Puregon from stimulation day 8 onwards up to and including the day of hCG administration.[36] A second group of patients, treated with daily injections of 200 IU Puregon, the most commonly prescribed drug for COS in ART programs, was used as an active control. Engage is the largest clinical trial conducted in IVF/ICSI to date and included 34 sites in Europe and North America. Both treatments included daily administration of the GnRH antagonist ganirelix (0.25 mg SC) starting on treatment day 5 up to and including the day of hCG; 5000 or 10,000 IU of hCG to induce final oocyte maturation; and progesterone (at least 600 mg/d vaginally, or at least 50 mg/d IM) for luteal support initiated on the day of oocyte retrieval and continued for at least 6 weeks, unless menses, or negative pregnancy test performed at least 14 days after embryo transfer.

The planned enrollment for the Engage trial was a total of 1400 patients, randomized in a 1:1 ratio (700 patients in each treatment group). Women from couples with an indication for COS and IVF or ICSI were included. Other inclusion criteria were: age ≥18 years but ≤36 years at the time of signing the informed consent; body weight >60 kg and ≤90 kg and body mass index ≥18 and ≤32 kg/m^2; and normal menstrual cycle length of 24 to 35 days.

The coprimary end points were ongoing pregnancy rate (assessed at least 10 weeks after embryo transfer) and the number of oocytes retrieved. Secondary end points included the following clinical outcome parameters: amount of Puregon needed (total and from treatment day 8 to day of hCG); endocrine parameters; number and size distribution of follicles (≥11 mm, ≥15 mm, and ≥17 mm) as documented by ultrasonography during treatment and on the day of hCG; number and quality of oocytes; normal fertilization rate; number and quality of embryos; implantation rate; miscarriage rate; and pregnancy rate. Safety evaluations included any adverse event (AE) (including OHSS, ectopic pregnancy, miscarriage, and moderate or severe score for any tolerance parameter).

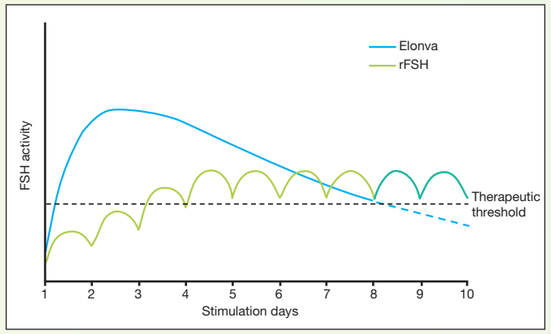

Figure 3. A single Elonva injection sustains FSH activity beyond the minimum threshold for at least 7 days and resembles a natural step-down protocol.[28,31]

Table 4. Clinical Outcomes (Pregnancy Rates) Following Elonva or rFSH in the Engage Trial

	Elonva (150 µg) n=756	rFSH (200 IU/d) n=750
Biochemical pregnancy (%)	364 (48.1)	352 (46.9)
Clinical pregnancy (%)	322 (42.6)	308 (41.1)
Vital pregnancy (%)	302 (39.9)	293 (39.1)
Ongoing pregnancy (%) Singleton (%, as a percentage of ongoing pregnancy) Multiple pregnancy (%, as a percentage of ongoing pregnancy)	294 (38.9) 211 (71.8) 83 (28.2)	286 (38.1) 220 (76.9) 66 (23.1)
Miscarriage (%)	27 (8.4)	21 (6.8)
Ectopic pregnancy (%)	7 (1.0)	9 (1.3)

A total of 1506 patients were enrolled and included in the intent-to-treat (ITT) group in the Engage trial, with 756 in the Elonva group and 750 in the active control group. Of these, 1472 patients (739 Elonva-treated patients and 733 active control–treated patients) comprised the per protocol (PP) group, which includes all patients without any major protocol violation.

