Synopsis

NAME OF SPONSOR/COMPANY

FERRING Arzneimittel GmbH

NAME OF FINISHED PRODUCT

Menogon® HP

NAME OF ACTIVE SUBSTANCE

Highly purified menotrophin

TITLE OF TRIAL

A prospective, open label, randomised, parallel group trial comparing the effects of highly purified Menotrophin and recombinant follicle stimulating hormone (rFSH, Follitropin alpha) administered subcutaneously to subfertile female patients undergoing IVF using antagonist down-regulation on progesterone serum levels during the follicular phase and their possible use as predictors for the success rate of ongoing pregnancies (PREDICT)

SIGNATORY INVESTIGATOR

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TRIAL SITE(S)

- Universitätsklinikum, Düsseldorf, Germany
- Fertility Center, Berlin, Germany
- Endokrinologikum, Ulm, Germany
- Praxisklinik Sydow am Gendarmenmarkt, Berlin, Germany
- Praxis für Kinderwunschbehandlung, Erlangen, Germany
- NOVUM Zentrum, Essen, Germany
- IVF Zentrum Saar, Saarbrücken, Germany
- Kinderwunschzentrum, Dortmund, Germany

PUBLICATION (REFERENCE)

None as of date of this report

TRIAL PERIOD	**CLINICAL PHASE**
First patient first visit (FPFV): 20 Oct 2010 *(Last patient last visit (LPLV): 22 Jan 2013*	IV

OBJECTIVES

Primary objective

To demonstrate that highly purified Menotrophin produced significant lower progesterone (P4) serum levels during the follicular phase in comparison to Follitropin alpha in the treatment of subfertile females undergoing an in vitro fertilisation (IVF) using a Gonadotrophin Releasing Hormone (GnRH) antagonist protocol for pituitary down-regulation.

Secondary objectives

- To investigate if the progesterone serum levels during the follicular phase were a useful predictor for the success rate of the ongoing-pregnancy rates in the Menotrophin group and the Follitropin alpha group
- To investigate if highly purified Human Menopausal Gonadotrophin (HP-hMG) was non-inferior or whether there were existing differences to Follitropin alpha in the treatment of subfertile females in IVF programme with respect to efficacy and safety.

ENDPOINTS

Primary endpoint

Serum progesterone (P4) level in the morning of the day of human Chorionic Gonadotrophin [hCG] administration

Secondary endpoints

Efficacy:

- Correlation between progesterone serum levels (blood sampling in the morning of visit 3, 4, 5, 6a-c) during the follicular phase and success of the ongoing pregnancy
- Ongoing pregnancy rate (defined as positive foetal heart action ≥ 9 weeks after the first positive pregnancy test)
- Number/diameter of follicles
- Number of oocytes (only M2 oocytes will be counted) retrieved
- Number of pronuclear oocytes, quality of pronuclear stage (PN) oocytes
- Number and quality of embryos transferred, number of frozen oocytes at pronuclear stage
- Endometrial thickness on day of hCG administration
- Progesterone levels at other time points (blood sampling in the morning, visit 3, 4 ,5, 6a-c)
- Estradiol levels at day of hCG administration
- Implantation rate
- Number of days stimulated with gonadotrophins and number of ampoules used
- Clinical pregnancy rate at 6 weeks after the first positive pregnancy test
- Pregnancy outcome (induced abortion/ectopic pregnancy/miscarriage/live birth/congenital abnormality).

Safety:

- Frequency and severity of reported treatment-emergent adverse events [(AEs), including injection site reactions and Ovarian hyperstimulation syndrome (OHSS)].

METHODOLOGY

Prospective, multi-centre, open-label, randomised, parallel group, comparative trial

NUMBER OF SUBJECTS

Table 1 Subjects' disposition

	Menotrophin n (%)	**Follitropin alpha n (%)**	**Total n (%)**
Subjects planned, n	55-60	55-60	110-120
Subjects screened, n	n.a.	n.a.	170
Subjects randomized	62 (100.0)	62 (100.0)	124 (100.0)
Subjects exposed	62 (100.0)	62 (100.0)	124 (100.0)
Subjects completed[a]	55 (88.7)	59 (95.2)	114 (91.9)

