1 TITLE PAGE

Safety and efficacy study comparing a new hMG formulation (hMG-IBSA) to a reference product (Menopur®) in patients undergoing ovarian stimulation for in vitro fertilisation (IVF).

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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: hMG-IBSA

NAME OF ACTIVE INGREDIENT : Menotrophin

TITLE OF STUDY: Safety and efficacy study comparing a new hMG formulation (hMG-IBSA) to a reference product (Menopur®) in patients undergoing ovarian stimulation for in vitro fertilisation (IVF).

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STUDY CENTER(S): [1]Groupe Hospitalier Cochin - Saint Vincent de Paul, Paris, France ; [2]First Dept. Obstetrics and Gynaecology, Semmelweis University Faculty of Medicine, Budapest, Hungary; [3]Midland Fertility Services, Aldridge - West Midlands -WS9 8LT, UK; [4]Fertility clinic at Hvidovre Hospital, Hvidovre-Copenhagen, Denmark; [5]Fertilitetsklinikken, Odense Universitetshospital, Odensee C, Denmark; [6]Universitätsspital Basel, Frauenklinik Abteilungsleiter gyn. Endokrinologie, und Reproduktionsmedizin, Basel, Switzerland.

PUBLICATION (REFERENCE): None

STUDIED PERIOD:	
Date of first patient enrolment:05MAR2011 Date of last patient completed: 10APR2013	**PHASE OF DEVELOPMENT:** Phase III

OBJECTIVES: To evaluate the clinical efficacy and the safety of two different subcutaneous hMG preparations (hMG-IBSA, IBSA Institut Biochimique SA vs Menopur®, Ferring Pharmaceuticals) when administered to patients undergoing controlled ovarian stimulation for IVF.

METHODOLOGY: This prospective, single blind, randomised, parallel-group, multicentre, two arm study was designed to compare the clinical efficacy and the safety of hMG-IBSA to Menopur for controlled ovarian stimulation in IVF.

Patients enrolled in a standard IVF protocol were eligible for the study. Those who expressed an interest in participating provided informed consent and were screened.

Pre-study treatment

Common down-regulation treatment using a standard, GnRH agonist long protocol, once daily (no depot preparation is allowed). The concomitant use of an oral contraceptive pill was allowed but not mandatory.

Study treatment

• The starting dose of hMG for ovarian stimulation was standard (150 IU for patients ≤35 years and 225 IU for patient >35 years daily) for the first 5 - 7 days. Then, the dose was adjusted according to the ovarian response monitored by means of serum E_2 levels and ultrasonographic measurement.

Daily hMG administration was continue until the criteria for triggering final follicular maturation were met (i.e. at least 2 follicles > 16 mm in diameter and/or serum E2 levels >400 pg/ml (1500 pmol/l).

• Coasting was not allowed. Patients needing coasting were withdrawn from the study.

• Ovulation was triggered by subcutaneous injection of 10,000 IU of human chorionic gonadotrophin (hCG). A reduction of the HCG dose was allowed only in case of an increased risk of OHSS.

• Luteal phase support was performed using progesterone according to the protocol followed at each centre, for at least 14 days after ET.

• Embryos were transferred at day 2-4 or at blastocyst stage day 5-6. All the embryos obtained were evaluated for quality on day 2.

• On the day of embryo transfer, OHSS symptoms were evaluated in each patient, following Golan Criteria.

• Pregnancy was be assessed 15±2 days after OPU. During this visit OHSS symptoms were re-evaluated.

• Pregnancy was re-assessed via TVUS 10-11 weeks after ET.

Patients with an on-going pregnancy at the final visit were provided with a pregnancy outcome form for

completion by their obstetrician following delivery and subsequently contacted by telephone 15 days after the expected delivery date if the completed form had not been received by that time.

During each visit, patients were asked to assess their overall health. Throughout the study, patients recorded adverse events (AEs) and concomitant medication usage in the patient diary. Any change in the clinical assessment of the patient compared to the previous visits was evaluated by the investigator and if considered relevant was reported in the AE form.

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Planned: 272 patients to provide 250 evaluable patients allowing for drop-outs (125 per treatment group).

Randomised: 270 patients (135 in both treatment groups).

Intent-to-treat (ITT) population (i.e. all randomised patients): 270 (135 in both treatment groups).

Per-protocol (PP) population (all the patients who had OPU, excluding major protocol violators): 255 (126 in the hMG-IBSA group and 129 in the Menopur group).

Follow-up variables (pregnancy out-comes), were analysed in the observed patient dataset.

DAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Inclusion criteria

- Women undergoing ovarian stimulation for IVF with the following characteristics:
- Able and willing to sign the Patient Consent Form and adhere to the study visitation schedule;
- ≥18 and <40 years old;
- BMI between 18 and 30 kg/m2;
- less than 3 previously completed IVF cycles (i.e. completed cycle = egg recovery);
- basal FSH <10 IU/L and E2 <80 pg/ml (~290 pmol/l);
- Within 12 months of the beginning of the study, uterine cavity consistent with expected normal function as assessed through transvaginal ultrasound, hysterosalpingogram, sonohysterogram or hysteroscopic examination;
- Successful down-regulation performed with a standard GnRH-Agonist long protocol (Criteria for successful down-regulation: endometrial thickness < 7mm or serum E2 level ≤50 pg/ml (~185 pmol/l).