As shown in Table 4, the ongoing pregnancy rate with Elonva was 38.9% compared with 38.1% with daily Puregon. This means that the estimated risk difference for ongoing pregnancy between Elonva and active control is 0.9% in the ITT group (and 1.1% in the PP group; data not shown). Since the predefined noninferiority margin was a difference of 8%, these results indicate that a single injection of Elonva demonstrates excellent efficacy and is noninferior to the active treatment with respect to ongoing pregnancy rates. Clinical outcomes (including the different pregnancy rates, miscarriage rate, and ectopic pregnancy rate) following COS were also similar between treatments (Table 4).

The estimated treatment difference in the number of oocytes retrieved is 1.2 cumulus-oocyte complexes in favor of Elonva in both the ITT and PP groups; this was within the predefined equivalence range of -3 to +5 oocytes, therefore the 2 treatments are equivalent even though this difference significantly favored Elonva (P=0.001). Both groups had similar basal antral follicle (<11 mm) counts on stimulation day 1 prior to the first injection (12.3 in the Elonva group and 12.4 in the active control group). COS with either treatment resulted in a similar increase in the number of follicles ≥11 mm (Figure 4). The number of follicles and size distribution of follicles

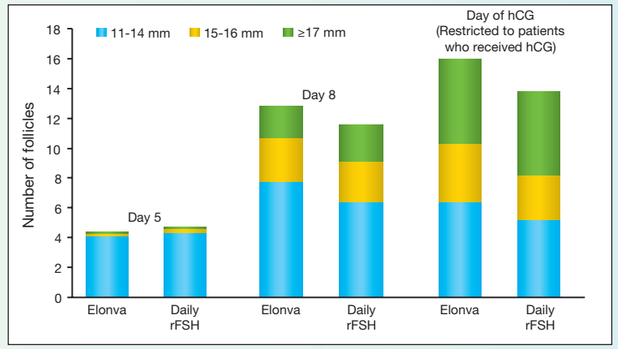

Figure 4. The number and size distribution of follicles during COS with Elonva or daily rFSH in the Engage clinical trial.

on treatment day 8 and the day of hCG were similar, although the mean numbers were higher in the Elonva group. As shown in Table 5, the number and quality of oocytes, fertilization rates, number and quality of embryos, and implantation rates following COS were all similar between treatments. The mean number of good-quality embryos transferred was 1.4 in both groups.

The median dose of Puregon administered from treatment day 8 onwards (400 IU) and the total mean number of stimulation days (9.0) was the same for both treatment groups in those patients who received hCG. Since patients receiving the active control had daily injections of Puregon, the cumulative dose was higher in those patients. The criterion for hCG (at least 3 follicles ≥17 mm) was met on or before treatment day 8 in 32.9% of Elonva-treated patients and 42.9% of patients in the active control group.

Serum concentrations of LH, estradiol, inhibin B, and progesterone were similar between the 2 treatment groups during and after stimulation. To determine if endogenous LH levels have any impact on ongoing pregnancy rates, a retrospective analysis was conducted to determine if an association could be observed between ongoing pregnancy rates and LH level. In both arms of the study, outcomes for patients with low, normal, or high endogenous LH levels during stimulation were equivalent.[37,38] Serum FSH immunoreactivity on stimulation day 5 was similar between treatments at baseline but higher in patients who had received a single injection of Elonva than in those who received Puregon as daily injections.

The safety of Elonva in the Engage study was similar to that of the active comparator, daily Puregon, since the rate of patients experiencing at least 1 AE was comparable between groups. The percentages of serious AEs (SAEs), patients with at least 1 drug-related AE, and patients with at least 1 in-treatment AE with an intensity of "severe" were also similar. The percentage of patients who discontinued the trial due to an AE or SAE was higher in patients in the Elonva group than in the daily Puregon group (2.1% vs 0.4%, respectively), generally due to too high of an ovarian response either before or after oocyte retrieval. The safety results from the Engage trial are discussed in greater detail in the *Safety and Adverse Events* section of this monograph.