[a] completed = subjects met the hCG criterion

MAIN CRITERIA FOR INCLUSION / EXCLUSION

Inclusion criteria

1. Signed informed consent
2. Subfertile premenopausal female patients eligible for IVF treatment (tubal factor, or unexplained causes)
3. Aged ≥ 34 and ≤ 42 years
4. Body mass index of > 18 and < 28 kg/m^2
5. Normal pelvic ultrasound (showing two ovaries, no ovarian abnormalities [ovarian cysts caused by endometriosis, myoma indicating surgery, distorted cavity were not accepted]) at Screening I (Visit 1)
6. No more than two previous gonadotrophin stimulated cycles of IVF or ICSI in the history of infertility treatment (gonadotrophin stimulated cycles not used for IVF or ICSI did not count; Clomifen cycles were no exclusion criterion)
7. At least 3 consecutive ovulatory menstrual cycles of 24 - 35 days, and documented evidence of ovulatory cycles within the previous 12 months prior to Screening I (Visit 1)
8. No fertility stimulating drugs at all (a contraceptive pill was no exclusion criterion) within the last 3 months prior to Visit 3 (first day of gonadotrophin administration)
9. Sperm of partner classified as normal according to WHO 2010 criteria within the year prior to Visit 3 (first day of gonadotrophin administration)
10. Negative urine beta human chorionic gonadotrophin (hCG) pregnancy test at Screening II (Visit 2)
11. Clinically normal baseline haematology, clinical chemistry, urinalysis values, at Screening I (Visit 1)
12. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within the last 6 months prior to Screening I (Visit 1). If data were not available, the tests had to be performed at Screening I
13. Endocrine test results (estradiol [E2], luteinising hormone [LH], follicle stimulating hormone [FSH], progesterone [P4], Anti-Müller-Hormone (AMH, > 1ng/mL), prolactin, thyroid stimulating hormone [TSH]) in early follicular phase within the clinically normal limits at Screening I (Visit 1, correlated TSH was allowed).

Exclusion criteria

1. Presence of any clinically relevant systemic disease (eg, insulin-dependent diabetes mellitus)
2. A history of or current endocrine disease (excluding treated hypothyreosis), including polycystic ovary syndrome (PCOS) and hyperprolactinaemia
3. A history of coagulation disorders
4. Persistent ovarian cysts (> 3 months)
5. Contraindications for the use of gonadotrophins or GnRH antagonists
6. A history of hypersensitivity to any of the constituents of the study medication or related compounds
7. A history of alcohol abuse (more than 30 units per week on a regular basis)
8. History of chemo- or radiotherapy
9. Currently breast-feeding, pregnant or with a contraindication to pregnancy
10. Diagnosed poor (< 3 oocytes) responders to prior gonadotrophin stimulated Assisted reproductive technology [ART]-cycle
11. History of severe OHSS (grade 4 or 5) in former gonadotrophin stimulated ART-cycle
12. Investigational drug within the last 30 days prior to Visit 3 or former enrolment into this study
13. Any other condition or history that the Investigator considered might increase the risk to the individual
14. Incapability to understand the aim, importance and consequences of the study and to give legal informed consent
15. Institutionalization due to regulatory or judicial order
16. Possible dependence on the Sponsor or Investigator

MEDICINAL PRODUCTS

Medicinal products were provided by the Sponsor as labelled study medication free of charge

- Gonadotrophins: Menotrophin (Menogon® HP) or Follitropin alpha (Gonal-f®) administered subcutaneously (s.c.) with a daily dose of 150 International Units (IU) for the first 5 days, after 5 days of gonadotrophin treatment, dosage could be increased up to 225 and 300 IU according to the Investigator´s experience; dosage could be reduced to 75 IU if hyperstimulation occurred at any time
- Cetrorelix (Cetrotide®) for pituitary down-regulation with a daily s.c. injectable dose of 0.25 mg/day
- Choriongonadotropin (Brevactid®) for ovulation induction with a single injection of 10,000 IU
- Progesterone (Crinone®8%) for luteal phase support performed intravaginally with 1x90 mg/day

DURATION OF TREATMENT

- Gonadotrophins (Menotrophin or Follitropin alpha) were administered daily from Day 1 (= Day 2 or 3 of menstrual cycle) up to a maximum of 13 days
- Cetrorelix was given daily from Day 5 of gonadotrophin administration throughout the period of gonadotrophin treatment. The last dose of cetrorelix was given on the day of ovulation induction
- Choriongonadotropin was administered once when the hCG criterion (three follicles ≥ 17 mm diameter) was met
- Progesterone was administered intravaginally daily for 30 days starting on the day of oocyte retrieval.

