1. TITLE PAGE

Prospective, open-label, uncontrolled clinical trial evaluating multiple controlled ovarian hyperstimulation cycles in oocyte donor, to assess the immunogenicity of FSH-IBSA.

Study No: 11E/FSH03

Eudract No: 2012-000269-19

Final Report, Version 1: 17 November 2014

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This study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. Federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2. SYNOPSIS

NAME OF COMPANY : IBSA Institut Biochimique SA	
NAME OF FINISHED PRODUCT: FSH-IBSA	
NAME OF ACTIVE INGREDIENT : Urofollitrophin	
TITLE OF STUDY: Prospective, open-label, uncontrolled clinical trial evaluating multiple controlled ovarian hyperstimulation cycles in oocyte donor, to assess the immunogenicity of FSH-IBSA.	
INVESTIGATORS: Dr. Buenaventura Coroleu Lletget	
STUDY CENTER(S): Dep. Obstet-Gynec.-Reproduction, Institut Universitari Dexeus, Gran Via Carles III. 71-75, 8028 Barcelona, Spain.	
PUBLICATION (REFERENCE): None	
STUDIED PERIOD: Date of first patient enrolment: 09.May.2013 Date of last patient completed: 16.July.2014	**PHASE OF DEVELOPMENT:** Phase IIIB
OBJECTIVES: The purpose of the study is to evaluate immunogenic potential of FSH-IBSA in healthy volunteers undergoing COH in an oocyte donation program.	
EVALUATION PARAMETERS: *Primary End Point* − To test the production of anti-FSH antibodies (IgG, IgM, and IgA) using a sensitive screening assay. *Secondary End Points* In case anti-FSH antibodies are detected: − To determine whether the antibodies detected are neutralizing in a bioassay. To determine whether the antibodies that are induced by the product cross-react with their endogenous counterpart or with other hormones that share the common alpha chain with FSH (LH, TSH). *Safety End Points* Adverse events and tolerability reactions that may be linked to an immunological reaction such as immediate or delayed hypersensitivity reactions at the injection site, or manifestations of systemic hypersensitivity.	
ANALITICS: Anti-FSH Antibodies will be determined in serum samples at KYMOS Pharma Services (Barcelona, Spain).	
NUMBER OF PATIENTS (PLANNED AND ANALYSED): **Planned:** The sample size was not based on a conventional statistical power calculation, but was set at 25 subjects, the rationale being that the study is intended to confirm the a priori expectation that women undergoing repeated administration of FSH-IBSA will not respond immunologically to either the FSH component of this preparation or the single excipient (lactose). **Screened**: 41 **Randomised:** 27 patients. **Completed:** 24 patients.	

DAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Inclusion Criteria

Healthy female volunteers undergoing controlled ovarian hyperstimulation for oocyte donation with the following characteristics:

- Able and willing to sign the Subject Consent Form and adhere to the study visit schedule;
- ≥18 and <35 years old;
- Regular menstrual cycle (26 – 35 days);
- BMI between 18 and 30 kg/m2;
- First gonadotrophin treatment (i.e. naïve Subjects with regard to exposure to human derived or recombinant gonadotrophins);
- basal FSH <10 IU/L and E2 <80 pg/ml (~290 pmol/l);
- Normal TSH levels;
- Willing to perform at least two consecutive oocyte retrieval cycles (with a wash out period of two months).

Exclusion Criteria

- Age <18 and ≥35 years;
- PCOS;
- Endometriosis;
- Subjects with evidences of autoimmune or rheumatic diseases;
- Hypersensitivity to the active substance or to any of the excipients (lactose);
- Abnormal bleeding of undetermined origin;
- Subject found to be positive to anti-thyroid antibodies (anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies)(i.e. suffering from thyroidal diseases);
- Uncontrolled adrenal dysfunction;
- Neoplasia;
- Severe impairment of renal and/or hepatic function;
- Use of concomitant medications that might interfere with study evaluations (e.g. immunosuppressant, non-study hormonal medications, therapeutics proteins like insulin, growth hormone…).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

FSH-IBSA (IBSA, Institut Biochimique SA), powder and solvent for solution for s.c. injection, supplied in vials containing 75 IU of FSH, along with prefilled syringes of solvent (physiological saline for injection).(Batch nr. 121024)

Other drugs: Commercially available oral contraceptive pill (Ovoplex- Wyeth Farma, S.A) for cycle synchronisation; GnRH-antagonist (Cetrotide – Merck Serono) for down-regulation; GnRH-agonist (Decapeptyl - Ipsen) for triggering final oocytes maturation.

