CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

MEDICAL REVIEW(S)

MAR 18 1997

Medical Officer's Original Summary of NDA 20-582

Sponsor's Name: Organon, Inc.

Proposed Trade Name: Follistim

Established Drug Name: Follitropin beta

Laboratory Code Name: Org 32489

Active Ingredient: Follicle stimulating hormone (recombinant)

Dosage Form: Lyophilized powder in vials for reconstitution

Strengths: 75 IU FSH activity

Prescription or OTC: Prescription

I. Proposed Indication:

A. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.

B. Induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

II. Foreign Country Approvals:

A. Scientific approval for ORG 32489 was obtained in Switzerland in August 1995.

B. ORG 32489 was approved in New Zealand November 8, 1995.

III. Dosages Recommended

A. Assisted Reproductive Technologies:

A starting dose of 150 to 225 IU of follitropin beta for injection is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient based upon their ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75 to 375 IU for six to twelve days are sufficient, although longer treatment may be necessary. The maximum, individualized, daily dose of Follistim that has been used in clinical studies is 600 IU. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles are induced by

administering hCG at a dose of 5,000 IU to 10,000 IU. Oocyte retrieval is performed 34 to 36 hours later. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of Follistim therapy; this will reduce the chance of developing OHSS.

B. Ovulation Induction:

Treatment usually starts with a 75 IU daily dose of Follistim which is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicular growth and/or serum estradiol levels indicate an adequate response. The maximum, individualized, daily dose of Follistim that has been safely used for ovulation induction in patients during clinical trials is 300 IU. The patient should be treated until ultrasonic visualizations and/or serum estradiol determinations indicate pre-ovulatory conditions equivalent to or greater than those of the normal individual followed by hCG, 5,000 IU to 10,000 IU. If the ovaries are abnormally enlarged on the last day of Follistim therapy, hCG must be withheld during this course of treatment; this will reduce the chances of developing OHSS.

During treatment with Follistim and during a two week post-treatment period, patients should be examined at least every other day for signs of excessive ovarian stimulation. It is recommended that Follistim administration be stopped if the ovaries become abnormally enlarged or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation.

IV. Pharmacologic Class:

Org 32489 is a drug substance containing FSH as the active ingredient prepared by recombinant DNA technology and is biochemically and pharmacologically almost identical to human follicle stimulating hormone (FSH). Follicle stimulating hormone is a glycoprotein necessary for both male and female reproduction by stimulating gamete growth and maturation and gonadal steroid production.

Follicle stimulating hormone has a dimeric structure and contains two glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and the 111 amino acid beta-chain have two N-linked oligosaccharide chains presented as complex heterogeneous structures. Variations in glycosylation pattern, particularly in the degree of sialytion, result in a spectrum of naturally-occurring FSH isoforms with differences in charge, bioactivity, and elimination half-life.

The active substance of Org 32489 is recombinant human FSH. It is produced by Chinese hamster ovary (CHO) cells transfected with a plasmid containing the two subunit DNA sequences encoding human FSH. As a result, biologically active recombinant human FSH is produced and secreted. Structural and conformational analysis showed that the amino acid sequence and the tertiary structure are identical to those of natural

human FSH. In addition, the carbohydrate chain structures of recFSH are very similar to those reported for natural hFSH, yet some small differences have been found. The different carbohydrate structures found in recFSH all comprise carbohydrate molecules that are found on other human glycoproteins. Further, the small structural differences do not affect the degree of charge heterogeneity, receptor binding affinity and the in vivo and in vitro bioactivities of recFSH relative to natural hFSH.

V. Pharmacology and Toxicology:

The results of nonclinical pharmacology and toxicology studies have demonstrated that Org 32489, a recombinant human FSH, is safe for use in humans for the same indications as accepted for the human FSH-containing preparations of urinary origin.

The *in vitro* bioactivity studies in rat Sertoli cell and granulosa cell bioassays demonstrated that the *in vitro* B/I ratio of Org 32489 and natural human FSH were indistinguishable. In addition, the almost identical neutralization profiles of recFSH and natural human FSH by various monoclonal antibodies supports the structural and functional similarity of these compounds. It was demonstrated in the *in vitro* Leydig cell bioassay that the intrinsic LH bioactivity of Org 32489 was very low, if not negligible.

The in vivo efficacy studies in immature hypophysectomized female rats demonstrated that Org 32489 was capable of inducing follicular growth, comparable to that observed with Metrodin®. Org 32489 and Metrodin® were equipotent in stimulating ovarian weight and ovarian aromatase activity. Org 32489 did not increase 17β-estradiol plasma levels except in the presence of hCG.

Ancillary pharmacology studies in anesthetized dogs and conscious rabbits demonstrated that Org 32489 produced no biologically significant effects on the cardiovascular system or regulatory functions of the autonomic nervous system. No biologically significant hemodynamic effects were observed.

Both single and multiple toxicity studies in rats and dogs demonstrated that Org 32489 produced no significant toxicological effects, even when administered to rats at doses up to 100 times and in dogs at up to 10 times the anticipated maximal daily human dose.

A local tolerance study in rats demonstrated that Org 32489 produced no treatment-related effects after intravenous or intramuscular administration.

Org 32489 was not mutagenic in an Ames test using both *S. typhimurium* and *E. coli* tester strains and did not produce an increase in chromosomal aberrations in an *in vitro* assay using human lymphocytes.

VI. Therapeutic Class: Infertility

VII. Consultations: None

VIII. Related Drug:

Metrodin® is a human FSH containing preparation of urinary origin. Follistim may be considered as a highly purified form of Metrodin®.

IX. Clinical Studies:

Seventeen clinical studies (Studies 37601, 37602, 37603, 37604, 37605/37614, 37607, 37608, 37609, 37611, 37612, 37613, 37616, 37617, RM-9211, RM-9361, Compassionate-Use for the proposed indications, and Compassionate-Use for non-indication) are included in this application. All seventeen clinical studies were conducted in the following countries: Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, The Netherlands, Norway, Spain, Sweden, Switzerland, and The United Kingdom. All clinical studies, except for two, were sponsored, conducted, and monitored by NV Organon. Two clinical studies (Studies RM-9211 and RM-9361) were completed in Japan and sponsored, conducted, and monitored by
As of the cutoff date of May 31, 1995, for the inclusion of clinical information in the NDA, there are no ongoing clinical studies worldwide and all subjects exposed to Org 32489 are reported in this NDA. No IND has been filed in the U.S.

A total of 1181 subjects have been exposed to Org 32489, including 1164 females and 17 males. In addition, 513, 42, and 16 females were administered Metrodin®, Humegon™, and Fertinorm® P, respectively as an active control. Finally, four and two males were exposed to Metrodin® and Humegon™, respectively, as an active control.

The dose regimen evaluated in the Phase III program to demonstrate that Org 32489 was as efficacious and safe as urinary-extracted FSH (Metrodin®, Humegon™, and Fertinorm® P) for the proposed indications was based on the following: 1) Historical dosing data based on the marketed urofollitropin preparations available in the U.S. and Europe, and administered for the treatment of infertility via ART programs and Classical Ovulation Induction (COI); 2) Nonclinical investigations comparing the in-vivo and in-vitro bioactivities, receptor-binding potency, neutralization of *in-vivo* bioactivity, and overall safety profiles of Org 32489 and urinary-extracted FSH; 3) Phase I single and multiple dose studies proving that Org 32489 was safe and biologically active in normal adult volunteers of both genders; and 4) A Phase II efficacy study (Study 37603) in females undergoing ART therapy proving that the proposed dose regimen for Org 32489 was similar to that recommended and used historically with urinary-extracted FSH preparations.