TRIAL PROCEDURES / ASSESMENTS

Examinations

- A general physical examination prior to treatment included a system review and documentation of menstrual cycles, general history, etiology of infertility, former infertility therapies, and pelvic ultrasound.
- Laboratory assessments in the 3 months prior to treatment (Visit 3) included baseline determination of biochemistry, haematology, serology, urinalysis, and baseline endocrine determinations (AMH, E2, FSH, hCG, LH, progesterone (P4), prolactin, and TSH) in the early follicular phase of the menstrual cycle. The blood samples had to be taken in the morning before any medication was used.
- The patient was subsequently assessed by pelvic ultrasound in the mid-luteal phase of the menstrual cycle prior to the IVF treatment cycle. A urinary beta-hCG test had to be performed and the result had to be negative.
- The patient was monitored and assessed before, during and after the IVF procedure by pelvic ultrasound and endocrine assessments.

Treatment

- IVF treatment cycle performed using GnRH antagonist down-regulation.
- Gonadotrophins (Menotrophin or Follitropin alpha) were administered s.c. from Day 1 (= Day 2 or 3 of menstrual cycle) at a fixed dose of 150 IU for the first 5 days; after the first 5 days of gonadotrophin stimulation, the dosage could be increased up to 225 and 300 IU, according to the Investigator´s experience; at any time the dosage could be reduced to 75 IU if hyperstimulation occurs. Treatment with gonadotrophins was up to a maximum of 13 days.
- Pituitary down-regulation was performed with a daily injectable antagonist formulation: Cetrorelix was given at 0.25 mg/day from Day 5 of gonadotrophin administration and was continued throughout the period of gonadotrophin treatment. The last dose of cetrorelix was given on the day of ovulation induction.
- Ovulation induction was performed with hCG in the form of choriongonadotropin (10,000 IU); the criterion for hCG administration was three follicles ≥ 17 mm diameter. Patients who had not met the hCG criterion after 13 days of gonadotrophin treatment were to be withdrawn.
- Luteal phase support was performed with progesterone (P4).

STATISTICAL METHODS

The serum progesterone levels on the day of hCG administration were compared among both study groups by the t-test adjusted for age strata. In Andersen (7) and Bosch (12) mean levels of progesterone (± standard deviation [SD]) were reported which yielded very similar standardised differences Δ/SD, Δ = raw difference rFSH – HP-hMG and SD = common SD across both groups, of 0.572 and 0.583. The number of patients needed for discriminating standardised differences of 0.57 or 0.58 at a significance level of α=0.05 two-tailed and a power of 1–β=0.8 was determined to be 50 or 48 per group, respectively. Taking into account a dropout rate of approximately 10%, 55 (– 60) patients per group were planned to be included. The age strata mentioned above were 34, 35, 36, 38 and 39, 40, 41, 42 years.

The primary analysis was the confirmative comparison between the treatment groups Menotrophin versus Follitropin alpha in the progesterone level (P4) at the day of hCG administration. The progesterone level at each day during the follicular phase was summarised by sample statistics. An age stratified, two-tailed t-test with a significance level of α=0.05 was used to compare both treatment groups. The intention-to-treat (ITT) population was used for the primary analysis, a sensitivity analysis was performed with the per protocol (PP) population.

Further, the correspondence between progesterone level and the secondary endpoints was evaluated by Pearson and Spearman correlation coefficients. The influence of the progesterone level on the ongoing pregnancy rate was determined by means of the receiver operating characteristic (ROC) curve. Additionally, regression models were used to determine the predictive properties of progesterone during the follicular phase for the success rates of the ongoing-pregnancy rates.

The secondary endpoints were described by sample statistics for continuous variables or frequencies for categorical variables. Treatment differences were evaluated by t-tests, Wilcoxon-Mann-Whitney-U-test or χ2-test as appropriate. All p-values for the secondary endpoints were interpreted in an explorative manner.

EFFICACY RESULTS

A total of 124 subjects was randomly assign to treatment with Menotrophin or Follitropin alpha, all 124 subjects, 62 in each treatment group were valid for safety and full analysis, 106 subjects (48 in the Menotrophin group and 58 in the Follitropin alpha group) without any major protocol violation were valid for the per protocol (PP) set.