DURATION OF TREATMENT: Daily FSH administration was continue until triggering of the final follicular maturation.

STATISTICAL METHODS: Only a descriptive statistical analysis of all the data captured in the CRF will be performed.

RESULTS:

Demography: subject included in the study were healthy, Caucasian women, of a mean age of 26 years (ranging from 18 to 35 years), normal BMI (mean 22 kg/m2), with regular menstrual cycle, normal gynaecological anamnesis, deprived of any autoimmune disorder and with normal thyroid function.

In general, all the subject responded well to the stimulation cycle. The total dose of FSH used was slightly less than 2000 IU (i.e. ~26 vials of Fostimon 75IU), with no difference between the first and the second cycle. The treatment took ~10 days and the mean number of oocytes retrieved was 13.4 in the first cycle and 15.7 in the

second one (p=NS for all the parameters). According to this data, the efficacy of the drug was not reduced in the second cycle confirming the absence of neutralising antibodies.

Safety: The tolerance at injection site was evaluated at each visit: pain, redness, swelling and itching were never reported, with the exception of one subject who reported mild itching on visit 2, and another subject who reported moderate pain and redness on visit 5.

Seven subjects reported totally 12 Non Serious Adverse Events, all of mild intensity and judged as not related to study treatment.

Only one, non-related, moderate Serious Adverse Event was reported (post oocytes retrieval haemorragia).

Analytics:

In total, 148 samples from 27 volunteers were analysed to detect antibodies against FSH.

24 out of the 27 randomised subjects completed the two treatment cycles and had all the 6 serum samples collected.

From the 148 samples analysed, 14 samples, coming from 6 volunteers, were positive after the screening assay. From those 14 positive samples in the screening assay, 8 samples were positive after confirmatory assay. These 8 samples came from 2 volunteers; both subjects had positive results at baseline (i.e. before FSH administration) . Therefore, no volunteers seroconverted during the study.

From the two volunteers with positive samples, only one volunteer had positive results at the end of the study.

The titre for the positive samples was: dilution 2 for two samples, dilution 4 for five samples and dilution 8 for one sample.

The cross-reactivity against TSH, LH and hCG was determined in those 8 samples. Regarding the cross-reactivity against TSH, one sample showed no cross-reactivity with TSH. From the 7 samples showing cross-reactivity, the percentage was ranged from 4.3 to 41.2%. Regarding the cross-reactivity against LH, two samples showed no cross-reactivity with LH. From the 6 samples showing cross-reactivity, the percentage was ranged from 7.9 to 22.1%. Regarding the cross-reactivity against hCG, the eight positive samples showed cross-reactivity with hCG with percentages ranged from 3.9 to 50.5%. These levels of cross-reactivity were expected since FSH, TSH, LH and hCG share a protein chain.

It is noteworthy to mention that the responses obtained from the positive samples were low (maximum response in the screening assay = 4BI) compared to the cut-point (1.3BI). Given the very high sensitivity of the assay and the low responses obtained, those positive results are, most probably, not clinically relevant. Also, taking into account that the patient did not show a reduced clinical response during the second cycle it was considered unnecessary to perform a neutralizing assay.

CONCLUSIONS:

Fostimon resulted to be well tolerated and efficient in inducing ovulation in oocyte donor subjects.

No reduction in the drug activity has been noted between cycle 1 and cycle 2, neither by comparing the number of oocytes retrieved nor by comparing the total dose of drug used.

No systematic nor local allergic reactions have been detected.

None of the subject seroconverted: Subjects with anti-FSH positive samples were already positive at baseline, suggesting that the results were actually a false positive due to the high sensitivity of the analytical method.

DATE OF THE FINAL REPORT: 17 November 2014