Title of Trial: A Phase IIIb/IV, open-label study to assess the efficacy and safety of a pre-defined, fixed dose of Gonal-f® (Filled by Mass in a Prefilled Pen) based on subject baseline characteristics, for ovarian stimulation in subjects undergoing *in vitro* fertilization (IVF).

Investigational Product: Gonal-f® (Follitropin alfa [r-hFSH])

Trial No.: 25198

Study Centers: This study was conducted in 18 clinical centers.

Trial Initiation Date: 22 September 2004

Trial Completion Date: 16 January 2006

Development Phase: Clinical Phase 3b/4

Publication (reference): None

Study Objectives:

Clinical validation of the assisted reproductive technology (ART) treatment guidelines, which determine the optimal dose of r-hFSH based on subject baseline characteristics/predictors of ovarian response.

Methodology:

Phase IIIb/IV, open-label, multi-centre, multi-regional study in healthy female partners of infertile couples undergoing ART treatment.

Subjects were to be treated first with a gonadotrophin releasing hormone (GnRH) agonist according to centre's standard practice (excluding depot formulations). Pituitary down-regulation was to be confirmed by oestradiol (E2) levels and/or ultrasound (US) scan depending on the centre's standard practice. Subjects were then to start r-hFSH treatment (Gonal-f® Prefilled Pen) at a pre-defined, fixed dose determined by the ART treatment guidelines computed by the study dosage algorithm. Dose reduction was to be allowed only in the case of risk of ovarian hyperstimulation syndrome (OHSS).

When at least 1 follicle ≥18 mm and 2 follicles ≥16 mm in diameter were developed, a single injection of 250 mcg of recombinant human chorionic gonadotrophin (r-hCG, Ovid[t]rel[le]®) was to be administered. Ovum pick up (OPU), in vitro fertilization (IVF), and embryo transfer (ET) were to be performed according to the centre's standard practice. A post-treatment safety visit was to be performed for all subjects on days 15-20 post r-hCG.

Number of Subjects (Planned and Analyzed):

A total of approximately 150 subjects were to be included in the study. A total of 166 subjects were enrolled in the study and received at least 1 dose of investigational product.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Infertile women seeking pregnancy, age 18 to 35 years (35 not included), justifying an in vitro fertilization/embryo transfer (IVF/ET) treatment. Male partner with semen analysis within the previous 6 months considered adequate per the centre's standard practice for IVF or intracytoplasmic sperm injection (ICSI). A regular spontaneous ovulatory menstrual cycle between 21 and 35 days in length, presence of both ovaries, and a normal uterine cavity. An early follicular phase (Day 2-4) serum level within the previous 3 months of follicle stimulating hormone (FSH) ≤12 IU/L, and E2 within the centre's local laboratory normal range.

Subjects were to be required to have at least 1 wash-out cycle, defined as ≥30 days since the last dose of clomiphene citrate or gonadotrophin treatment.

Subjects were to be excluded if they had had 2 previous ART cycles with inadequate or excessive response, extra-uterine pregnancy within the previous 3 months, previous severe OHSS, body mass index (BMI) >30 kg/m2, history of 3 or more miscarriages (early or late) due to any cause, abnormal gynaecological bleeding of undetermined origin, tumours of the hypothalamus or pituitary gland, ovarian enlargement or cyst of unknown aetiology, hepatitis, HIV infection, or ovarian, uterine or mammary cancer.

Study Treatment:

Follitropin alfa (Gonal-f®) Prefilled Pen (300 IU, 450 IU, and 900 IU) was to be administered subcutaneously (SC) per the ART treatment guidelines specified in the protocol.

Duration of Treatment**:** One cycle of treatment was to be administered.

Reference Therapy(s), Dose and Mode of Administration: No reference therapy was included in the design of the study.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the total number of oocytes retrieved per subject.

