CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

Date:

NDA #: 20-582

Applicant: Organon Inc.

Name of Drug: ORG 32489 (follitropin beta for injection)

Indication: The development of multiple follicles in ovulatory patients participating in assisted reproductive technology programs and 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.

Documents Reviewed: Volumes 1.1,1.35, 1.44-1.53, 1.60, 1.67-1.70 and 1.80

Statistical Reviewer: Joy D. Mele, M.S. (HFD-715)

Medical Input: Ridgely Bennett, M.D. (HFD-580)

Introduction

The applicant has submitted the results for 4 clinical trials (Table 1) to support two indications; development of multiple follicles (ovarian hyperstimulation) for patients participating in assisted reproduction programs and induction of ovulation in anovulatory infertile patients. Studies 37604 and 37611 are reviewed in a separate document by Kate Meaker (statistical reviewer for FDA's Division of Biometrics II, HFD-715). Studies 37608 and 37609 are reviewed here. In addition, Study 37613 (an open-label study to compare intramuscular (IM) dosing to subcutaneous (SC) dosing) is briefly summarized and reviewed.

Table 1. Summary of Randomized, Controlled, Assessor-blinded Comparative Studies

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms (# Randomized)	Indication	Duration of Treatment
37604 (3/92 to 12/94)	1 (Netherlands)	Follitropin (n=66) Humegon (n=43)	Ovarian hyperstimulation and induction of ovulation	1 cycle
37608 (3/92 to 1/95)	18 (11 European Countnes)	Follitropin (n=615) Metrodin (n=412)	Ovarian hyperstimulation and induction of ovulation	3 cycles
37609 (6/92 to 1/95)	12 (9 European Countries)	Follitropin (n = 109) Metrodin (n = 69)	Induction of ovulation in anovulatory infertile patients	3 cycles
37611 (8/92 to 1/95)	6 (France)	Follitropin (n=60) Metrodin (n=39)	Ovarian hyperstimulation and induction of ovulation	1 cycle

Study 37608

Study 37608 is a multicenter randomized clinical trial designed to compare the safety and efficacy of ORG 32489 (recombinant FSH) to Metrodin (urinary FSH) for the induction of controlled ovarian hyperstimulation in infertile pituitary-suppressed (via buserelin) women undergoing in vitro fertilization (IVF) and embryo transfer (ET).

The preparer and administrator of FSH treatment was unblinded because ORG 32489 was packaged in vials while Metrodin was packaged in ampules. Patients, however, were monitored by blinded assessors who were responsible for adjusting the FSH doses.

The treatment schedule is outlined below in Table 2.

Table 2. Study 37608 Treatment Schedule

Treatment Period	Treatment
Day 1- until E_2 < 50 pg/ml (Max of 5 weeks)	Buserelin (pituitary agonist)
Minimum of 4 Days	FSH treatment with ORG 32489 (150 or 225 IU) or Metrodin im
Physician discretion	Individualized dosing of FSH
When at least 3 follicles≥17 mm	hCG (10,000 IU)
For at least 2 weeks after HCG	Luteal phase support by 3 injections of hCG or progesterone[1]
	Oocyte retrieval
	Embryo transfer

Patients could be treated for a maximum of 3 cycles but efficacy was based on only the results of the first cycle as specified in the protocol. Following the first cycle, treatment was unblinded and buserelin dosing, immunoglobulins and progesterone` assessments were optional.

[1]The treatment for luteal support is determined by each center.

The variables listed in Table 3 are the protocol-specified primary and secondary variables. Other variables were examined by the applicant but are not reviewed here after consultation with the medical reviewer.

Table 3. Study 37608 Efficacy Variables

Primary
# of oocytes collected in first cycle
ongoing pregnancy rate by USS[1] per 1st attempt
ongoing pregnancy rate by USS per 1st transfer
Secondary
# of FSH vial/ampules
and size of follicles on day of hCG
of mature oocytes
max level of E2 before hCG injection
fertilization rate
quality of embryos
cumulative ongoing pregnancy rate

This trial was powered on **clinically relevant differences** on the primary efficacy variables defined in the protocol as the following:

1. a difference of 1.2 oocytes for # of oocytes collected,
2. a difference of 6% in pregnancy rates per attempt and
3. a difference of 7% in pregnancy rates per transfer.

Patient Disposition

A total of 1027 patients were randomized to treatment (615 to ORG 32489 and 412 to Metrodin, 2:1 randomization) at 18 European centers. About 1/3 of the patients were randomized to 3 centers (Brussels, Oslo and Trondheim) with about 60-80 patients in each treatment group of each center; the remainder of centers averaged less than 20 patients in each treatment group.