Table 5. Efficacy Outcomes Following Elonva or Daily rFSH in the Engage Trial

	Elonva (150 µg) n=756	Daily rFSH (200 IU/d) n=750
Mean (SD) number of oocytes retrieved	13.7 (8.2)[a]	12.5 (6.7)[a]
Number of patients with oocyte quality assessment[b]	n=413	n=417
Number of oocytes	13.8 (7.6)	12.1 (6.3)
Number of metaphase I oocytes	1.1 (1.5)	0.9 (1.3)
Number of metaphase II oocytes	10.8 (6.5)	9.2 (5.1)
Number of germinal vesicles stage oocytes	1.5 (1.9)	1.7 (2.2)
Number of metaphase II oocytes as a percentage of total (%)	78.9 (18.9)	77.4 (18.1)
Number of patients with fertilization rate assessment[c]	n=727	n=737
Fertilization rate (%)	66.0 (23.4)	67.6 (22.9)
Number of patients with embryo assessment at Day 3[d]	n=714	n=729
Total	8.3 (5.6)	7.4 (4.8)
Good quality	4.6 (4.3)	4.4 (3.9)
Number of patients with embryo transfer[e]	n=672	n=704
Total number of embryos transferred	1.7 (0.4)	1.7 (0.4)
Number of patients with 1 embryo transferred	173 (25.7)	190 (27.0)
Number of patients with 2 embryos transferred	496 (73.8)	514 (73.0)
Number of patients with 3 embryos transferred	3 (0.4)	0
Good quality transferred	1.4 (0.7)	1.4 (0.7)
Implantation rate[e] (%)	36.2 (41.6)	32.2 (40.1)

[a] P=0.001; [b]Including 3 patients for whom the quality of oocytes was assessed, but for whom ICSI was not performed; [c]Restricted to patients with IVF and/or ICSI; [d]Excluding patients who had embryos transferred or cryopreserved before day 3; [e]Restricted to patients with embryo transfer.

Ensure

The Ensure clinical trial was also a randomized, double-blind, active-controlled, equivalence (noninferiority) clinical trial to investigate the efficacy and safety of a single injection of Elonva 100 µg to initiate and sustain multiple follicular development for COS in women with a body weight of ≤60 kg.[39] Nineteen participating sites from Europe and Asia were involved in this trial. Following a single injection of Elonva, daily doses of Puregon ≤200 IU per day were started 1 week later (on treatment day 8). As in the Engage trial, daily Puregon was used as an active comparator reference in Ensure; however, the daily dose was 150 IU per day. Both treatment groups received daily administration of the GnRH antagonist ganirelix (0.25 mg SC, stimulation day 5 to day of hCG); hCG to induce final oocyte maturation; and luteal phase support following IVF or ICSI.

The planned patient enrollment for the Ensure trial was a total of 330 patients, randomized in a 2:1 ratio, with 220 patients receiving Elonva and 110 receiving daily Puregon. Women from couples with an indication for COS and IVF or ICSI were included. Other inclusion criteria were: age ≥18 years but ≤36 years at the time of signing the informed consent; body weight ≤60 kg and body mass index ≥18 and ≤32 kg/m^2; and normal menstrual cycle length of 24 to 35 days.

The primary end point of the Ensure trial was the number of oocytes retrieved, with an equivalence margin and the 95% confidence limits of the difference between -3 and +5 oocytes. Unlike the Engage trial, this study was not powered to determine pregnancy rates, although this measure was among the other variables evaluated. These additional variables included the cancellation rate; total Puregon dose (total and from treatment day 8 to day of hCG); endocrine parameters; number and size distribution of follicles; fertilization rate; number and quality of embryos; implantation rate; miscarriage rate; and pregnancy rate. Safety evaluations included any SAE (including OHSS), local tolerance, and the development of anti–corifollitropin alfa antibodies.

A total of 396 patients were enrolled, 268 in the Elonva group and 128 in the active control group. The mean number of cumulus-oocyte complexes (± standard deviation) retrieved per started cycle was higher in patients treated with Elonva followed by Puregon (13.3 ± 7.3) compared with those patients who received daily Puregon alone (10.6 ± 5.9). This resulted in a treatment difference of 2.5, which was statistically significant in favor of Elonva (P<0.001) but within the equivalence margin of -3 to +5 oocytes. Using these criteria, Elonva 100 µg was noninferior to daily Puregon for COS in women weighing ≤60 kg (Table 6).