Exclusion criteria

- age <18 and ≥40 years;
- primary ovarian failure or women known as poor responders (i.e. requiring more than 225 IU of hMG as a starting dose in previous treatment cycles or having less than 3 oocytes retrieved, or with a pre-ovulatory E2 serum concentration <500pg/ml (~1800 pmol/l));
- PCOS
- one or both ovaries inaccessible for oocyte retrieval;
- ovarian cysts >10 mm;
- hydrosalpinx that have not been surgically removed or ligated;
- stage 3 or 4 endometriosis;
- oocyte donation;
- implantation of previously frozen embryos;
- patients affected by pathologies associated with any contraindication of being pregnant;
- hypersensitivity to the study medication;
- abnormal bleeding of undetermined origin;
- uncontrolled thyroid or adrenal dysfunction;
- neoplasias;
- severe impairment of renal and/or hepatic function;
- use of concomitant medications that might interfere with study evaluations (e.g. non-study hormonal medications, prostaglandin inhibitors, psychotropic agents).

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

hMG-IBSA (IBSA Institut Biochimique SA), 75 IU/vial, subcutaneous (s.c.) injection (100526; 120128)

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Menopur (Ferring), 75 IU/vial, subcutaneous (s.c.) injection (CE0149A, CE0141A, CE0223A, CF0003A)

DURATION OF TREATMENT: Daily hMG administration was continue until the criteria for triggering final follicular maturation were met (i.e. at least 2 follicles > 16 mm in diameter and/or serum E2 levels >400 pg/ml (1500 pmol/l).

STATISTICAL METHODS:

The ITT (i.e. all the patients receiving at least one dose of test product) was the primary population for the efficacy analyses. Analyses were also performed on the Per Protocol (PP) population (i.e. all the patients who underwent OPU), as well as the population who became pregnant.

The total number of oocytes retrieved 34-36 hours after hCG administration was used to test non-inferiority of hMG-IBSA versus Menopur. Least-squares means and their associated standard errors were used to calculate the 95% confidence interval of the difference between the two groups. If the lower bound of the 95% confidence interval of the difference between means (hMG-IBSA minus Comparator) was greater than -2.1, then hMG-IBSA was considered to be not-inferior to the comparator.

Once the analysis of variance performed, in order to organize and summarize the results of the analyses, an ANOVA table was performed. A multivariate analysis of variance was used to calculate the 95% Confidence Interval for the difference between treatment groups using investigational centre, women's age and body mass index as covariates. The primary effectiveness analysis including the main effects (treatment and investigational centre) was repeated with the addition of a treatment group by centre interaction term.

For secondary continuous variables, statistical analyses were performed using analysis of variance (ANOVA) models with factor for treatment group (hMG-IBSA versus Menopur). For ordered categorical variables, the effect of treatment group was analysed using the Cochran-Mantel-Haenszel test, while for non-ordered categorical variables by means of the Fisher's exact test.

Incidence of AEs was compared using Fisher's exact test comparisons of hMG-IBSA versus Menopur.

All statistical calculations were performed with SAS® software.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The ITT population included 270 patients, of whom 259 had oocytes retrieval performed. Overall, the HMG-IBSA and Menopur group were well matched in terms of baseline demographic characteristics. The mean age of patients was approximately 33 years in each treatment group, with a BMI of 23.5 kg/m^2 and >93% of patients in each group were Caucasian. The patients were generally healthy and were considered representative of the patient population undergoing IVF treatment. No notable differences between the treatment groups in infertility history, infertility diagnostic variables, infertility classification, gynaecological examination, mean basal FSH and E_2 levels, prior and concomitant pathology and prior and concomitant medication use were reported. The mean duration of infertility was 49.7 month in the hMG-IBSA group and 45.5 months in the Menopur group and 'male factor' was the most frequently reported cause of infertility (around 60% of patients in each group).

In the ITT population, the total number of oocytes retrieved was statistically significantly higher in the hMG-IBSA group compared to the Menopur group (11.6 ± 6.6 in the hMG-IBSA group and 9.7 ± 5.9 in the Menopur group). However, because the study was designed to show Non-inferiority of hMG-IBSA compared to Menopur and since the lower bound of the 95% Confidence Interval observed (0.43) was greater than the predefined non-inferiority margin of −2.1, the non-inferiority of hMG-IBSA compared to Menopur was established. Similar results were obtained for the PP population (12.3 ± 6.2 in the hMG-IBSA group and 10.1 ± 5.7 in the Menopur group), with a lower bound of the 95% CI equal to 0.68.