In four clinical pharmacology studies (Studies 37601, 37602, 37605/37614, and 37607), a total of 81 subjects, including 68 females and 13 males, received FSH. Fifty-nine females and 13 male subjects received Org 32489 to determine the following parameters:

1)pharmacokinetics; 2) bioavailability; 3) dose-proportionality; 4)dose-tolerance; and 5)pharmacodynamics (e.g., number of maturing follicles, serum estradiol, inhibin, progesterone, testosterone, androstenedione, and LH levels, and the formation of FSH-antibodies.)

There were five uncontrolled studies.

In one uncontrolled study, 18 female subjects were given Org 32489 for compassionate use.

In a Phase III study (37612) in hypopituitary males, four subjects were administered Org 32489 and two subjects received Humegon™. The study was abandoned due to legal reasons (patent litigation).

In two Japanese studies, 78 female subjects were given FSH. Six subjects were exposed to Org 32489 in Study RM-9211 (a Phase I study). In Study RM-9361, 56 and 16 subjects were administered Org 32489 and Fertinorm® P, respectively. RM-9361 was a Phase II study comparing the efficacy and safety of Org 32489 with Fertinorm® P.

Under the Compassionate-Use Program for Org 32489, three female subjects were exposed to Org 32489 for a non-indication use (i.e., allergy testing).

There were eight controlled clinical studies (Studies 37603, 37604, 37608, 37609, 37611, 37613, 37616, and 37617) that provided evidence for the efficacy and safety of Org 32489 and hCG given in a sequential manner for the proposed indications. All Subjects treated in the controlled clinical studies were female. There were 1554 subjects exposed to FSH (1029 to Org 32489, 498 to Metrodin®, and 42 to Humegon™) in the eight controlled clinical studies.

There were three controlled studies that were not adequate and well controlled. The first, study 37603, was a Phase II, open, one cycle study conducted in females undergoing ART therapy. In addition, the use of Org 32489 with or without concurrent GnRH agonists (triptorelin and buserelin) was examined. The treatment regimens for the GnRH agonists followed a short-term (buserelin or triptorelin) or long-term (buserelin or triptorelin) protocol. Buserelin was administered intranasally and triptorelin was administered either intramuscularly or subcutaneously. Fifty subjects completed treatment with Org 32489 in Study 37603.

The second, Study 37616, was abandoned following the recruitment and administration of Org 32489 to four subjects due to legal issues (patent litigation).

The third, Study 37617, was an open, one cycle, single center study conducted in females undergoing ART therapy. Thirteen subjects were treated with Org 32489 and seven with Humegon™.

Of the five adequate and well controlled studies, study 37613 was unique in that it was not assessor blinded and had as its primary objective the assessment of safety and local tolerance of Org 32489 given subcutaneously compared to the intramuscular route in infertile women undergoing in vitro fertilization and embryo transfer. Study 37613 is summarized below.

Study 37613:

Title of the study:

An open, randomized, group-comparative, multi-center study to assess the tolerance, safety and efficacy of Org 32489 administered subcutaneously, as compared with the intramuscular route in infertile women undergoing in vitro fertilization and embryo transfer.

Studied period:

August, 1993 - September, 1994

Clinical Phase:

Phase III

Objectives:

Primary Objectives: To assess the safety and local tolerance of Org 32489 given subcutaneously (SC) as compared to the intramuscular (IM) route in infertile women undergoing in vitro fertilization (IVF) and embryo transfer (ET).
Secondary Objective: To assess the efficacy of Org 32489 given subcutaneously compared to the intramuscular route measured as the number of oocytes retrieved in infertile women undergoing IVF and ET.

Methodology:

An open, randomized, group-comparative, multi-center study in infertile pituitary-suppressed women.

Number of subjects (total and for each treatment):

Two hundred and eighteen subjects randomized, 195 FSH-treated subjects (Org 32489 IM: 77; Org 32489 SC: 118).

Diagnosis and criteria for inclusion:

- Infertile women (aged 18-39 years) in good physical and mental health, having a menstrual cycle between 24 and 35 days and an intra-individual variation of plus or minus three days (but never outside the 24-35 days range);
- Body weight between 80 and 130% of the ideal body weight;
- Cause of infertility potentially solvable by in vitro fertilization; and
- Willing to give informed consent to participate.

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

Org 32489 (CP 092146). Subjects were treated with 150 IU or 225 IU in vivo bioactivity subcutaneously or intramuscularly for the first 4 days, after which the dose was adjusted individually.

Duration of treatment:

One treatment cycle.

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

None

Criteria for evaluation:

Local tolerance:

Incidence of bruising, pain, redness, swelling, and itching at the injection site on each day of Org 32489 treatment.

Safety:

Safety analysis was performed by evaluating the number and nature of adverse experiences and by evaluating vital signs, hematology, blood biochemistry, urinalysis, and serum anti-FSH antibodies.

Efficacy:

Although efficacy assessment was a secondary objective, the following efficacy parameters were analyzed: the total of oocytes recovered and the ongoing pregnancy rate per attempt and per transfer. Furthermore, the total number of FSH ampules, length of FSH treatment (days), number of follicles with diameters $\geq$ 15 mm and $\geq$ 17 mm on the last USS before the hCG injection, serum E_2, LH, P, and FSH concentration on the day of hCG injection, total number of mature oocytes recovered, number of oocytes with two

pronuclei, number of oocytes fertilized, normal fertilization rate, total number of embryos of Types 1 and 2, cycle cancellation rate, embryo development rate, cleavage rate, and the number and type of embryos transferred were analyzed and/or evaluated.

Summary results:

A total of 218 subjects (Org 32489 IM: 86, Org 32489 SC: 132) were randomized, 211 subjects (Org 32489 IM: 84, Org 32489 SC: 127) started buserelin pre-treatment, and 195 subjects (Org 32489 IM: 77, Org 32489 SC: 118) started FSH treatment. One hundred and seventy five subjects (Org 32489 IM: 69, Org 32489 SC: 106) had an embryo transfer.

Local tolerance:

One hundred and thirty of the 195 FSH-treated subjects (66.7%) had some local tolerance symptoms for at least one day: 49 subjects in the Org 32489 IM group (63.6%) and 81 subjects in the Org 32489 SC Group (68.6%).

Overall Local Tolerance

	Org 32489 IM (N=77)		Org 32489 SC (N=118)	
	N	%	N	%
Overall Local Tolerance:				
Subjects without data	0	0.0	3	2.5
Subjects without symptoms	28	36.4	34	28.8
Subjects with symptoms	49	63.6	81	68.6
Mild	35	45.5	52	44.1
Moderate	9	11.7	22	18.6
Severe	5	6.5	7	5.9
Bruising:				
Subjects without data	1	1.3	3	2.5
Subjects without symptoms	47	61.0	51	43.2
Subjects with symptoms	29	37.7	64	54.2
Mild	23	29.9	47	39.8
Moderate	6	7.8	14	11.9
Severe	0	0.0	3	2.
Pain:				
Subjects without data	0	0.0	3	2.5
Subjects without symptoms	53	68.8	82	69.5
Subjects with symptoms	24	31.2	33	28.0
Mild	15	19.5	19	16.1
Moderate	5	6.5	9	7.6
Severe	4	5.2	5	4.2
Redness:				
Subjects without data	0	0.0	3	2.5

Subjects without symptoms	67	87.0	96	81.4
Subjects with symptoms	10	13.0	19	16.1
Mild	7	9.1	18	15.3
Moderate	2	2.6	1	0.8
Severe	1	1.3	0	0.0
Swelling:				
Subjects without data	0	0.0	3	2.5
Subjects without symptoms	71	92.2	108	91.5
Subjects with symptoms	6	7.8	7	5.9
Mild	5	6.5	5	4.2
Moderate	0	0.0	2	1.7
Severe	1	1.3	0	0.0
Itching:				
Subjects without data	0	0.0	3	2.5
Subjects without symptoms	72	93.5	111	94.1
Subjects with symptoms	5	6.5	4	3.4
Mild	2	2.6	4	3.4
Moderate	2	2.6	0	0.0
Severe	1	1.3	0	0.0

Remark: subjects may be reported in more than one category.