Table 6. Fertilization Rate, Number of Good-Quality Embryos, and Clinical Outcomes Following a Single Dose of Elonva (100 µg) or Daily rFSH (150 IU) in the Ensure Trial

	Elonva (100 µg)	rFSH (150 IU/d)
Fertilization rate, mean percent (SD)	67.6 (22.5) n=264	67.7 (25.4) n=124
Number of good-quality embryos, mean (SD)[a]	3.4 (3.0) n=264	3.0 (3.0) n=124
Number of good-quality embryos transferred, mean (SD)[b]	1.3 (0.8) n=246	1.3 (0.8) n=121
Clinical outcome (%)	n=268	n=128
Biochemical pregnancy	37.7	45.3
Clinical pregnancy	29.1	37.5
Vital pregnancy	25.7	35.2
Ongoing pregnancy	25.4[c]	34.4[c]

[a]Good-quality embryos at day 3, restricted to patients with IVF/ICSI; [b]Restricted to patients with embryo transfer; [c] P=0.06.

Among the other variables measured in the Ensure trial, endocrine parameters were similar between treatments except for serum immunoreactive FSH, which was higher in Elonva-treated patients on stimulation days 3 and 5. Because of the treatment design, the total dose of Puregon and the number of days treated with Puregon were higher in patients in the active comparator group, but the dose of Puregon from day 8 to day of hCG (300 IU in Elonva-treated patients and 275 IU in patients treated with daily Puregon) and the total number of stimulation days were similar (median 9.0 and range 6-15 for both treatments). On average, 2 days of Puregon treatment were needed following a single injection of Elonva. The percentage of patients reaching hCG criteria on or before day 8 of the treatment also was similar (32.8% in Elonva-treated patients and 39.8% in patients receiving daily Puregon). As shown in Table 6, fertilization rates, the number of good-quality embryos, and clinical outcomes were comparable. The mean number of good-quality embryos obtained for the Elonva group was 3.4 vs 3.0 for the Puregon group. The same number of good quality embryos was transferred (1.3) in each group. The biochemical pregnancy rate for Elonva was 37.7% vs 45.3% for the Puregon group. Ongoing pregnancy rate was 25.4% vs 34.4% for Elonva vs Puregon, respectively. No differences between the groups were statistically significant. Safety evaluations indicated that the rates of AEs and SAEs were similar; these data are discussed in greater detail in the *Safety and Adverse Events* section of this monograph.

Safety and Adverse Events

Preclinical data have revealed no special hazard for humans based on conventional studies of single and repeated dose toxicity and safety pharmacology with corifollitropin alfa. Clinical safety data have demonstrated that Elonva is safe and well-tolerated. AEs are generally low in incidence and mild to moderate in severity, and consistent with those experienced during COS with daily Puregon injections. The most frequently reported adverse drug reactions during treatment with Elonva in clinical trials are pelvic discomfort (5.5%), OHSS (5.2%), pelvic pain (4.1%), headache (3.2%), nausea (1.7%), fatigue (1.4%), and breast complaints (including tenderness) (1.2%).

The main adverse drug reactions in women treated with Elonva (according to body system and frequency) in clinical trials are listed in Table 7. Ectopic pregnancy, miscarriage, and multiple gestations also have been reported following administration of Elonva, but these are considered to be related to the ART procedure or subsequent pregnancy.