Multiple regression modelling demonstrated that the number of oocytes retrieved was influenced by the study

sites and the BMI of the patients.

A statistically significant difference between the treatment groups were reported for the duration of the stimulation (that was shorter in the hMG-IBSA group), for the total number of oocytes fertilised (higher in the hMG-IBSA group). However, the units of drug needed to retrieve one single oocyte were equivalent in both treatment groups.

Embryo quality resulted to be equivalent in the two treatment groups.

No statistically significant differences between the treatment groups were reported for any other the secondary efficacy endpoints (i.e. fertilisation rate, cleavage rate, mean implantation rate, positive β-hCG test rate, clinical pregnancy rate).

No statistically significant differences between the treatment groups were reported for delivery and live births rate, abortion rate as well as for the new-born efficacy parameters (including gestational age at delivery, baby weight, singleton and multiples rate).

SAFETY RESULTS:

The total number of AEs and the proportion of patients experiencing AEs were comparable between the two treatment groups (221 events in 42.2% of patients in the HMG-IBSA group and 208 events in 43.7% of patients in the Menopur group).

Based on SOC, the most frequently reported AEs were gastrointestinal disorders (25.2% and 23.7% in the HMG-IBSA and Menopur groups, respectively), with abdominal distension, abdominal pain and nausea the more reported events, with similar frequency in both groups.
The second most frequently reported AEs were nervous system disorders (23.7% in the HMG-IBSA group and 26.7% in the Menopur group). The most reported individual AE being headache (21.5% in the HMG-IBSA group and 23.0% in the Menopur group).

There was no statistically significant difference between the two treatment groups for the most frequently reported AEs, except for vascular disorders, mainly related to hot flushes, which were more often reported in the hMG-IBSA group. The majority of AEs in both treatment groups were mild in intensity, with only 1 severe AEs reported in both the HMG-IBSA and Menopur groups.

The frequency and incidence of treatment-related AEs (144 and 127, respectively), and the proportions of patients experiencing these events (17.0% and 18.5%, respectively) were comparable between the HMG-IBSA and Menopur groups.

The most frequently reported treatment-related AEs based on SOC were adverse events associated with gastrointestinal disorders (abdominal pain, abdominal distension and nausea): 8.9% of the patients in both treatment groups.
The next most frequently reported AEs were related to nervous system disorders (prevalently headache and dizziness), which were equally reported in both groups (12.6%).
Fatigue and malaise were also reported in both treatment groups with the same frequency, while hot flushes were reported more frequently in the hMG-IBSA group.

All the other PTs were reported by <2% of patients in each treatment group.

No statistically significant difference in the proportion of patients experiencing SAEs was reported between the HMG-IBSA and Menopur groups (5.9% in both treatment groups). Only 4 events in 3 patients in the hMG-IBSA group (abdominal pain lower, constipation, ovarian hyperstimulation and ovarian torsion) were considered related to the study drug. In the Menopur group, only one case of OHSS was considered related to the study drug.

Follow-up data were collected for 95 patients: 45 for the hMG-IBSA group and 50 for the Menopur group. Ten patients in both treatment groups reported the onset of at least one adverse event during the gestation period, with no statistically significant difference between the two groups. As expected, the majority of events were related to the pregnancy, puerperium and perinatal conditions SOC. All the Adverse Events were considered Non Serious. Information about 117 babies (57 in the hMG-IBSA group and 60 in the Menopur group) was

therefore available. Only two babies (3.5%) in the hMG-IBSA group and 1 (1.7%) in the Menopur group reported abnormalities at birth.

Tolerability at injection site resulted to be very good in both treatment groups, with few patients reporting pain, redness, tenderness or itching. In those cases reporting pain, the intensity was mainly mild and limited to the time of injection.

At the pre-study visit and on the day of hMG treatment start, ≥97% of patients in each treatment group were considered very healthy, with no notable differences reported between the two groups. Patient wellbeing remained high throughout the study in both treatment groups, with only 17% of patients in the hMG-IBSA group and 14% in the Menopur group considered mildly unhealthy at Visit 3, showing an improvement as the treatment progressed. No statistically significant differences in patient wellbeing between the two treatment groups were reported during the study ($p>0.05$).

None of the 25 patients analysed produced anti-FSH, anti-LH and anti-HCG antibodies.

CONCLUSIONS:

HMG-IBSA resulted to be non-inferior to Menopur in inducing controlled ovarian hyperstimulation in patients undergoing IVF, as demonstrated by the primary efficacy end-point "total number of oocytes retrieved". With regard to the secondary end-point, the higher number of oocytes fertilised and cleaved on day 2 is a direct consequence of the higher number of oocytes retrieved in the hMG-IBSA, however, this values, even if statistically significantly different, did not influenced the other secondary end-points like the fertilisation rate, the cleavage rate, the mean implantation rate, the positive β-hCG test rate and the clinical pregnancy rate.

The safety and tolerability of HMG-IBSA was generally comparable to Menopur treatment.

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