Safety:

Twenty of 195 FSH-treated subjects (10.3%) experienced at least one AE (including subjects with SAEs): 5 in the Org 32489 IM Group (6.5%) and 15 in the Org 32489 SC Group (12.7%). A total of 7 subjects in the All-Subjects-Treated Group (3.6%) had drug-related AEs: 2 subjects in the Org 32489 IM Group (2.6%) and 5 subjects in the Org 32489 SC Group (4.2%). One subject treated IM with Org 32489 (1.3%) and 6 subjects treated SC with Org 32489 (5.1%) experienced SAEs.

In both treatment groups the majority of subjects with an AE had a "reproductive disorder": 3 subjects in the Org 32489 IM Group (3.9%) and 11 subjects in the Org 32489

SC Group (9.3%). Most frequently reported AEs in this body system were ovarian hyperstimulation syndrome [Org 32489 IM: 2 (2.6%), Org 32489 SC: 7 (5.9%)] and ectopic pregnancy [Org 32489 IM: 1 (1.3%), Org 32489 SC: 2 (1.7%)].

Serum anti-FSH antibodies were not detectable in any of the subjects.

The two treatment groups were similar with respect to the incidence of markedly abnormal laboratory values. A significant difference in trends between the Org 32489 IM and the Org 32489 SC groups was found for the percentage of monocytes. No other significant differences between the groups were found. In both treatment groups a decreased value was found for total protein, hemoglobin, hematocrit, and the percentage of lymphocytes. A decreased value was also found for sodium and the number of erythrocytes in the Org 32489 IM Group.

An increased value was found in both treatment groups for the number of leucocytes, neutrophils, and monocytes in the Org 32489 IM Group, and for the percentage of neutrophils in the Org 32489 SC Group. A difference between the Org 32489 IM and the Org 32489 SC groups was found with respect to notable downward shifts for eosinophils. In both treatment groups, more than 10% of the subjects had a notable downward shift for inorganic phosphorus, hemoglobin, hematocrit, lymphocytes, and basophils. Furthermore, notable downward shifts were found in the Org 32489 IM Group for eosinophils and in the Org 32489 SC Group for erythrocytes. In both treatment groups more than 10% of the subjects had notable upward shifts for leucocytes and neutrophils.

Efficacy:

The mean total number of oocytes recovered, adjusted for center, was 9.8 oocytes in the Org 32489 IM Group and 10.4 oocytes in the Org 32489 SC Group. The estimated treatment difference, adjusted for center, was 0.6 oocytes in favor of Org 32489 SC with a corresponding 95% confidence interval [-2.2;+1.0].

The ongoing pregnancy rate per attempt (per transfer), adjusted for center, was 27.1% (30.1%) in the Org 32489 IM Group and 26.1% (29.3%) in the Org 32489 SC Group. The treatment difference, adjusted for center, was 1.0% (0.9%) in favor of Org 32489 IM with a corresponding 95% confidence interval [-11.6%;+13.6%] ([-12.9%;+14.6%]).

Conclusions:

There was no clinically relevant difference in the overall occurrence of local tolerance symptoms (bruising, pain, redness, swelling, and itching) and safety parameters between the IM and SC administration of Org 32489 in infertile women treated with Org 32489. Bruising was seen more often in subjects receiving Org 32489 subcutaneously, probably due to the more superficial injection site.

Additional non-confirmatory analyses revealed no clinically relevant differences in efficacy between Org 32489 administered either subcutaneously or intramuscularly with respect to the number of oocytes retrieved and ongoing pregnancy rates.

Studies 37604, 37608, 37611, and 37609:

The other four adequate and well controlled clinical studies support the approval of two indications. Studies 37604, 37608, and 37611 support the use of Org 32489 for the development of multiple follicles in ovulatory patients participating in an ART program and study 37609 supports the use of Org 32489 for the induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure. Based on the mechanism of action of FSH (induction of ovarian follicular development and maturation), efficacy data from subjects participating in an ART program are also used as support for the efficacy claim for the use of Org 32489 for the induction of ovulation in the infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

For ethical reasons, placebo-controlled clinical studies were not conducted. All efficacy claims from the controlled clinical studies are based on the following types of studies: 1) Completed active concurrent control studies comparing Org 32489 to either Metrodin® (Studies 37608, 37609, and 37611) or Humegon™ (Studies 37604 and 37617); or 2) Completed open-label, no-treatment concurrent control studies (Studies 37613 and 37616). Studies 37604, 37608, 37609, 37611, and 37617 were assessor-blind studies. In addition, both active control agents (Metrodin® and Humegon™) used as a reference in the controlled clinical studies are approved in the U.S. for the proposed indications. Org 32489 was administered intramuscularly in almost all of the clinical studies. Study 37613, along with the bioavailability studies, demonstrated that Org 32489 was efficacious and safe when administered subcutaneously as well as intramuscularly.

The initial daily dose of Org 32489 used in the ART studies was 150 to 225 IU for the first four days and for ovulation induction the initial dose was 75 IU for the first week. Depending on the ovarian response of each individual subject, the daily dose of Org 32489 was individualized after initial treatment.

In studies 37608 and 37611 a GnRH agonist (Buserelin or Triptorelin) was administered to suppress the pituitary before FSH treatment. Pituitary function was not suppressed in studies 37604 and 37609. Studies 37604, 37608, 37611 and 37609 are summarized below.

Study 37604

Title of the study:

A randomized, assessor-blind, group comparative, single center safety and efficacy study

of Org 32489 in infertile women treated by in vitro fertilization with Org 32489 or Humegon™ without GnRH agonist treatment.

Investigator:

Dr. C. Jansen

Study Center:

Diaconessenhuis, Voorburg, The Netherlands

Studied Period:

March, 1992- February, 1994

Clinical Phase:

Phase III

Objectives:

To assess the safety and efficacy of Org 32489 in relation to Humegon™ for induction of controlled ovarian superovulation in infertile women treated by IVF.

Methodology:

A randomized, assessor-blind group comparative single center study.

Number of subjects (total and for each treatment):

109 (Org 32489: 66; Humegon™: 43)

Diagnosis and criteria for inclusion:

- Infertile women (aged 18-39 years) in good physical and mental health, having a menstrual cycle between 24 and 35 days and an intra-individual variation of plus or minus three days (but never outside the 24-35 day range), body weight between 80% and 130% of the ideal body weight;
- Cause of infertility potentially solvable by in vitro fertilization;
- Maximum of three previous IVF, GIFT, OR ZIFT attempts, in which oocytes were collected at least once; and
- Willing to give informed consent to participate.

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

Org 32489 (CP 091077, 091134, and 092146). Subjects were treated with 150 IU or 225 IU intramuscularly for the first four days (starting on Day 3 of the menstrual cycle), after which the dose was adjusted individually.