Injection site reactions following injection, including redness, itching, pain, swelling, and/or bruising, were rare and rated as mild when they occurred; none were rated as "moderate" or "severe."[27] No drug-related teratogenicity has been observed. Hematologic measures were within normal parameters, and no clinically relevant shifts in hematologic, biochemical, or laboratory results were reported.[27,28] During the dose-selection and dose-finding studies, safety was similar among treatments, indicating that no difference in safety occurred with higher doses of Elonva.[31]

Table 7. The Main Adverse Drug Reactions in Women Treated With Elonva, According to Body System and Frequency

Body System	Frequency	Undesirable Effect
Nervous system disorders	Common (≥1%, <10%)	Headache
	Uncommon (≥0.1%, <1%)	Dizziness
Gastrointestinal disorders	Common (≥1%, <10%)	Nausea
	Uncommon (≥0.1%, <1%)	Abdominal pain, vomiting, diarrhea, constipation and abdominal distension
Reproductive system and breast disorders	Common (≥1%, <10%)	OHSS, pelvic pain and discomfort, breast complaints
	Uncommon (≥0.1%, <1%)	Ovarian torsion
General disorders and administration site conditions	Common (≥1%, <10%)	Fatigue

In clinical trials in which daily Puregon was used as an active comparator, the rates of AEs and SAEs were generally comparable between treatments.[3,30,31] The use of Elonva for COS has the associated risks of all gonadotropin treatments as well as ARTs, including the potential for multiple pregnancies. Therefore, couples should be advised of the potential risks for the mother and for the neonate. Since women undergoing ART often have tubal abnormalities, the incidence of ectopic pregnancy may be increased. Although the incidence of ectopic pregnancy with Elonva was similar to that with Puregon (Table 4), ultrasound examination should be conducted to exclude the possibility of extrauterine pregnancy.

Ovarian Hyperstimulation Syndrome

OHSS is medically distinct from ovarian enlargement and is the most serious risk of treatment with gonadotropins.[40] Clinical signs and symptoms of mild and moderate OHSS include abdominal pain, nausea, diarrhea, and mild to moderate enlargement of the ovaries and of ovarian cysts. Severe OHSS, which may be life-threatening, includes the following clinical signs and symptoms: large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnea, oliguria, hematologic abnormalities, and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.[40] OHSS generally develops if the patient has had an excessive response to gonadotropins and has produced a large number (≥20) of follicles with an associated increase in estrogen production.[40] It is not clear why OHSS occurs, and because of its idiosyncratic nature, the syndrome cannot be avoided completely in COS.[40]

The rate of OHSS following Elonva generally was similar to that with daily Puregon in clinical trials. No cases of OHSS occurred in women with anovulatory infertility.[30] In the dose-response and dose-finding studies for COS, the rates of OHSS observed following a single injection of Elonva were comparable to those with daily Puregon.[3,31] In the Engage trial, the incidence of OHSS (mild, moderate, and severe) was 7.0% in the Elonva group, and 6.3% in the Puregon group. A total of 4.2% of Elonva-treated patients and 2.6% of patients treated with daily Puregon reported moderate or severe signs of OHSS (P=0.15). Hospitalization for OHSS was required in 1.9% of patients treated with Elonva and 1.2% of patients treated with daily Puregon. Similar rates of OHSS were noted in the Ensure clinical trial.

At this writing use of Elonva is not recommended in women with a history of OHSS. Moreover, its use has not been analyzed in cases where the basal antral follicle count is >20.

Immunogenicity

Corifollitropin alfa was produced by well established cell lines derived from Chinese hamster ovaries (CHO) transfected with the genes encoding the α- and β-subunits from human FSH and the carboxy-terminal peptide from hCG.[24,27] Most of the clinical studies showed that no patients had anti–corifollitropin alfa antibodies.[27,28,30,31] The Engage trial was the only study in which the posttreatment sample of 2 patients had a significant increase in the binding

of anti–corifollitropin alfa. The antibody activity was extremely low and appeared to be without neutralizing activity and, thus, did not interfere with the activity of Elonva. Both patients had a normal ovarian response and were able to have oocytes retrieved (16 and 15 oocytes collected, respectively), and both became pregnant. One patient had headache and nausea during stimulation and pain after oocyte retrieval, while the other patient had no AEs.