Both treatment groups were comparable with regard to the demographic and baseline characteristics. The mean age of all subjects was 36.6 ± 2.4 years, 99 subjects (79.8%) were younger than 39 years and 25 subjects (20.2%) were 39 years or older. Vital signs at baseline were within the expected ranges for the trial population.

The mean duration of infertility before treatment was 43.2 ± 30.7 months with a range from 6.0 to 180.0 months, for which 76 subjects (61.3%) had formerly received a mean of 4.0 ± 2.9 treatments. The reasons for infertility were documented as “idiopathic” (69, 55.6%), “tubal factor” (38, 30.6%), or “endometriosis” (7, 5.6%).

Pelvic ultrasound findings showed a mean of 6.5 ± 2.5 right and left antral follicles, with a median of 6 .0 in both treatment groups. No ovarian cysts were detected in any of the subjects.

Primary endpoint

The primary endpoint was the serum progesterone level (P4) at the day of hCG administration. The raw estimates were 0.69 ± 0.34 ng/mL (mean ± SD, Menotrophin group) versus 0.89 ± 0.41 ng/mL (Follitropin alpha group). Regarding the primary confirmatory analysis, the age-group-adjusted values were 0.64 ± 0.05 ng/mL versus 0.85 ± 0.05 ng/mL (mean ± standard error). The lower progesterone levels in the Menotrophin group were confirmed by a p-value of 0.002 (ANOVA). The sensitivity analyses confirmed this result. Table 2 summarizes the results for the primary analysis.

Table 2 Serum progesterone level [ng/mL] at the day of hCG administration

	Menotrophin	Follitropin alpha	p-value
Raw estimates: all strata (N=62/62)			
Mean ± SD	0.69 ± 0.34	0.89 ± 0.41	0.003 [a]
median [range]	0.59 [0.2-1.9]	0.80 [0.26 – 2.2]	
Age-adjusted estimates (N=62/62)			
mean ± SE	0.64 ± 0.05	0.85 ± 0.05	0.002 [b]
[95%-CI]	[0.54 – 0.75]	[0.74 – 0.95]	

a t-test, b analysis of variance (ANOVA)

Secondary endpoints

In the FAS, 8 subjects (12.9%) in the Menotrophin group and 4 subjects (6.5%) in the Follitropin alpha group failed a successful embryo transfer. This difference was, however not statistically significant (p=0.36). In the PP set this relation was vice versa with 2 subjects (4.2%) in the Menotrophin group and 4 subjects (6.9%) in the Follitropin alpha group. The pregnancy rates in subjects with successful embryo transfer were higher in subjects of the Follitropin alpha group, but without statistical significance. All over, the differences between the treatment groups were descriptively lower in the PP set (Table 3).

Table 3 Secondary efficacy endpoints: embryo transfer and pregnancy rates (PP and FAS)

	PP set n/N (%)			FAS n/N (%)		
	Menotrophin	Follitropin alpha	p-value	Menotrophin	Follitropin alpha	p-value
Subjects with embryo transfer	46/48 (95.8)	54/58 (93.1)	0.69	54/62 (87.1)	58/62 (93.5)	0.36
First biochemical pregnancy test	19/46 (41.3)	25/54 (46.3)	0.69	24/54 (44.4)	28/58 (48.3)	0.71
Second biochemical pregnancy test [a]	16/46 (34.8)	24/54 (44.4)	0.41	19/54 (35.2)	27/58 (46.6)	0.25
Clinical pregnancy [b]	14/46 (30.4)	18/54 (33.3)	0.83	17/54 (31.5)	19/58 (32.8)	1.00
Ongoing pregnancy [c]	14/46 (30.4)	18/54 (33.3)	0.83	16/54 (29.6)	19/58 (32.8)	0.84

a 7 days after the 1st positive pregnancy test
b 6 weeks after the 1st positive pregnancy test
c defined as positive foetal heart action ≥9 weeks after the first positive pregnancy test established at Visit 12 by the investigator

The influence of progesterone on the ongoing pregnancy rate was determined by ROC analyses and the logistic progression model. For the PP set and the FAS, the ROC curves were close to the no-discrimination line and the area under the curve was nearly 0.5, the p-value of the logistic regression model was 0.90 and 0.88 (PP and FAS), showing that there was no indication for progesterone as a reliable predictor for ongoing pregnancy.