Patient disposition by treatment phase and treatment group is shown in Table 4 below. The treatment groups were comparable with regard to discontinuation rates and also with regard to reasons for dropout. Patients administered at least one FSH dose comprised the intent-to-treat sample (585 ORG 32489 and 396 Metrodin) on which the analyses are based.

Table 4. Study 37608 Patient Disposition

	ORG 32489	Metrodin
Randomized	615 (100%)	412 (100%)
Buserelin-treated	603 (98%)	406 (99%)
FSH-treated (ITT sample)	585 (95%)	396 (96%)
hCG-treated	550 (89%)	367 (89%)
Oocytes retrieved	546 (89%)	361 (88%)
Incubation done	545 (89%)	361 (88%)
Embryo(s) transported	500 (81%)	329 (80%)

[1]USS = ultrasound scan

A total of 18 patients dropped out after randomization and before buserelin treatment; 8 patients were found to be pregnant (6 ORG and 2 Metrodin). Another 28 patients (18 ORG and 10 Metrodin) dropped out before FSH treatment; the primary reason for dropout in both groups was lack of adequate suppression.

Most of the dropouts in this study occurred following FSH treatment and following/during the incubation phase. The primary reason for discontinuation following FSH treatment was "low responder"[1] (about 4% of the ORG 32489 patients and about 6% of the Metrodin patients). The primary reason for discontinuation during the incubation phase was "failed fertilization"[2] (about 5% of the ORG 32489 patients and about 4% of the Metrodin patients).

Demographics

Treatment groups were comparable with regard to demographic, menstrual cycle and infertility characteristics. The mean age of the patients was 32 years old. About 60% of the patients were between 30 and 40 years (39 was the maximum allowed according to the protocol, however, two 40 year old ORG-treated patients were included in the study at Center Cardiff). Patients had normal menstrual cycles as dictated by the protocol.

Fifty-six percent of the patients had secondary infertility. The major cause of infertility for patients with secondary infertility was tubal abnormalities (about 80% of the patients). For patients with primary infertility, about half the patients had tubal abnormalities, another 13% were diagnosed with endometriosis and about 30% had unknown causes of infertility.

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[1] Reasons for a low response included too few or too small follicles or low E_2.

[2] Reasons for failed fertilization included no oocytes fertilized.

Efficacy Results for Primary Efficacy Variables

Oocyte Recovery

Significantly more oocytes were recovered in patients treated with ORG 32489 than Metrodin (see Table 5 below, $p<.0001$, ANOVA). The applicant only reported values for patients who had undergone a puncture; those values along with the ITT results are presented here. For the ITT sample, patients without a puncture are assigned a value of zero for # of oocytes recovered. The protocol specified that a difference of 1.2 oocytes is clinically important; so these results suggest that the treatment difference is both statistically and clinically significant (based on the applicant's criterion for clinical significance).

About 6% of the patients in each treatment group had no oocytes recovered (i.e. no puncture done).

Table 5. Number of Oocytes Recovered
Study 37608

	ORG 32489	Metrodin	Difference (95% CI)[1]
ITT Sample	(N=585)	(N=396)	
Mean # oocytes (SD)	10.9 (7.2)	9.0 (5.9)	1.9 (1.0, 2.8)
% of pts w/ no oocytes recovered	6.5%	6.0%	
% of pts w/ <3 oocytes recovered	9.1%	12.4%	
Patients with puncture	(N=546)	(N=361)	
Mean # oocytes (SD)	11.6 (6.8)	9.9 (5.5)	1.7 (0.9, 2.5)
% of pts w/ <3 oocytes recovered	2.6%	3.9%	

The treatment groups also differed significantly in the number of mature oocytes recovered (Table 6, $p<.0001$, ANOVA). For patients with a puncture, a very small percentage had no mature oocytes recovered (2-3%); for more than half of these patients (56% ORG-treated and 54% Metrodin-treated), 100% of the recovered oocytes were mature oocytes.

Table 6. Number of Mature Oocytes Recovered
Study 37608

	ORG 32489	Metrodin	Difference (95% CI)
ITT Sample	(N=583)[2]	(N=396)	
Mean # oocytes (SD)	9.1 (6.6)	7.3 (5.8)	1.8 (1.0, 2.6)
% of pts w/ no mature oocytes	8.4%	11.9%	
Patients with puncture	(N=546)	(N=361)	
Mean # oocytes (SD)	9.8 (6.4)	8.0 (5.6)	1.8 (1.0, 2.6)
% of pts w/ no mature oocytes	1.8%	3.3%	

[1] Positive values favor ORG 32489.

