Synopsis XM17-05

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: XM17 Drug Product	Volume:	
Name of Active Ingredient: Follitropin alfa (INN), code XM17	Page:	

Title of Study:

Efficacy, safety and tolerability of XM17 compared to Gonal-f® in women undergoing assisted reproductive technologies

A multi-national, multi-centre, randomised, controlled, assessor-blind, parallel group Phase III study including follow-up periods

Main Study

Co-ordinating Investigator: [redacted] Belgium

Investigators: Please refer to list of investigators (refer to: *Appendix 16.1.4*)

Study centres: 22 centres in 5 countries: 4 in Belgium (2 did not randomise any patients), 5 in the Czech Republic, 7 in Germany, 2 in Hungary, 4 in Poland

Publication (reference): Not applicable

Studied Period (Main Study):	Date of first patient enrolled: 19 March 2010 Date of last patient completed: 27 January 2011
Phase of development:	III

Objectives:

Primary: To demonstrate the equivalence of XM17 compared to Gonal-f® with respect to the primary efficacy endpoint of the number of oocytes retrieved in infertile but ovulatory women undergoing superovulation for assisted reproductive technologies (ART).

Secondary:

1) To compare the efficacy of XM17 against that of Gonal-f® with respect to the following parameters: total dose (IU) of recombinant human follicle-stimulating hormone (r-hFSH) and number of days of r-hFSH stimulation, number of patients needing dose adaptations, number of oocytes retrieved in patients with no r-hFSH adaptation, number of follicles (≤ 10 mm, > 10–14 mm, > 14–17 mm, > 17 mm) on Stimulation Day 6 prior to dose adaptation and number of follicles > 14 mm on the day of human chorionic gonadotropin (hCG) injection, 17-β oestradiol serum concentration on Stimulation Day 6 prior to dose adaptation and on the day of hCG injection, endometrial thickness on Stimulation Day 6 prior to dose adaptation and on the day of hCG administration, cancellation rate prior to oocyte retrieval, oocyte maturity (only intracytoplasmic sperm injection [ICSI]), oocyte quality, fertilisation rate, clinical pregnancy rate (per randomised patient, per oocyte retrieval, per embryo transfer)
2) To demonstrate the safety and tolerability of XM17 compared to Gonal-f® in women undergoing ART

Methodology:

This was a multi-national, multi-centre, randomised (1:1), controlled, assessor-blind, parallel-group Phase III study with Follow-up Part A and Follow-up Part B. The Main Study consisted of a fixed-dose phase and a dose adaptation phase).

Patient eligibility was assessed at Visit 1. In eligible patients, pituitary down-regulation was started with the gonadotropin-releasing hormone (GnRH) agonist Metrelef® (buserelin acetate) at around Day 21 of the patient cycle (Visit 2). After confirmation of down-regulation, the patient was randomised to treatment with r-hFSH: XM17 or Gonal-f® (Visit 3). Following completion of r-hFSH treatment and confirmation of adequate follicular development, hCG (Ovitrelle®) was administered for final follicular maturation (Visit 5). Oocyte retrieval (Visit 6) was performed 34 to 37 hours after administration of hCG. Biochemical pregnancy (β-hCG test) was evaluated at Visit 7 around 16 to 19 days after oocyte retrieval and clinical pregnancy (gestational sac with heart activity) at Visit 8 about 5 to 7 weeks after oocyte retrieval. A blood sample for antibody testing was drawn at Visit 9, 3 months after oocyte retrieval.

r-hFSH (XM17 or Gonal-f®), Metrelef®, and Ovitrelle® were investigational medicinal products (IMPs). XM17 (test product) and Gonal-f® (reference product) were the study drugs.

Number of patients (planned and analysed):

140 patients were to be randomised per treatment group. 398 patients were screened and 299 were randomised and treated: 146 with Gonal-f®, 153 with XM17. 12 (8.2%) Gonal-f® patients and 11 (7.2%) XM17 patients discontinued prematurely. The most common primary reasons for discontinuation were no embryo transferred (1 vs 5 patients) and no oocytes fertilised (4 vs 1 patient).