Duration of treatment:

One treatment cycle

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

Humegon™ (CP 091151 and 093133). Subjects were treated with 150 IU or 225 IU intramuscularly for the first four days (starting on Day 3 of the menstrual cycle), after which the dose was adjusted individually.

Criteria for evaluation:

For efficacy analysis, the following variables were evaluated statistically:

Main parameters:

- Total number of oocytes recovered; and
- Ongoing pregnancy rate per attempt and per transfer.

Secondary parameters:

- Number of follicles ≥ 15 mm on the last USS before the hCG injection;
- Maximum serum E_2 concentration before the hCG injection;
- The total number of FSH/hMG ampules and the duration of the treatment for subjects with an oocyte retrieval;
- Number of mature oocytes collected;
- Number of Type 1 and Type 2 embryos obtained; and
- Clinical pregnancy rate (per attempt and per transfer).

Summary results:

A total of 109 subjects (Org 32489: 66; Humegon™: 43) were randomized; 89 subjects (Org 32489: 54 subjects; Humegon™: 35) started FSH treatment. Twenty-three subjects (Org 32489: 15; Humegon™: 8) started FSH treatment but did not have an embryo transfer.

The various reasons for cycle cancellations were evenly distributed across the two treatment groups.

On the day of the hCG injection, median serum LH was 3.8 IU/L and 4.1 IU/L in the Org 32489 Group and the Humegon™ Group, respectively. For serum E_2, this was 2915 pmol/L and 2480 pmol/L and for P it was 1.9 nmol/L and 1.8 nmol/L. The median normal fertilization rate was 46.2% in the Org 32489 Group and 61.8% in the Humegon™ Group. The percentage of subjects with polyspermy was 34.0% in the Org 32489 Group and 43.8% in the Humegon™ Group. The median cleavage rate was 100% in both treatment groups.

Evaluation of parameters revealed the following:

Main parameters

	Mean		**Org 32489 minus Humegon™**
	Org 32489	**Humegon™**	**95% confidence interval**
Total number of oocytes recovered	11.2	8.3	-1.1 to 6.8 (p=0.15)
Ongoing pregnancy rate/attempt (%)	22.2	17.1	-12.1 to 22.2 (p=0.56)
Ongoing pregnancy rate/transfer (%)	30.8	22.2	-13.4 to 30.5 (p=0.45)

Secondary parameters

	Mean	**Org 32489 minus Humegon™**

	Org 32489	Humegon™	95% confidence interval
Number of follicles ≥ 15 mm	5.5	5.4	-1.3 to 1.5 (p=0.87)
Maximum serum E_2 before hCG	3889	3145	-365 to 1855 (p=0.19)
Total number of ampules used	18.8	18.2	-0.7 to 1.9 (p=0.39)
Treatment length (days)	6.2	6.0	-0.2 to 0.6 (p=0.32)
Number of mature oocytes recovered	10.6	7.5	-0.7 to 6.9 (p=0.11)
Number of Type 1 and Type 2 embryos	3.1	3.0	-1.8 to 2.0 (p=0.92)
Clinical pregnancy rate/attempt (%)	24.1	22.9	-16.9 to 19.3 (p=0.90)
Clinical pregnancy rate/transfer (%)	33.3	29.6	-19.3 to 26.7 (p=0.75)

A total of five subjects experienced at least one adverse experience (including one subject with a serious AE): 3 in the Org 32489 Group (5.6%) and 2 in the Humegon™ Group (5.7%). Three AES were classified as fetal disorders (miscarriages), one was classified as an autonomic nervous system disorder (vasovagal syncope), and one as a female reproductive disorder (ectopic pregnancy). None of the AEs were reported as drug-related. One subject in the Org 32489 Group (ectopic pregnancy) and none in the Humegon™ Group experienced an SAE. Serum anti-FSH antibodies were not detectable in any of the subjects.

The Org 32489 Group and the Humegon™ Group were similar with respect to the incidence of markedly abnormal laboratory values. There were no markedly abnormal vital sign values. The trends and shifts of the laboratory parameters and vital signs were without clinical significance.

Conclusions

There was no significant difference between Org 32489 and Humegon™ in controlled ovarian hyperstimulation in infertile non-pituitary-suppressed women undergoing IVF-ET, as assessed by the number of oocytes retrieved and ongoing pregnancy rates per attempt and per transfer.

There were no apparent differences in safety parameters between Org 32489 and Humegon™.

Study 37608:

Title of the study:

A randomized, assessor-blind, group comparative multicenter safety and efficacy study of Org 32489 in infertile women treated by in vitro fertilization with Org 32489 or Metrodin®, both after pituitary suppression with buserelin.

Study period:

March, 1992 through March, 1994

Clinical Phase:

Phase III

Objectives:

To assess the safety and efficacy of Org 32489 in relation to Metrodin® for induction of controlled ovarian hyperstimulation in infertile pituitary-suppressed women undergoing in vitro fertilization and embryo transfer.

Methodology:

A randomized, assessor-blind, group-comparative, multicenter study. The blinded assessor adjusted the FSH dosage.

Number of subjects (total and for each treatment):

Treatment Cycle 1: 1027 (Org 32489: 615; Metrodin®: 412)
Treatment Cycle 2: 370 (Org 32489: 209; Metrodin®: 161)
Treatment Cycle 3: 142 (Org 32489: 86; Metrodin®: 56)

Diagnosis and criteria for inclusion:

- Infertile women (aged 18-39 years) in good physical and mental health, having a menstrual cycle between 24 and 35 days and an intra-individual variation of plus or minus three days (but never outside the 24-35 day range);
- Cause of infertility potentially solvable by in vitro fertilization;
- body weight between 80-130% of the ideal body weight:
- Maximum of three previous IVF, GIFT, or ZIFT attempts in which oocytes were collected at least once; and
- willing to give informed consent to participate.

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

Org 32489 (CP 091134, 091077, and 092146). Subjects were treated with 150 IU/day or 225 IU/day intramuscularly for the first four days, after which the dose was adjusted individually. When at least 3 follicles reached at least 17 mm, hCG 10,000 IU was administered. Luteal phase support for at least 2 weeks was provided.

Duration of treatment:

The study period covered one, two, or three treatment cycles.

Reference therapy, dose and mode of administration, batch no.:

Metrodin® (CP 092139, 093057, 093107, 092047, and 091163). Subjects were treated with 150 IU/per day or 225 IU/per day intramuscularly for the first 4 days, after which the dose was adjusted individually.

Criteria for evaluation:

For efficacy analysis the following variables in the first treatment cycle were evaluated statistically:

Main parameters

- total number of oocytes recovered; and
- ongoing pregnancy rate per attempt and per transfer.

Secondary parameters

- number of follicles ≥ 15 mm and ≥ 17 mm on the last USS before the hCG injection;
- serum FSH concentration and the maximum serum E_2 concentration before the hCG injection;
- the total number of FSH ampules and the duration of the FSH treatment for subjects undergoing oocyte retrieval;
- number of mature oocytes collected;
- sum of the number of Type 1 and 2 embryos obtained;
- implantation rate; and
- clinical pregnancy rate (per transfer and per attempt).

In addition, ongoing pregnancy rates after the first treatment cycle, including frozen embryo cycles following that cycle, were tested.