Secondary efficacy endpoints included total dose of r-hFSH used (in IU), total number of r-hFSH stimulation treatment days, cycle cancellation rate for excessive or inadequate response to r-hFSH, number of subjects needing r-hFSH dose adjustment for over stimulation, mean daily r-hFSH dose, implantation rate (sacs per total number of embryos transferred), total and clinical pregnancy rate per subject who underwent ET, and multiple pregnancy rate.

The tertiary efficacy endpoint was the percentage of subjects responding to items on the ease-of-use questionnaire concerning the Gonal-f® Prefilled Pen.

Safety: The following parameters were to be monitored for the evaluation of safety: incidence and severity of OHSS, incidence and severity of adverse events (AEs), and serious adverse events (SAEs).

Statistical Methods:

This study was designed to be descriptive only. Descriptive statistics were to be presented for all variables. The primary statistical analysis of both safety and efficacy was to include data on all subjects who received at least 1 dose of investigational product and who were allocated to a group containing at least 5 subjects (the intention-to-treat [ITT] population).

Dosage groups that contained fewer than 5 subjects were to be presented in data listings only. Efficacy analyses were to be repeated for the per protocol (PP) population if a high proportion of protocol deviators was identified in the ITT population.

Results:

Subject Disposition: A total of 172 subjects were allocated to treatment, of which 166 subjects were enrolled in the study and received at least 1 dose of investigational product. Of these 166 subjects, 161 were allocated to an r-hFSH dosage group that contained at least 5 subjects: 48 subjects at 75 IU, 45 subjects at 112.5 IU, 34 subjects at 150 IU, 24 subjects at 187.5 IU, and 10 subjects at 225 IU; and 5 subjects were allocated to dosage groups with fewer than 5 subjects. Of these 5 subjects, 1 subject was allocated to receive 37.5 IU, 2 subjects were allocated to receive 262.5 IU, and 2 subjects were allocated to receive 300.0 IU. These 5 subjects started pituitary down-regulation and then stimulation with r-hFSH. For the purposes of this report, the term "allocated to an r-hFSH dosage group" refers only to the 161 subjects allocated to a dosage group containing at least 5 subjects.

All of the 161 subjects allocated to a dosage group started pituitary down-regulation, and then stimulation with r-hFSH. Overall, of the 161 subjects allocated to a dosage group who started stimulation with r-hFSH, 139 (86.3%) received r-hCG. One hundred thirty-five of 160 subjects (84.4%) underwent OPU, and 127 of 157 subjects (80.9%) underwent ET.

Demographics and Baseline Characteristics: The mean ± SD age of the 161 infertile women inthe ITT population was 31.1 ± 2.9 years, and the mean ± SD body mass index (BMI) was 22.36 ±2.65 kg/m^2. Ninety-seven subjects (60.2%) presented with primary infertility.

Efficacy Results: The primary efficacy endpoint in this study was the total number of oocytes retrieved per subject. Overall, the mean ± SD number of oocytes retrieved per subject was 10.3 ± 5.7 oocytes per subject (median 9.0 oocytes per subject).

The percentage of cancelled cycles due to inadequate or excessive response overall for subjects in the ITT population was 14.9% (24/161). Twenty-three (14.3%) cycles were cancelled due to an inadequate response, 12 of them in the 75 IU dosage group. Only 1 (0.6%) cycle in the ITT population was cancelled due to an excessive response. Although the cancellation rate for the PP population was similar (13/118 [11.0%]), all 13 cancelled cycles in the PP population were cancelled due to an inadequate response and no cycle in the PP population was cancelled due to an excessive response.

Of the 161 subjects in the ITT population, 138 (85.7%) required no dose adjustment during the course of the study. Fourteen (8.7%) subjects required an increase in dose, 4 (2.5%) subjects required a decrease in dose, and 5 (3.1%) subjects required an increase followed by a decrease.

The overall mean ± SD implantation rate (sacs per number of embryos transferred) across the 5 dosage groups in the ITT population was 29.8% ± 38.5%. Implantation rates across the 5 dosage groups ranged from a high of 37.1% ± 40.5% for the 187.5 IU dosage group and 36.5% ± 42.8% for the 75 IU dosage group to a low of 11.9% ± 20.9% for the 225 IU dosage group.