The numbers of patients in each analysis population were as follows:

	Gonal-f®	XM17	Total
According-to-protocol (ATP) population:	145	152	297
Intent-to-treat (ITT) and safety populations:	146	153	299

Diagnosis and main criteria for inclusion:

Main inclusion criteria: Infertile female patients undergoing superovulation for ART aged 18 to 37 years at the time of enrolment, with regular menstrual cycles of 21 to 35 days and presumed to be ovulatory, body mass index (BMI) between 18 and 29 kg/m².

Main exclusion criteria: more than 2 consecutive previously unsuccessful *in vitro* fertilisation (IVF) cycles (i.e. completed cycle = oocyte retrieval), more than 3 miscarriages, history of severe ovarian hyperstimulation syndrome (OHSS), malformations of sexual organs incompatible with pregnancy, cysts of more than 2 cm, patients with insulin-dependent diabetes mellitus.

Patients fulfilling any of the following criteria at Visit 3 could not be randomised to study treatment: serum oestradiol ≥ 50 pg/mL, ovarian cysts > 10 mm (verified by ultrasound), pregnancy test positive.

Test product, dose and mode of administration, batch number:

XM17 was supplied in glass cartridges each containing 900 IU of XM17 in 1.5 mL solution (batch number 0943481, drug substance batch number 10841 or 2009010184). Each cartridge was loaded into an XM17 pen (CE-marked medical device).

Fixed-dose phase: The patient received a fixed subcutaneous (s.c.) dose of 150 IU of XM17 once daily for 5 days. The first dose was given by the drug administrator at the centre. Subsequent doses were self-administered by the patient.

Dose adaptation phase: The s.c. XM17 dose could be reduced or increased from Stimulation Day 6 on to achieve adequate follicular development. The investigator decided whether this was required based on serum oestradiol levels and ultrasound examinations. Adjustments were to be made no more than every 3 to 5 days, in steps of 37.5 IU or multiples of 37.5 IU, but no more than 150 IU at each adjustment. Doses greater than 450 IU/day were not recommended. Due to a risk of OHSS the investigator could decide to withhold XM17 for a defined time period (coasting).

Duration of treatment:

Fixed-dose phase 5 days, dose adaptation phase up to 15 days

Reference therapy, dose and mode of administration, batch number:

Gonal-f® was supplied in pre-filled pens each containing 900 IU follitropin alfa in 1.5 mL solution (batch numbers Y13B8890 and Y14B8282). Dose and mode of administration were as described for XM17.

Criteria for evaluation:

Efficacy

Primary and secondary efficacy endpoints are listed above under objectives.

Safety

Adverse events (AEs), laboratory tests, vital signs (blood pressure and heart rate), body weight, physical examination, 12-lead electrocardiogram (ECG), overall and local tolerability, patient satisfaction with pen, antibody levels.

Statistical methods:

Populations: The full analysis set (ITT population) comprised all randomised patients. The ATP population comprised all patients of the full analysis set who did not have any major protocol violations. Efficacy analyses were performed on the ATP and ITT populations. Results were almost identical as the populations differed by only 2 patients (297 vs 299 patients). Except for the analysis of the primary efficacy endpoint where ATP was the primary population, attention was focused on the ITT population.

The safety population was used for the safety analyses and comprised all patients of the ITT population who received at least 1 dose of r-hFSH.

Primary efficacy endpoint (number of oocytes retrieved): Equivalence of XM17 and Gonal-f® was considered to be shown if the two-sided 0.95 confidence interval (CI) for the difference in the number of oocytes retrieved lied entirely within the equivalence range of [–3 oocytes, +3 oocytes]. For the main analysis, a zero-inflated Poisson (ZIP) regression model was used that included randomised treatment and country as fixed factors and age as a covariate. Exploratory sensitivity analyses were performed using other statistical models: ZIP model with interaction terms between treatment and country as well as between treatment and age; unadjusted ZIP model with treatment as fixed effect; Poisson regression model with treatment and country as fixed factors and age as a covariate only for patients with performed oocyte retrieval; analysis of covariance (ANCOVA) with treatment group and country as fixed effects and age as explanatory variable. The ATP population was the primary analysis population for this endpoint.