Pregnancy outcome at the long-term follow-up visit was comparable between the treatment groups: 92.9% (PP) and 93.3% (FAS) of the subjects in the Menotrophin group and 100.0% (PP) and 94.1% (FAS) of the subjects in the Follitropin alpha groups had live births. One ectopic pregnancy was reported for the Menotrophin group and each 1 miscarriage and 1 congenital abnormality (1 case of mucoviscidosis) were reported in the Follitropin alpha group.

With $p < 0.05$ (Wilcoxon-test), the number of follicles, the number of cumulus-oocyte-complexes retrieved, the number of pronuclear oocytes and the number of frozen oocytes at 2PNstage were in both analysis sets statistically remarkable higher in the Follitropin alpha group than in the Menotrophin group.

The number of embryos transferred, the best quality of an embryo transferred, the number of days stimulated with gonadotrophins and the number of ampoules used did not differ statistically remarkable between both treatment groups in either analysis set ($p > 0.05$).

The maximum follicle diameter, the average follicle diameter, the endometrial thickness, and the estradiol level (E2) at day of hCG administration did not differ statistically remarkable between both treatment groups in either analysis set ($p > 0.05$).

The mean maximum follicle diameter was 20.1 ± 2.4 mm in the Menotrophin group and 19.9 ± 1.8 mm in the Follitropin alpha group for both analysis sets. The average diameter of follicles was 17.6 ± 1.8 mm (PP) and 17.5 ± 1.8 mm (FAS) in the Menotrophin group and 18.1 ± 1.2 mm (PP and FAS) in the Follitropin alpha group.

The mean endometrial thickness was 10.8 ± 2.1 mm (PP) and 10.9 ± 2.2 mm (FAS) in the Menotrophin group and 11.0 ± 2.2 mm (PP and FAS) in the Follitropin alpha group.
The mean estradiol level was 1.81 ± 1.21 ng/mL (PP) and 1.72 ± 1.16 ng/mL (FAS) in the Menotrophin group and 1.65 ± 0.87 ng/mL (PP) and 1.66 ± 0.86 ng/mL (FAS) in the Follitropin alpha group.

SAFETY RESULTS

A total of 262 TEAEs was reported for 88 subjects (71.0%), mostly of mild intensity (80, 64.5%). Two subjects (1.6%, Menotrophin group) experienced a total of 8 serious TEAEs, 1 of them was a moderate event of OHSS. For 52 subjects (41.9%), TEAEs were rated to be drug-related. Two subjects (nos. 4903/36 and 4905/8, Menotrophin group) were withdrawn from the trial due to a TEAE. Injection site reactions were documented as TEAE in 47 subjects (37.9%), OHSS was documented as TEAE in 3 subjects (2.4%). None of the subjects died during this trial.

A total of 75 subjects (60.5%) experienced non-treatment emergent AEs, 47 subjects (37.9%) experienced pre-treatment and 41 subjects (33.1%) experienced post-treatment AEs which were all documented as non-serious. In 1 subject (1.6%) in the Follitropin alpha group a serious pre-treatment AE was documented, and in 2 subject (3.2%) in the Menotrophin group and 4 subjects (6.5%) in the Follitropin alpha group, serious post-treatment AEs were documented.

An overview on all AEs is given in Table 4.

Table 4 All subjects with AEs (safety set)

Subjects with	Menotrophin N=62	Follitropin alpha N=62	Total N=124
Any TEAE	43 (69.4)	45 (72.6)	88 (71.0)
Intensity mild	38 (61.3)	42 (67.7)	80 (64.5)
moderate	9 (14.5)	14 (22.6)	23 (18.5)
severe	3 (4.8)	2 (3.2)	5 (4.0)
Drug-related	28 (45.2)	24 (38.7)	52 (41.9)
Non-serious	43 (69.4)	45 (72.6)	88 (71.0)
Serious	2 (3.2)	0 (0.0)	2 (1.6)
OHSS	2 (3.2)	1 (1.6)	3 (2.4)
Injection site reaction	25 (40.3)	22 (35.5)	47 (37.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal due to AE	2 (3.2)	0 (0.0)	2 (1.6)
Discontinuation due to AE	1 (1.6)	0 (0.0)	1 (0.8)
Any non-treatment emergent AE	36 (58.1)	39 (72.6)	75 (60.5)
Pre-treatment non-serious	23 (37.1)	24 (38.7)	47 (37.9)
Pre-treatment serious	0 (0.0)	1 (1.6)	1 (0.8)
Post-treatment non-serious	20 (32.3)	21 (33.9)	41 (33.1)
Post-treatment serious	2 (3.2)	4 (6.5)	6 (4.8)