Ongoing pregnancy rate/transfer	26.0%	22.0%	-1.9% to 9.8% (P=0.19)	p=0.64

Secondary parameters

	Mean adjusted for Center		Org 32489 minus Metrodin®	
Parameters	**Org 32489**	**Metrodin®**	**95% confidence interval**	**test for interaction**
Number of follicles ≥ 15mm	7.5	6.7	0.4 to 1.2 (p=0.0002)	p=0.01
Number of follicles ≥ 17 mm	4.6	4.4	-0.0 to 0.5 (p=0.09)	p=0.03
Maximum serum E2 before hCG	6084	5179	494 to 1317 (p<0.0001)	p=0.04
Serum FSH on day of hCG	11.5	12.1	-1.1 to -0.1 (p=0.03)	p=0.01
Total number of ampules used	28.5	31.8	-4.5 to -2.1 (p<0.0001)	p=0.06
Treatment length (days)	10.7	11.3	-0.9 to -0.3 (p<0.0001)	p=0.02
Number of mature oocytes recovered	8.6	6.8	1.1 to 2.4 (p<0.0001)	p=0.89
Number of type 1 and 2 embryos	3.1	2.6	0.2 to 0.8 (p=0.003)	p=0.57
Implantation rate	0.11	0.10	-0.0 to 0.0 (p=0.48)	p=0.72
Clinical pregnancy rate/attempt	29.3%	25.3%	-1.6% to 9.6% (p=0.17)	p=0.85
Clinical pregnancy rate/transfer	34.3%	30.5%	-2.6% to 10.3% (p=0.25)	p=0.89

Ongoing pregnancy rates (adjusted for center) after the first treatment cycle, including frozen embryo cycles following that cycle, were 25.6% and 20.4% in the Org 32489 Group and in the Metrodin® Group, respectively (p=0.051).

Second treatment cycle

A total of 370 subjects (Org 32489: 209; Metrodin®: 161) Started buserelin pre-treatment and 362 subjects (Org 32489: 206; Metrodin®156) started FSH treatment. Thirty-five subjects (Org 32489: 22; Metrodin®: 13) started FSH treatment but did not have an ET. The mean number of ampules administered and the treatment duration was 32.5 and 11.2 days for the Org 32489 Group and 39.2 and 12.1 days for the Metrodin® Group, respectively, in the subjects with oocyte retrieval.

The mean total number of oocytes recovered (range) unadjusted for center was 10.0 (1-33) in the Org 32489 Group and 9.4 (0-26) in the Metrodin® Group. The overall ongoing pregnancy rate per attempt (unadjusted for center) was 18.4% in the Org 32489 Group and 19.2% in the Metrodin® Group. The overall ongoing pregnancy rates per transfer (unadjusted for center) in the Org 32489 and Metrodin® Groups were 20.7% and 21.0%, respectively.

Third treatment cycle

A total of 142 subjects (Org 32489: 86; Metrodin®;: 56) started buserelin pre-treatment and 139 (Org 32489: 84; Metrodin®: 55) started FSH treatment. Fourteen subjects (Org 32489: 8; Metrodin®: 6) started FSH treatment but did not have an ET. The mean total number of ampules administered and the duration of treatment was 33.7 and 11.1 days for the Org 32489 Group and 37.2 and 11.6 days for the Metrodin® Group, respectively, in subjects with oocyte retrieval.

The mean total number of oocytes recovered (range) unadjusted for center was 9.3 (1-30) in the Org 32489 Group and 9.1 (1-29) in the Metrodin® Group. The overall ongoing pregnancy rate per attempt (unadjusted for center) was 17.9% in the Org 32489 Group and 29.1% in the Metrodin® Group. The overall ongoing pregnancy rates per transfer (unadjusted for center) were 19.7% and 32.7% in the Org 32489 and in the Metrodin® Groups, respectively.

Safety in all treatment cycles

A total of 176 subjects experienced at least one adverse experience (AES including subjects with serious AES); 114 in the Org 32489 (19.3%) and 62 in the Metrodin® Group (15.6%). In addition, one Metrodin®-treated subject (906) experienced an AE (ectopic pregnancy) that was not recorded as an AE but was later classified as a SAE. Fifty-five subjects of the Org 32489 Group (9.3%)and 28 of the Metrodin® Group (7.0%) had drug-related AES. Fifty-five subjects of the Org 32489 Group (9.6%) and 35 of the Metrodin® Group (8.8%) experienced SAEs. The SAE count includes subject 906 (Metrodin®). In both treatment groups (Org 32489 and Metrodin®), the majority of AES were classified as "reproductive disorder" (13.0%, 10.3%). Most frequently reported AES in this body system were "ovarian hyper stimulation syndrome" (5.2%, 4.3%) and

"ectopic pregnancy" (3.0%, 3.8%).

None of the subjects had detectable levels of serum anti-FSH antibodies or anti-CHO cell-derived protein antibodies. The Org 32489 and Metrodin® Groups were similar with respect to the incidence of markedly abnormal laboratory values and markedly abnormal vital sign values. Significant differences in trends between the Org 32489 Group and the Metrodin® Group were found for potassium, calcium, alkaline phosphatase, ALAT, bilirubin, and thrombocytes. Significant differences between the Org 32489 and Metrodin® Groups were found in a notable downward shift for bilirubin and in a notable upward shift of alkaline phosphatase, LDH, and lymphocytes.

Conclusions

Org 32489 was more efficacious than Metrodin® in controlled ovarian hyper stimulation in infertile pituitary-suppressed women who were undergoing IVF-ET, as assessed by the number of oocytes retrieved in the first treatment cycle.

No differences were found between Org 32489 and Metrodin® in ongoing pregnancy rates per attempt and per transfer in the first treatment cycle.

There was less than one days difference in treatment length between Org 32489 and Metrodin® in the first cycle. An average of 2.7 ampules per day was required for Org 32489 and 2.9 ampules per day for Metrodin®. These differences are not clinically significant.

There were no relevant differences between Org 32489 and Metrodin® with respect to safety.

Study 37611:

Title of the study:

A randomized, assessor-blind, group comparative multi center safety and efficacy study of Org 32489 in infertile women treated by in vitro fertilization with Org 32489 or Metrodin®, both after pituitary suppression with Decapeptyl®.

Study Period:

August, 1992 through July, 1994.

Clinical phase:

Phase III

Objectives:

To assess the safety and efficacy of Org 32489 in relation to Metrodin® for induction of controlled ovarian superovulation in infertile pituitary-suppressed women treated by IVF.

Methodology:

A randomized, assessor-blind, group comparative, multi center study.

Number of subjects (total and for each treatment):

99 subjects (Org 32489: 60; Metrodin®:39).

Diagnosis and criteria for inclusion:

Infertile women (aged 18-39 years) in good physical and mental health, having a menstrual cycle between 24 and 35 days and an intra-individual variation of plus or minus three days (but never outside the 24-35 day range); cause of infertility potentially solvable by in vitro fertilization; maximum of three previous IVF, GIFT, or ZIFT attempts, in which oocytes were collected at least once; and willing to give informed consent to participate.

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

Org 32489 (CP 091077, 092146, and 091134). Subjects were treated with 150 IU or 225 IU intramuscularly for the first four days, after which the dose was adjusted individually. When at least 3 follicles ≥ 17 mm were observed on ultrasound, ovulation was induced by an injection of hCG.

Duration of treatment:

One treatment cycle

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

Metrodin® (CP 092047, 092139, 093057, and 093107). Subjects were treated with 150 IU or 225 IU intramuscularly for the first four days, after which the dose was adjusted individually.

Criteria for evaluation:

For efficacy analysis the following variables were evaluated statistically:

Main parameter: Total number of oocytes recovered.

Secondary parameters: The total number of FSH ampules and the duration of the FSH treatment; number and size of follicles on the day of the hCG injection; number of mature oocytes collected; quality of embryos; and on going pregnancy rate per attempt and per transfer.