Secondary efficacy endpoints: Treatment groups were compared using descriptive statistics. Descriptive p-values were calculated with the appropriate statistical tests but were regarded as supportive only. No adjustment of the significance levels for multiple testing were made.

Other endpoints: Demographic and baseline characteristics, AEs, and other safety endpoints were presented as descriptive statistics (continuous variables) or frequency tables (categorical variables).

Summary – Conclusions

Demographic and baseline characteristics were comparable across the treatment groups. The mean ± standard deviation (SD) age overall was 31.6 ± 3.2 years and the mean BMI 22.7 ± 2.9 kg/m². Male factor was the most common cause of infertility (163, 54.5% patients), followed by idiopathic causes (80, 26.8%), tubal factor (56, 18.7%), and endometriosis (20, 6.7%). IVF and/or ICSI procedures were performed in 117 (39.1%) patients before study entry.

Efficacy Results:

Primary efficacy endpoint: Similar numbers of oocytes were retrieved in the two treatment groups of the ATP population. Using imputation for patients without oocyte retrieval, the mean ± SD numbers of oocytes per patient were 12.0 ± 6.8 in the Gonal-f® group and 12.2 ± 6.8 in the XM17 group.

The main ZIP regression analysis resulted in an estimate of 0.03 oocytes for the mean difference between the treatment groups with a 0.95 CI of [−0.76, 0.82]. These values were well within the prespecified equivalence range of [–3 oocytes, +3 oocytes]. The model showed that age and country had a statistically significant effect on the number of oocytes ($p < 0.001$).

The robustness of the estimated treatment effect in the ATP population was confirmed by the 4 exploratory sensitivity analyses based on other statistical models. Furthermore, the findings for the ITT population supported those for the ATP population: the estimated mean treatment difference in the ITT population was 0.03 oocytes with a 0.95 CI of [−0.76, 0.82].

Secondary efficacy endpoints: The mean (median) total dose of r-hFSH was slightly lower in the XM17 group than in the Gonal-f® group: 1535.8 (1425) IU vs 1614.3 (1500) IU. These findings are in agreement with the slightly shorter treatment duration in the XM17 group: 9.3 (9) days vs 9.7 (10) days. The proportion of patients requiring dose adaptations (mostly increases) of r-hFSH was slightly lower in the XM17 group than the Gonal-f® group (51.0% vs 58.2%).

Administration of r-hFSH was accompanied by a 3-fold increase in mean endometrial thickness from 3.7 mm at Visit 3 to 10.9 mm at Visit 5 in both treatment groups. The distributions of follicle size at the end of the fixed-dose phase on Stimulation Day 6 (Visit 4) were comparable in the 2 groups. The majority of follicles were ≤ 14 mm in diameter. Between the beginning and the end of the r-hFSH dose adaptation phase (Visits 4 and 5) there was a clear shift in size distributions reflecting follicle growth in both treatment groups. The proportion of patients with small follicles ≤ 10 mm decreased from 97% in both groups at Visit 4 to below 60% at Visit 5 (59% in the Gonal-f® group, 51% in the XM17 group). The proportion of patients with large follicles > 17 mm simultaneously increased from below 5% to over 95%. Pronounced increases were also seen for follicles > 14 to 17 mm: from 14% to 94% in the Gonal-f® group and from 27% to 93% in the XM17 group. Oestradiol levels at the end of the fixed-dose phase were very variable and were higher in the XM17 group than in the Gonal-f® group. The endometrial thickness was similar in the two treatment groups.

The two groups were comparable with regard to the number of follicles > 14 mm, serum oestradiol, and endometrial thickness on the day of hCG administration. Cancellation rates prior to oocyte retrieval were low: 3 (2.1%) Gonal-f® patients, 1 (0.7%) XM17 patient.