[2] For 2 patients, oocytes were not classified. Including these 2 patients with values of 0 did not change the results.

Pregnancy Rates

The pregnancy rate which is named as a primary efficacy variable (and also quoted in the labeling) is the ongoing pregnancy rate. An ongoing pregnancy is defined as a pregnancy confirmed at 12 to 16 weeks of gestation by ultrasound. The pregnancy rates for ITT patients (per attempt rate) and for all patients with 1 or more embryos transferred (per transfer rate) were not significantly different between the 2 treatment groups. The ORG 32489 rates were about 4% higher than the Metrodin rates (95% CI of -1% to 9%) and the ORG treated patients had about a 20-30% higher chance of having a pregnancy than the Metrodin patients (note that the increase was not statistically significant).

Table 7. Pregnancy Rates
Study 37608

	ORG 32489	Metrodin	Relative Risk[1]	95% CI
Per Attempt (ITT)	129/585 (22%)	72/396 (18%)	1.3	0.9, 1.8
Per Transfer	129/500 (26%)	72/329 (22%)	1.2	0.9, 1.7
Per Transfer By # Transferred				
1 Embryo	2/32 (6%)	4/41 (10%)	1.6	0.3, 9.5
2 Embryos	66/218 (30%)	36/139 (26%)	1.2	0.8, 2.0
3 Embryos	30/150 (20%)	55/223 (25%)	1.3	0.8, 2.2
4-5 Embryos	4/18 (22%)	4/8 (50%)	0.3	0.1, 1.7

Adjustments for age or infertility type did not change notably the relative risk estimates presented here.

[1] Values greater than 1 favor ORG 32489.

Efficacy Results for Secondary Efficacy Variables

The 3 bolded variables listed in Table 8 are considered to be the most important secondary efficacy variables (all 3 are included in the applicant's proposed labeling). Only these 3 variables were reanalyzed by this reviewer and the results presented here are those of the reviewer. The results for the remaining variables are the applicant's results extracted from the NDA.

The first 2 variables, total number of FSH vials/ampules used on treatment and the total number of days on treatment, essentially measure the same thing and the results for both favor ORG 32489 over Metrodin statistically. The clinical relevance of a less than one day difference (4 vials) needs to be addressed by the medical reviewer. The average number of vials/ampules used per day ranged from 1 to 5 (75 to 375 IU) with about 80% of the patients averaging 3 or fewer vials per day.

Table 8. Study 37608 Results for Secondary Efficacy Variables

	ORG 32489	Metrodin	Treatment Difference (95% CI)	P-value
# of FSH vial/ampules	29.7 (12.0)	33.5 (13.6)	-3.8 (-5.3, -2.3)	.0001
Length of FSH treatment (days)	11.0 (2.5)	11.6 (2.9)	-0.6 (-0.9, -0.3)	.001
Max level of E2 before hCG injection	6637 (4208) Med = 5900	5692 (3699) Med = 4800		.0002
# of follicles by size[1] ≥15 mm ≥17 mm	 7.5 4.6	 6.7 4.4	 0.8 (0.4, 1.2) 0.2 (0, 0.5)	 <.05 .09
Median Fertilization rate[2]	64.7%	62.5%	not given	not given
Quality of embryos (# of Type 1 and 2)	3.1	2.6	0.5 (0.2, 0.8)	<.05
Cumulative ongoing pregnancy rate after 3 cycles[3] Kaplan-Meier Crude rate	 57% 35%	 51% 33%	 not given	 not given

[1] The protocol specified that the measurement was to be done on the day of hCG injection. About 70% of the patients in each group had their ultrasound on the day of hCG; another 20% on the following day and the remainder, 2 or more days later. The applicant showed that the number of large follicles drops with time from injection (mean of about 8 on day of injection or the next day; mean of about 4, 3 or more days after injection).

[2]For subjects with sperm/oocyte incubation; about 91% of the ITT sample.

[3] These are per attempt rates using all 3 cycles. Cycles 2 and 3 were open-label/unblinded and buserelin dosing was optional.

Reviewer's Comments on Study 37608

ORG 32489 (follitropin) significantly increased oocyte recovery (both total number of oocytes and mature oocytes) compared to Metrodin. The treatment difference of about 2 oocytes was both statistically significant and clinically significant according to protocol specified criterion (a difference of 1.2 oocytes, Tables 5 and 6).