The clinical pregnancy rate for the ITT population was 34.2% (55/161). Clinical pregnancy rates ranged from a high of 50.0% (12/24) in the 187.5 IU dosage group to a low of 20.0% (2/10) in the 225 IU dosage group. For subjects who underwent OPU, 38.5% (55/143) of subjects became clinically pregnant. For subject who underwent ET, 40.4% (55/136) became clinically pregnant. There were 12 multiple pregnancies among the 55 clinical pregnancies in the ITT population, for a multiple pregnancy rate of 12/55 (21.8%).

The tertiary endpoint was the percentage of subjects responding to items on the ease-of-use questionnaire. In the ITT population, 94/143 (65.7%) subjects reported that they administered their r-hFSH injections themselves, using the Gonal-f® Prefilled Pen. There were no major differences among the 5 dosage groups in the percentage of subjects self-injecting with the Gonal-f® Prefilled Pen. Most subjects (110/136 [80.9%]) reported that injection took no more than 30 seconds. Most subjects (87/143 [60.8%]) responded that the Gonal-f® Prefilled Pen was very practical to use and another 32.9% responded that it was practical to use. Overall, 53/70 (75.7%) subjects responded that the Gonal-f® Prefilled Pen was more or a lot more practical than the injection method used previously. Finally, 114/142 (80.3%) subjects responded that they were highly satisfied or very satisfied with use of the Gonal-f® Prefilled Pen; and 128/143 (89.5%) subjects responded that they were very comfortable or comfortable using the Gonal-f® Prefilled Pen.

Safety Results: Overall, 45/161 (28.0%) subjects in the ITT population of subjects allocated to an r-hFSH dosage group reported a total of 70 treatment-emergent AEs. The percentages of subjects in each of the 5 dosage groups reporting treatment-emergent AEs were comparable. The most commonly reported treatment-emergent AEs were headache (15 subjects reporting 18 events) and OHSS (11 subjects reporting 11 events). Of the 11 subjects with OHSS, 8 cases occurred during the study and 3 cases were late and associated with pregnancy. The majority of the treatment-emergent AEs reported were mild (42/70 events). The remaining AEs were moderate (20/70) or severe (8/70 events). The severe treatment-emergent AEs reported were OHSS (2 subjects, 2 events), ovarian torsion (1 subject, 1 event), diarrhea (1 subject, 1 event), injection-site pain (2 subjects, 2 events), ectopic pregnancy (1 subject, 1 event), and jugular vein thrombosis (1 subject, 1 event).

Injection-site reactions that occurred were generally mild or moderate. Mild bruising (24 [14.9%] subjects), mild injection-site pain (13 [8.1%] subjects), and mild redness (11 [6.8%] subjects) were the most common injection-site reactions. Mild itching (6 subjects), swelling (5 subjects), and tenderness (1 subject) were also reported. Moderate injection-site redness

(3 subjects), pain (2 subjects), itching (1 subject), and bruising (1 subject) were also reported. One case of severe injection-site pain was reported.

Overall, 10 treatment-emergent SAEs were reported by 8 subjects during the study. In addition to these treatment-emergent SAEs, pre-treatment SAEs were reported for 2 subjects. Five subjects withdrew from the study due to an AE. Four subjects withdrew from the study due to a treatment-emergent AE: vaginal bleeding (2 subjects), OHSS, and ovarian cyst. In addition, 1 subject withdrew from the study due to a pre-treatment AE (transitional cell carcinoma of the bladder).

Overall, the safety profile of the r-hFSH fixed dose administered by the Gonal-f® Prefilled Pen was as expected, and no new or unexpected treatment-emergent AEs were reported.

Conclusions:

Although this was a descriptive study, not a randomised, controlled study, and the number of subjects in each of the 5 dosage groups was small and varied among the dosage groups, the data suggest that the starting dose for r-hFSH can be selected in an evidence-based manner by using individual baseline characteristics that influence a subject's ovarian response.