ICSI fertilisation procedures alone were used in the majority of patients (77.9%) and IVF procedures alone in 14.0%; both procedures were used in 6.4% patients. Fertilisation rates were similar in the two treatment groups and higher for the ICSI procedure (65.4% patients) than for IVF (44.2%). The maturity (ICSI procedure) and quality of the retrieved oocytes were similar for the Gonal-f® and XM17 patients.

In both groups, a median of 3 embryos (range 0 to 22) were obtained per patient and a median of 2 embryos (range 0 to 3) were transferred. The biochemical pregnancy rate was 41.1% (60 patients) in the Gonal-f® group and 37.9% (58 patients) in the XM17 group. As expected, the clinical pregnancy rate was lower in both groups: 35.6% vs 28.1% for all patients in the ITT population and 38.8% vs 30.5% for patients with embryo transfer. In addition there were four patients who got pregnant after frozen embryo transfer, thus in total 53 pregnant patients in the Gonal-f® group and 46 patients in the XM17 group will be observed in Follow-up Part A.

Safety Results:

Frequencies of treatment-emergent AEs (TEAEs) and treatment-emergent adverse drug reactions (TEADRs) were as follows:

AE category	Gonal-f® N=146		XM17 N=153		Total N=299	
	n	%	n	%	n	%
Any TEAE	22	15.1	25	16.3	47	15.7
Related TEAE (TEADR)	5	3.4	11	7.2	16	5.4
Serious TEAE	7	4.8	9	5.9	16	5.4
Serious TEADR	3	2.1	4	2.6	7	2.3
Severe TEAE	4	2.7	3	2.0	7	2.3
Severe TEADR	1	0.7	1	0.7	2	0.7
Discontinuation due to TEAE	2	1.4	1	0.7	3	1.0
Discontinuation to TEADR	2	1.4	1	0.7	3	1.0
Death	0	–	0	–	0	–

All of the TEAEs had resolved at the end of the Main Study except for 1 OHSS event (outcome unknown) in an XM17 patient. OHSS was the most common event in 4 (2.7%) Gonal-f® patients and 7 (4.6%) XM17 patients. Abdominal pain was more common in the XM17 group than in the Gonal-f® group: 5 (3.3%) vs 1 (0.7%) patients. This imbalance was not considered clinically relevant as all of the events resolved and none of them led to premature discontinuation; the only severe event of abdominal pain was observed in a patient treated with Gonal-f®. AEs belonging to the category pregnancy loss (abortion) were reported in 4 vs 3 patients and ectopic pregnancy was reported in 1 vs 2 patients. There were no embolic or thrombotic events.

The most frequent serious TEAEs comprised OHSS in 2 Gonal-f®-treated patients vs 3 XM17-treated patients (all TEADRs) and ectopic pregnancy in 1 vs 2 patients. The serious OHSS events led to premature discontinuation in 2 vs 1 patients. There were no other discontinuations due to AEs.

Results for laboratory safety variables, vital signs, body weight, 12-lead ECG, and physical examination did not give rise to any safety concerns. Overall and local tolerability were favourable and comparable between treatment groups. Patients were also highly satisfied with the Gonal-f® pens and the XM17 pens. Anti-FSH antibodies were not detected.

Conclusion

- XM17 was equivalent to Gonal-f® with respect to the primary efficacy endpoint of the number of oocytes retrieved in infertile women undergoing superovulation for ART. The estimate of the mean difference between the Gonal-f® and XM17 groups was 0.03 oocytes with a two-sided 0.95 CI of [−0.76, 0.82] (ATP population, main ZIP regression analysis). The values for the 0.95 CI were well within the prespecified equivalence range of [–3 oocytes, +3 oocytes].
- The robustness of the treatment effect for the primary endpoint in the ATP population was supported by sensitivity analyses using other statistical models and by analyses of the ITT population.
- There were no clinically relevant differences between the treatment groups with regard to secondary efficacy endpoints.
- XM17 showed a favourable safety and tolerability profile, corresponding to that of the comparator Gonal-f®. There were no new or unexpected findings.
- XM17 is an effective, safe r-hFSH for stimulation of follicular development in infertile women who are undergoing ART.

Date of report

Version 1 - 06 December 2011