Large, comparative, randomized double-blind trial confirming noninferiority of pregnancy rates for corifollitropin alfa compared with recombinant follicle-stimulating hormone in a gonadotropin-releasing hormone antagonist controlled ovarian stimulation protocol in older patients undergoing in vitro fertilization

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Objective: To compare corifollitropin alfa with recombinant FSH treatment in terms of the vital pregnancy rate in older patients undergoing IVF.
Design: Phase 3 randomized, double-blind, noninferiority trial.
Setting: Multicenter trial.
Patient(s): A total of 1,390 women aged 35–42 years.
Intervention(s): A single injection of 150 μg of corifollitropin alfa or daily 300 IU of recombinant FSH for the first 7 days then daily recombinant FSH until three follicles reach $\geq$17 mm in size. Ganirelix was started on stimulation day 5 up to and including the day of recombinant hCG administration. If available, two good quality embryos were transferred on day 3.
Main Outcome Measure(s): Vital pregnancy rate (PR), number of oocytes, and live birth rate.

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Result(s): Vital PRs per started cycle were 23.9% in the corifollitropin alfa group and 26.9% in the recombinant FSH group, with an estimated difference (95% confidence interval) of -3.0% (−7.4 to 1.4). The mean (SD) number of recovered oocytes per started cycle was 10.7 (7.2) and 10.3 (6.8) in the corifollitropin alfa and the recombinant FSH groups, respectively, with an estimated difference of 0.5 (−0.2 to 1.2). The live birth rates per started cycle were 21.3% in the corifollitropin alfa group and 23.4% in the recombinant FSH group, with an estimated difference (95% confidence interval) −2.3% (−6.5 to 1.9). The incidence of serious adverse events was 0.4% versus 2.7% in the corifollitropin alfa and recombinant FSH groups, respectively, and of ovarian hyperstimulation syndrome (OHSS; all grades) was 1.7% in both groups.
Conclusion(s): Treatment with corifollitropin alfa was proven noninferior to daily recombinant FSH with respect to vital PRs, number of oocytes retrieved, and live birth rates, and was generally well tolerated.
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Key Words: Corifollitropin alfa, recombinant FSH, assisted reproductive technology, GnRH antagonist, women aged 35–42 years

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Corifollitropin alfa is a novel recombinant gonadotropin analogue with FSH activity that has an extended duration of action, enabling it to initiate and sustain multifollicular growth for 7 days (1). This FSH analogue is composed of an α subunit identical to that of human FSH and a hybrid β subunit, consisting of the FSH β unit and the carboxyterminal peptide of hCG β subunit (2). As a result of the extended half-life of this agent, a single injection of corifollitropin alfa replaces 7 days of daily recombinant FSH in an assisted reproductive technology (ART) treatment protocol.

The efficacy and safety of corifollitropin alfa in women $\leq$36 years of age were prospectively studied in two phase 3, double-blind, randomized, controlled studies (3–5). In both studies, treatment with corifollitropin alfa produced a similar therapeutic response compared with treatment with recombinant FSH, and was generally well tolerated (6). The ENGAGE study, which compared 150 μg of corifollitropin alfa to 200 IU of recombinant FSH in a GnRH antagonist protocol in 1,506 IVF patients, demonstrated similar ongoing pregnancy rates (PRs) in both groups (39.0% corifollitropin alfa vs. 38.1% recombinant FSH) (4).

The number of women >35 years of age seeking infertility care continues to increase (7). This older population faces unique challenges with respect to fertility because aging has a major impact on the success of infertility treatments. The decline in ovarian reserve and the reduction in oocyte quality associated with aging (8, 9) result in fewer good quality oocytes available for use in the ART cycle. In 2012, the reported PRs in older women after ART were 26% at age 40 years, 22% at age 41 years, and 17% at age 42 years (7). In addition, the rates of spontaneous abortion increase with aging as a consequence of the decline in oocyte quality, causing even lower live birth rates (18% at age 40 years, 13% at age 41 years, and 9% at age 42 years) (7). These data highlight the importance of evaluating the efficacy and safety of infertility treatments in older women; however, there are no published studies of corifollitropin alfa use in this age cohort. This double-blind, randomized, active-controlled trial compared the efficacy and safety of corifollitropin alfa with recombinant FSH in women $\geq$35 to $\leq$42 years of age seeking treatment for infertility.

MATERIALS AND METHODS

Pursue was a phase 3, randomized, double-blind, double-dummy, active-controlled, noninferiority trial conducted at 33 IVF centers in the United States from July 2010 to October 2012. The trial was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was provided by all subjects.

Study Population

Women aged $\geq$35 to $\leq$42 years with a body weight of $\geq$50 kg and a body mass index (BMI) of $\geq$18 and $\leq$32 kg/m^2 were eligible for enrollment in the study. All subjects had a history of regular spontaneous menstrual cycles (cycle length, 24–35 days), and had access to ejaculatory sperm for IVF or intracytoplasmic sperm injection (ICSI).

Subjects were excluded if they had a history of ovarian hyper-response (including a previous controlled ovarian stimulation [COS] cycle with more than 30 follicles $\geq$11 mm on ultrasound) or a history of ovarian hyperstimulation syndrome (OHSS), a current diagnosis or a history of polycystic ovary syndrome (PCOS) (10), a history of non- or low ovarian response to FSH/hMG treatment (e.g., previous COS cycle cancelled due to insufficient ovarian response or <4 oocytes obtained), more than three unsuccessful COS cycles (i.e., no pregnancy achieved) since the last established ongoing pregnancy (if applicable), or a history of $\geq$3 miscarriages. The following were exclusion criteria: subjects with >20 basal antral follicles on ultrasound (<11 mm, both ovaries combined), or FSH >15 IU/L or LH >12 IU/L in the early follicular phase; current or recent history of alcohol or drug abuse in the past 12 months, contraindications for the use of gonadotropins, a significant endocrine abnormality within the past 3 years, epilepsy,