Safety analysis was performed by evaluating the number and nature of adverse experiences and by evaluating vital signs, hematology, blood biochemistry, urinalysis, serum anti-FSH antibodies, and serum anti-CHO cell-derived protein antibodies.

Summary Results:

A total of 99 subjects (Org 32489: 60; Metrodin®: 39) were randomized; 94 (Org 32489: 58; Metrodin®: 36) started Decapeptyl® pre-treatment and 90 (Org 32489: 57; Metrodin® 33) started FSH treatment. Ten subjects (Org 32489; 8; Metrodin®: 2) started FSH treatment but did not have an embryo transfer.

The most frequently reported reason for cycle cancellations for the Org 32489 Group was "failed fertilization" (n=4). In the Metrodin® Group, the only reason given was "low responder" (n=2).

On the day of the hCG injection, median serum LH (unadjusted for center) was 1.5 IU/L and 1.6 IU/L in the Org 32489 and the Metrodin® Groups, respectively; for serum E_2 this was 2057 pg/ml and 1502 pg/ml, and for serum progesterone this was 1.4 nmol/L and 0.9 nmol/L.

Evaluation of parameters revealed:

Main Parameter

	Mean adjusted for center		**Org 32489 minus Metrodin**		
Parameter	Org 32489	Metrodin	Estimate of difference	95% confidence interval	Test for interaction

Total no. of oocytes recovered (based on 86 subjects)	9.7	8.9	0.8	-1.7 to 3.2 (p=0.53) ($p_{wilcoxon}$ =0.46)	p=0.16

Secondary parameters

Parameters measured	**Mean adjusted for center**		**Org 32489 minus Metrodin®**		
	Org 32489	Metro-din ®	Estimate of difference	95% confidence interval	Test for interaction
Total number of ampules used	30.2	29.6	0.6	-3.2 to 4.4 (p=0.75) (pwilcoxon =0.83)	p=0.31
Treatment length (days)	10.2	10.3	-0.1	-0.8 to 0.7 (p=0.88) (pwilcoxon=0.88)	p=0.22
Number of follicles ≥ 17 mm	5.4	5.5	-0.1	-1.2 to 0.9 (p=0.84) (pwilcoxon=0.83)	p=0.44
Number of follicles ≥ 15 mm	7.3	7.2	0.2	-1.2 to 1.5 (p=0.83) (pwilcoxon=0.96)	p=0.27

Secondary Parameters(continued)

Parameters measured	Mean adjusted for center		Org 32489 minus Metrodin®		
	Org 32489	Metrodin®	Estimate of difference	95% confidence interval	Test for inter-action
No. Of mature oocyte recovered	8.1	6.9	1.2	-1.1 to 3.4 (p=0.31)(pwilcoxon= 0.27)	p=0.34
Sum of no. Of Type 1 and 2 embryos	3.7	4.0	-0.3	-1.7 to 1.1 (p=0.69)(pwilcoxon= 0.54)	p=0.68
Ongoing pregnancy rate/attempt (%)	30.2	17.4	12.8	-6.4% to 31.9% (p=0.19)	p=0.83
Ongoing pregnancy rate/transfer (%)	34.0	18.8	15.2	-5.5% to 35.9% (p=0.15)	p=0.72
Clinical pregnancy rate/attempt (%)	35.4	26.6	8.8	-12.1% to 29.6% (p=0.41)	p=0.92
Clinical pregnancy rate/transfer (%)	40.8	28.6	12.3	-10.3% to 34.8% (p=0.29)	p=0.81

Eight subjects in the Org 32489 Group and nine in the Metrodin® Group had a first frozen embryo cycle with two ongoing pregnancies (one in the Org 32489 Group and one in the Metrodin® Group) reported. Only one Metrodin® treated subject had a second frozen embryo cycle and became pregnant.

There were no maternal deaths in this study. Three subjects in the Org 32489 Group (5.3%) and one in the Metrodin® Group (3.0%) had a SAE. The Org 32489 subjects had ovarian hyper stimulation syndrome and the Metrodin® subject had abdominal pain which occurred after the subject completed the study. Only one subject (079) was discontinued from this study due to an AE. This subject discontinued, prior to FSH treatment, due to an allergic response to Decapeptyl®. A total of 13 subjects experienced at least one adverse experience (including subjects who had SAEs): 9 in the Org 32489 Group (15.8%) and 4 in the Metrodin® Group (12.1%). In addition, there were seven subjects with miscarriages either with or without proof but these events were not classified as AEs by the investigator. The Organon Inc. Medical Monitor considers these

events additional AEs. The body system with the largest number of AEs was Reproductive disorders, female. The most frequently reported AE within this body system was ovarian hyper stimulation syndrome.

In none of the subjects were serum anti-FSH antibodies or anti-CHO cell-derived protein antibodies detectable. The Org 32489 Group and the Metrodin® Group were similar with respect to the incidence of markedly abnormal laboratory values. Significant differences in trends between the Org 32489 Group and the Metrodin® Group were found for urea. No significant differences in notable downward and upward shifts or in vital signs between the Org 32489 Group and the Metrodin® Group were found. Five subjects in the Org 32489 Group had a relatively large increase in body weight.

Conclusions

There was no significant difference between Org 32489 and Metrodin® in the outcome of controlled ovarian hyper stimulation in infertile, pituitary-suppressed women who were undergoing IVF-ET, as assessed by the number of oocytes retrieved.

There were no apparent clinically relevant differences in the safety profile between Org 32489 and Metrodin® subjects in this study.

Study 37609:

Title of the study:

A randomized, assessor-blind, group-comparative, multi center safety and efficacy study of Org 32489 and Metrodin® in women with chronic anovulation (WHO Group II).

Study period:

June, 1992 through March, 1994

Clinical Phase:

Phase III

Objectives:

To compare the safety and efficacy of Org 32489 and Metrodin® for induction of ovulation in the subjects with chronic anovulation (WHO Group II) who failed to ovulate and/or conceive during clomiphene citrate treatment.

Methodology:

A randomized, assessor-blind, group comparative multi center study. The blind assessor adjusted the FSH dosage.

Number of subjects (total and for each treatment):

178 randomized (Org 32489: 109; Metrodin®: 69).

Diagnosis and criteria for inclusion:

- Infertile women (aged 18-40 years, body mass index between 19 and 32 kg/m^2) in good physical and mental health but with chronic anovulation;
- Positive progesterone withdrawal bleeding or spontaneous menstrual bleeding;
- Clomiphene citrate resistance;
- Normal serum concentrations of FSH, prolactin, and thyroid stimulating hormone for the early follicular phase;
- Serum concentrations of testosterone, androstenedione, dehydroepiandrosterone sulfate, and 17-hydroxoyprogesterone below 7, 20, 25, and 20 nmol/L, respectively;
- Normal uterine cavity and patency of at least one fallopian tube in subjects who ovulated but failed to conceive with clomiphene citrate; and
- Willing to give informed consent to participate.

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

Org 32489 (CP no. 091077, 091134, and 092146). Subjects were treated intramuscularly according to the following treatment scheme:

	IU FSH/day during	
Treatment day	**Treatment Cycle 1**	**Treatment Cycles 2 and 3**
1-7	75	75
8-14	75	112.5
15-21	112.5	150
22-28	150	187.5
29-35	187.5	225
36-42	225	225

Within a cycle, upward adjustments in dose were determined by ovarian response and the number of days of treatment. When one follicle reached ≥ 18 mm or two or more follicles

reached ≥ 15 mm, hCG 10,000 I.U. was given.