The most common categories of TEAEs reported were:

- General disorders and administration site conditions 50 (40.3%), mostly due to injection site erythema (10, 16.1% under Menotrophin and 7, 11.3% under Follitropin alpha), injection site pruritus (9, 14.5% under Menotrophin and 7, 11.3% under Follitropin alpha), and injection site pain (7, 11.3% under Menotrophin and 5, 8.1% under Follitropin alpha)
- Gastrointestinal disorders 41 (33.1%), mostly due to abdominal pain (9, 14.5% under Menotrophin and 12, 19.4% under Follitropin alpha)
- Nervous system disorders 28 (22.6%), %), mostly due to headache (11, 17.7% under Menotrophin and 13, 21.0% under Follitropin alpha), and

- Reproductive system and breast disorders 17 (13.7%), 10 (16.1%) under Menotrophin and 7 (11.3%) under Follitropin alpha

Accordingly, the most common drug-related TEAEs reported were:

- Gastrointestinal disorders 21 (16.9%), mostly due to abdominal pain, 8 (12.9%) under Menotrophin and 9 (14.5%) under Follitropin alpha,
- General disorders 31 (25.0%), mostly due to injection site erythema, 7 (11.3%) under Menotrophin and 3 (4.8%) under Follitropin alpha; injection site pain and injection site pruritus, each 6 (9.7%) under Menotrophin and 3 (4.8%) under Follitropin alpha, and
- Nervous system disorders 10 (8.1%), mostly due to headache, 5 (8.1%) under both treatments.

During this trial, 2 subjects in the Menotrophin group experienced a total of 8 SAEs: 1 subject experienced circulatory problems documented as 6 SAEs which occurred 5 days after exposure to Menotrophin and resolved after 3 days. None of these SAEs was assessed to be related to the study medication but possibly related to Cetrorelix (allergic reaction), no other treatment was given due to these events, and study treatment remained unchanged. The other subject experienced mild OHSS and abdominal rigidity as a peritoneal reaction after follicle punctuation. The event of mild OHSS was assessed to be possibly related to study treatment. Remedial treatment was given and both events resolved after 17 days without change in study treatment.

Furthermore, 7 subjects (2 in the Menotrophin group and 5 in the Follitropin alpha group) experienced 7 serious pre- or post-treatment AEs, which mostly assessed to be unrelated to study treatment. Except for 1 case of congenital abnormality (child with suspected mucoviscidosis) all of these SAEs had an outcome recovered.

Two subjects in the Menotrophin group were withdrawn from the trial due to TEAEs. These were a severe event of nasopharyngitis and a severe event of premature ovulation. Both events were not assessed to be drug-related.

Occurrence of OHSS and injection site reactions were documented as AEs of special interest. During this trial, 7 subjects (3 in Menotrophin group and 4 in Follitropin alpha group) experienced an event of OHSS, 3 events were treatment-emergent, and 1 event (Follitropin alpha group, not treatment-emergent) was of severe intensity. The outcome for all OHSS events was recovered.

A total of 47 subjects (37.9%) experienced injection site reactions, a well-known side-effect of hormone therapies applied by injection.

Endocrine values during the course were comparable between the treatment groups and within the expected ranges. Haematology and clinical chemistry parameters remained constant from baseline until the end of the trial. There were no differences between the treatment groups regarding mean values and mean changes during the trial.

Four subjects (6.9%) in the Menotrophin group and 6 subjects (9.8%) in the Follitropin alpha group showed changes in pelvic ultrasound from normal to abnormal. An incidence of risk to develop OHSS was found for 6 subjects (9.7%) in both treatment groups.

CONCLUSIONS

The primary objective of this trial - to demonstrate that highly purified Menotrophin produces significant lower progesterone (P4) serum levels during the follicular phase in comparison to Follitropin alpha in the treatment of subfertile females - was met. A predictive role for progesterone serum levels on ongoing pregnancy, however, could not be concluded.

Pregnancy outcome with a live birth rate over 90% was comparable between the treatment groups.

Regarding the AE profile, evaluation of laboratory and other safety related parameter, the non-inferiority of Menotrophin with regard to safety as a secondary endpoint could be shown in this trial.

The results of this trial are in line with former studies showing that Menotrophin is efficacious and safe.