SUMMARY AND CONCLUSIONS

A surprisingly large proportion of couples ranging from 39.9% to 62.2% discontinue ART or IVF programs without achieving the live birth of a child.[11,12] Because discontinuation of the treatment program deprives the couple of an optimal cumulative chance of successfully achieving pregnancy, “dropping out” may be considered an adverse treatment outcome.[8] Patients drop out of ART and IVF programs for a number of reasons, but the physical and psychological burden associated with treatment is the most frequently cited.[8] Treatment of infertility is extremely stressful because of the complexity of the process, costs, and the physical and emotional demands that lead to high levels of negative emotions, including constant worry and anxiety.[5] The development of new treatments that reduce the stress and burdens associated with COS, including the development of more “patient-friendly” regimens, may result in increased continuation in ART programs and therefore result in a higher number of patients achieving their goal of a live birth.[8,9]

Elonva (corifollitropin alfa) is a novel recombinant fertility hormone that has been designed as a sustained follicle stimulant with the same pharmacodynamic profile as rFSH, but with a markedly prolonged duration of FSH activity. Due to its ability to initiate and sustain multiple follicular growth for an entire week, a single subcutaneous injection of the recommended dose of Elonva replaces the first 7 injections of any daily rFSH preparation in a COS treatment cycle.

Elonva is indicated for COS in combination with a GnRH antagonist for the development of multiple follicles and pregnancy in women participating in an ART program. The efficacy of Elonva has been proven in the largest clinical study program in IVF to date. Elonva in a GnRH antagonist protocol can reduce the number of injections by 70% (from 35 to 10) compared with conventional daily gonadotropin in a long-agonist protocol. Elonva should be administered as a single SC injection, preferably in the abdominal wall, during the early follicular phase of the menstrual cycle and is available in prefilled syringes at doses of 100 µg/0.5 mL (for patients weighing ≤60 kg) and 150 µg/0.5 mL (for patients weighing >60 kg). A single injection of the appropriate dose results in serum immunoreactive FSH levels on day 2 that remain above the minimal FSH threshold until day 8 (Figure 3). The use of the higher dose of Elonva would provide no additional benefit, since outcomes are similar to those with the recommended doses even with the higher doses employed in the feasibility and dose-finding studies.[3,31]

The daily dose of Puregon employed depends on ovarian response, although a fixed dose of 150 IU from stimulation day 8 onwards appears to be sufficient to reach the criteria for hCG. Importantly, about 33% of all patients treated with Elonva achieved hCG criteria and did not require additional Puregon. Treatment with a GnRH antagonist should be started on stimulation day 5 (or day 6 if the ovarian response appears to be delayed) to prevent the occurrence of premature LH surges. The doses of Elonva have only been established with a treatment regimen that employs the use of a GnRH antagonist.

The incidence of AEs is generally low, and the severity of AEs is mild to moderate, consistent with those experienced during COS with daily Puregon injections. Injection site reactions were rare and rated as mild when they occurred. No anti–corifollitropin alfa antibodies of clinical significance were detected. The incidence of OHSS with hospital admission was low (1.9% in Engage), similar to rates seen with daily rFSH treatments, and within the ranges of current care using various GnRH analog regimens for COS. Thus, both 100-µg and 150-µg tested doses of Elonva were safe and well-tolerated.

In conclusion, Elonva is a novel recombinant fertility hormone that can be administered as a single injection to initiate and sustain multiple follicular development for the first 7 days of an ovarian stimulation regimen. The use of Elonva in a GnRH antagonist protocol for COS can substantially reduce the number of daily injections for patients.[3] A single injection of Elonva results in comparable efficacy and safety to 7 daily injections of Puregon. Across clinical trials, Elonva results in comparable numbers of oocytes collected, embryos available for transfer, and pregnancy rates as daily Puregon. Elonva offers an alternative, more simplified treatment regimen for COS in IVF/ICSI that is more patient-friendly and potentially less stressful. These attributes of Elonva should lead to fewer patients discontinuing participation in an ART program because of the psychological and physical burden and, therefore, may lead to overall improvement in outcomes.

elonva® corifollitropin alfa

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