Duration of treatment:

Three treatment cycles at most.

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

Metrodin® (CP no. 091163, 092047, 092139, 093057, 093107, and 093177). Subjects were treated intramuscularly according to the treatment scheme above.

Criteria for evaluation:

For efficacy analysis, the following variables were evaluated:

Primary efficacy variables:

- Number of cycles before ovulation is achieved; and
- Overall cumulative ovulation rate after three cycles.

Secondary efficacy variables:

- number of cycles before pregnancy is achieved;
- overall cumulative pregnancy rate after three cycles; and
- per cycle, the duration of follicular phase before ovulation is achieved, defined as the duration of FSH treatment in the corresponding cycle.

In addition, the reasons for cycle cancellation, the number and size of follicles, and serum E_2, LH, FSH, and P were considered.

Summary Results:

A total of 178 subjects (Org 32489: 109; Metrodin®: 69) were randomized. One hundred seventy-two subjects (Org 32489: 105; Metrodin®: 69) were treated in the first treatment cycle, 111 (Org 32489: 69; Metrodin®: 42) subjects in the second, and 78 subjects (Org 32489: 49; Metrodin®: 29) in the third treatment cycle.

Primary efficacy parameters

The Org 32489 and the Metrodin® Groups did not differ statistically significantly with respect to the number of cycles before ovulation was achieved for both the Intent-to-Treat and the Per Protocol Groups. Also for both groups, no significant interactions between treatment and center were found.

	Org 32489 versus Metrodin®			
	Log rank test for treatment effect	Hazard ratio estimate	95% Confidence interval	Test for inter-action
Time to ovulation, ITT	p=0.41	1.1	0.8 to 1.5	P=0.92
Time to ovulation, PP	p=0.88	1.0	0.7 to 1.4	p=1.00

The cumulative ovulation rate after three cycles is presented below. None of the differences were statistically significant. The reported rates were calculated by the Kaplan-Meier procedure.

	Org 32489	Metrodin®	Org 32489 minus Metrodin®		
Cumulative ovulation rate after 3 cycles (unadjusted for center)			Estimate of difference	Standard error	95% confidence interval (p-value)
Intent-to-Treat	0.95	0.96	-0.01	0.05	-0.10 to 0.08 (p=0.89)
Per protocol	0.98	1.00	-0.02	0.02	-0.06 to 0.02 (p=0.30)

Crude cumulative rates in labeling would be easier to interpret by physicians and patients.

Secondary efficacy parameters

Thirty-seven subjects (24/13) became pregnant in the study [34 singletons (Org 32489: 22; Metrodin®: 12), 2 twins (Org 32489: 1; Metrodin®: 1), and 1 triplets (Org 32489: 1)]. All pregnancies were confirmed after at least 12 weeks after the hCG injection.

The two treatment groups did not differ statistically significantly with respect to the number of cycles before pregnancy was achieved in both analyses as expressed by the log rank test (adjusted for center): p=0.37 for Intent-to-Test and p=0.64 for Per Protocol.

The cumulative pregnancy rates after 3 cycles (unadjusted for center) were in the Intent-to-Treat Group 0.27 for Org 32489 and 0.24 for Metrodin®, and in the Per Protocol Group 0.23 and 0.26, respectively. None of the differences were statistically significantly different.

The median number of ampules used and the median duration of FSH treatment for subjects with ovulation in the Metrodin® Group were higher than those in the Org 32489 Group for the first two cycles and were consistent across the center.

	Org 32489			Metrodin®		
	Cycle 1 n=76	Cycle 2 n=45	Cycle 3 n=34	Cycle 1 n=42	Cycle 2 n=30	Cycle 3 n=20
Median number of ampules	10.0	11.0	10.5	13.8	19 0	10.5
Median duration of FSH treatment (days)	10 0	10 0	10.5	13 0	17 0	10.0

The mean number of follicles with diameters of at least 12 mm and of at least 15 mm on the day of hCG were higher in the Org 32489 Group than in the Metrodin® Group.

The median serum estradiol concentrations for subjects in the Org 32489 Group was consistently higher than that in the Metrodin® Group in all three cycles. The reverse, but to lower extent, was the case for the median FSH concentration.

Adverse experiences were reported in 54 subjects: 31 (29.5%) in the Org 32489 Group and 23 (34.3%) in the Metrodin® Group. The events included OHSS, ectopic pregnancy, miscarriage, ovarian cyst, vaginal hemorrhage, abdominal pain, and discomfort. For 12 of these subjects (seven on Org 32489, five on Metrodin®) the AEs were also serious. There were 11 subjects [Org 32489: 8(7.6%); Metrodin®: 3(4.5%)] with OHSS and one of these events in the Org 32489 Group was reported as an serious adverse experience. In each treatment Group, the investigator considered about 18 percent of adverse experiences as related to study drug. Serum anti-FSH antibodies were not detected in any of the subjects.

The Org 32489 Group and the Metrodin® Group were similar with respect to the incidence of markedly abnormal laboratory values. Significant differences in trends ($p \leq 0.05$) between the two groups during the treatment phase were found for chloride (Cycles 2 and 3), glucose (Cycle 1), inorganic phosphorus (Cycle 1), alk. phosphatase (Cycle 1 and 3), bilirubin (Cycle 2), leukocytes (Cycle 3), and eosinophils (Cycle 2). No statistically significant differences ($P \leq 0.05$) were found between the two treatment groups with respect to notable downward or upward shifts for minimum or maximum post-baseline value. Increase in weight of at least 7% was found in 13 subjects on Org 32489 and in six Subjects on Metrodin®. No significant differences ($p \leq 0.05$) were found between the two treatment groups with respect to vital signs.

Conclusions

There were no statistically significant differences in efficacy between Metrodin® and Org 32489 for induction of ovulation in subjects with chronic anovulation (WHO Group II) who failed to ovulate and /or conceive during clomiphene citrate treatment. This was assessed by the number of cycles before ovulation was achieved and cumulative ovulation rate after three cycles.

There were no apparent clinically relevant differences between Metrodin® and Org 32489 with respect to the incidence of adverse experiences, serious adverse experiences. or shifts/trends in vital signs and laboratory variables.

X. Resume and Evaluation:

Follicle-stimulating hormone (FSH) is a gonadotropin hormone produced by the anterior pituitary gland. The active ingredient of Org 32489 is a recombinant human FSH.

The efficacy and safety of Org 32489 in the treatment of female infertility by ART and in classical ovulation induction was evaluated in 17 studies in Europe, Middle East Asia, and Japan. Five of these studies were adequate and well controlled and three of these were pivotal studies. Org 32489 was shown to be efficacious when administered intramuscularly or subcutaneously and to be at least equivalent to currently available urinary FSH preparations. It is pharmacodynamically equivalent to commercially marketed urinary gonadotropin preparations in this country (Pergonal and Humegon™) and a urinary FSH preparation (Metrodin®) regarding biological activity of the FSH component.

Study 37613 was the only clinical study where Org 32489 was administered subcutaneously as well as intramuscularly. No clinically relevant differences in the overall occurrence of local tolerance symptoms between I.M. and S.C. administration of Org 32489 were observed and no clinically relevant differences in efficacy between I.M. and S.C. administration of Org 32489 were observed.

Three adequate and well controlled clinical studies support the approval of an indication for the development of multiple follicles in ovulatory patients participating in an ART program.

Study 37604 is the pivotal study supporting development of multiple follicles in ovulatory patients whose pituitary function is not suppressed by a GnRH agonist prior to administration of Org 32489.

Studies 37608 and 37611 support development of multiple follicles in ovulatory patients whose pituitary function is suppressed by a GnRH agonist prior to administration of Org 32489. Study 37608 is the pivotal study for this mode of administration because it consisted of 615 subjects being treated with Org 32489 and 412 subjects being treated

with Metrodin® while study 37611 consisted of only 60 subjects being treated with Org 32489 and 39 subjects being treated with Metrodin®.

There were no significant differences in efficacy or safety in the one study (37604) comparing Org 32489 with Humegon™.

Studies 37608 and 37611 revealed that Org 32489 was as safe as Metrodin® and no less effective than Metrodin®.

There was one study (37609) which was designed specifically to support an indication for induction of ovulation in subjects with chronic anovulation (WHO Group II) who failed to ovulate and/or conceive during clomiphene citrate treatment. No differences in efficacy or safety between Org 32489 and Metrodin® were found.

Based on the mechanism of action of FSH (induction of ovarian follicular development and maturation), efficacy data from subjects participating in an ART program (studies 37604, 37608, and 37611) were also used as support for the efficacy claim for the use of Org 32489 for the induction of ovulation in the infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

In general, few adverse events were associated with the use of Org 32489. The most prevalent adverse experiences observed during the clinical trials were principally associated with the pharmacological effects of gonadotropins and are among the historically recognized side effects of gonadotropins.

The most serious complication is ovarian hyperstimulation syndrome (OHSS). OHSS occurs when there is excessive stimulation of ovarian follicles with resultant enlargement of the ovaries and may, in rare cases, progress to the development of ascites, hypotension, and shock. The incidence rates of OHSS observed during the clinical development of Org 32489 were similar for Org 32489-treated women and women treated with the urinary FSH preparation (5.2%, 53/1029 for Org 32489 vs. 4.0%, 20/498 for Metrodin®). Approximately one-half of the cases in each group were considered serious.

The following medical events were reported subsequent to pregnancies resulting from FSH treatment:

- Ectopic Pregnancy - Ectopic pregnancies occur with a slightly higher incidence following gonadotropin treatment compared to naturally established pregnancies, but this could be related to the type of population studied (i.e., female infertility, most frequently of tubal cause). The incidence of ectopic pregnancy in the Org 32489 Group was similar to that observed in women treated with Metrodin® (2.2%, 23/1029 and 3.4%, 17/498, respectively).

- Miscarriage - The observed percentage of miscarriages in the Org 32489 Group

(8.3%, 85/1029) was similar to that observed in women treated with Metrodin® (11.0%, 55/498), and does not exceed the known figures in naturally established pregnancies.

- Multiple Gestations - Multiple pregnancies occur with a higher frequency following gonadotropin treatment compared to naturally established pregnancies. Of the pregnancies achieved by Org 32489 treatment followed by IVF-ET, 31% (84/272) were multiple pregnancies. Eight percent (2/24) of the pregnancies conceived in Org 32489-treated subjects in Study 37609 for classical ovulation induction were multiple pregnancies. These rates are comparable to those observe in subjects receiving Metrodin® in the assisted reproductive program (38%, 47/124) and for classical ovulation induction (8%, 1/13).

The only other adverse experiences that occurred with an incidence that was greater than 1% were abdominal pain and vaginal hemorrhage. The incidence of abdominal pain was similar between Org 32489-treated women and women treated with Metrodin® (1.9%, 20/1029, and 2.4%, 12/498, respectively) as was the incidence of vaginal hemorrhage (1.1%, 11/1029 and 1.0%, 5/498, respectively).

Because recombinant FSH is not of human origin, it was considered to have a potential for antibody formation. Org 32489 treatment, even for multiple cycles, did not result in the production of anti-FSH antibodies. Further, anti-CHO cell derived proteins, which might be present in extremely low amounts in Org 32489, also did not result in the production of antibodies in any subject in the entire clinical program.

The production of Org 32489 using genetically engineered mammalian cells has several significant advantages over the currently marketed urine derived FSH preparations which are obtained by urine collection. These include:

- No need to depend on the collection of urine from women in order to produce the drug.
- Greatly improved purity (≥99%) with negligible contaminating proteins.
- Improved batch to batch consistency.
- Subcutaneous administration allowing for trained self administration or trained partner administration.
- Complete absence of LH activity.

XI. Labeling Evaluation:

The draft labeling is satisfactory. However, it is suggested that the sponsor revise the values listed in the labeling for study 37604 (page 35) to reflect the true intent-to-treat group as shown in Table 5b of Kate Meaker's Statistical Review. It is also suggested that the sponsor revise the values listed in the labeling for study 37608 (page 33) to use the

unadjusted means as shown in tables 5,6 and 8 of Joy Mele's Statistical Review and revise the rates listed in the labeling for study 37609 (page 36) to show crude rates as shown in tables 16 and 17 of Joy Mele's Statistical Review instead of Kaplan-Meir estimates so that they are more easily interpretable by physicians and patients.

XII. Conclusion:

Overall, the benefit of Org 32489 in the treatment of infertility in women outweigh the associated risks.

XIII. Recommendation:

It is recommended that this new drug application be approved for development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and for induction of ovulation in the anovulatory infertility patent in whom the cause of infertility is functional and is not due to primary ovarian failure.

Ridgely C. Bennett

Ridgely C. Bennett, M.D., M.P.H.
December 13, 1996

Agree that application is approvable.
H Fuhrman MD 3/18/97

August 26, 1997
Organon, Inc.

SEP 11 1997

NDA 20-582
Follistim

Medical Officer's Review of Safety Update Dated 5/14/97

Submission dated May 14, 1997 includes a Safety Update which covers the period through October 31, 1996.

No studies have been performed in the United States. There are only post-approval marketing studies underway in Europe and local trials in Asia. Nine studies are currently being conducted in Europe, the Middle East, and Japan. These studies were initiated between the period of the cutoff date for the 120-Day Safety Update (April 30, 1996) and the cutoff date for this report. None of the studies were conducted under an IND.

The daily dose of Follistim in study 38602 ranged from 75 IU per day to 600 IU per day. Drug exposure ranged from 7 days to 18 days. In study E-1631, the only completed subject received Follistim at a dose of 400 IU per day for 10 days.

The six serious adverse events were two subjects with ovarian hyperstimulation syndrome, two subjects with ectopic pregnancies, one subject with pelvic inflammation, and one subject with fever. Five of the subjects recovered. One subject who had not completed the study was still experiencing ovarian hyperstimulation syndrome at the cutoff date for this report. No subject in these two studies discontinued for an adverse event.

A total of 12 subjects (17.6%) had at least one adverse event during the period of treatment with Follistim alone. No individual adverse experience occurred with an incidence greater than 5%. The most frequently reported adverse events were injection site pain, reported by three subjects (4.4%) and headache, reported by two subjects (2.9%). The adverse experience profile is unchanged from that reported in the Integrated Summary of Safety Information.

Clinical laboratory parameters (hematology, biochemistry, urinalysis) were in agreement with those from the Integrated Summary of Safety Information.

Follistim has been launched in eight countries since June, 1996. No spontaneous postmarketing adverse drug events have been reported to the sponsor.

No new published literature exists reporting any adverse events not previously reported.

No long-term adverse effects have been reported from any source.

There is no evidence reported of any withdrawal effects after Follistim treatment.

There are no relevant adverse experience reports from any other sources.

Conclusion: The Safety Update dated May 14, 1997 confirms the safety profile reported in the original NDA submission. It did not change during this updating period.

Ridgely C. Bennett

Ridgely C. Bennett, M.D., M.P.H.

M Jolson 9/11/97