The treatment groups were comparable with regard to pregnancy rates. The per attempt pregnancy rate for ORG 32489 was 22% and the per transfer rate was 26%. These rates were not confounded by number of embryos transferred, age or infertility type.

For two secondary variables (follicle size and length of FSH treatment), a statistically significant treatment by center interaction was observed. This reviewer did not consider the interactions to be important since, upon inspection of the center results, it is clear that the significance is primarily due to differences in magnitude across centers, not due to a reversal of effects. Center-adjusted means are similar to the unadjusted means.

Study 37609

Study 37609 is a multicenter randomized clinical trial designed to compare the safety and efficacy of follitropin compared to Metrodin for the induction of ovulation in patients with chronic anovulation who failed to ovulate and /or conceive during clomiphene citrate treatment.

As for Study 37608, patients were monitored by a blinded assessor but drug was administered unblinded due to the difference in packaging of the treatments.

The treatment schedule is outlined below in Table 9.

Table 9. Study 37609 Treatment Schedule

Treatment Period	Treatment
Day 1-14 (7 for 2nd and 3rd cycle)	(ORG 32489 (75 IU) or Metrodin im
Day 15-42	Increase dose by ½ vial/ampule every 7 days until an ovarian response is seen
When at least 1 follicle diameter≥18 mm or 2-3 follicles≥15 mm	hCG 10,000 IU

The variables listed in Table 10 are the protocol-specified primary and secondary variables. Other variables were examined by the applicant but are not reviewed here after consultation with the medical reviewer.

Table 10. Study 37609 Efficacy Variables

Primary # of cycles before ovulation is achieved overall cumulative ovulation rate at 3 cycles
Secondary # of cycles before ongoing pregnancy overall cumulative pregnancy rate at 3 cycles # of days of FSH administration before ovulation

This trial was powered to detect a **clinically relevant treatment difference** of 16% in incidence of ovulation as defined in the protocol.

Patient Disposition

A total of 178 patients at 12 centers were randomized to follitropin (109) or Metrodin (69) (3:2 randomization). One center (London 2) enrolled 37 patients while the remaining 11 centers randomized about 12 patients each.

Table 11. Study 37609 Patient Disposition

	ORG 32489 N (% of Rand.)	Metrodin N (% of Rand.)
Randomized	109	69
Cycle 1		
Treated (ITT Sample)	105 (96%)	67 (97%)
Pregnant	15 (14%)	7 (10%)
Discontinued	21 (19%)	18 (26%)
Cycle 2		
Treated	69 (63%)	42 (61%)
Pregnant	5 (5%)	5 (7%)
Discontinued	15 (14%)	8 (12%)
Cycle 3		
Treated	49 (45%)	29 (42%)

Six randomized patients were not treated with FSH and are not included in the ITT analyses; 3 of these patients were not treated because the study was stopped for legal reasons, 1 patient became pregnant and the remaining 2 were unwilling to participate.

The treatment groups were comparable with regard to discontinuation rates (Table 11) and reasons for discontinuation (Table 12). Most of the discontinuations were due to stoppage of the study by the company for legal reasons.

Table 12. Study 37609 Reasons for Discontinuation

	ORG 32489	Metrodin
Cycle 1		
Total # discontinued	21	18
Study stopped	13	5
Patient uncooperative	5	10
ADE	2	1
Lack of Efficacy	0	1
Other	1	1
Cycle 2		
Total # discontinued	15	8
Study stopped	8	5
Patient uncooperative	4	1
Lack of Efficacy	0	1
Other	3	1

About ⅓ of the patients in each group had treatment discontinued due to cycle cancellation (slightly more than ⅔ of these patients remained on study for another cycle). The primary reason for cycle cancellation in both treatment groups was hyperovarian response; those results are summarized below in Table 13. In Cycles 2 and 3, about twice as many ORG-treated patients had an hyperovarian response as Metrodin patients. There were 6 ORG-treated patients and 2 Metrodin patients who had an hyperovarian response in more than 1 cycle.

Table 13. Study 37609
Number of Patients Canceling Cycle due to Hyperovarian Response

	ORG 32489 N (% of # on Study)	Metrodin N (% of # on Study)
Cycle 1	12 (11%)	7 (10%)
Cycle 2	11 (16%)	3 (7%)
Cycle 3	8 (16%)	2 (7%)

Demographics

The treatment groups were balanced with regard to age (mean of 29 years, range of 19 to 39), height, weight, BMI, reason for diagnosis of chronic anovulation and duration of infertility (mean of 4 years). The percentage of patients with primary infertility in the Organon group (76%) was significantly larger ($p = .006$) than in the Metrodin group (55%).

Efficacy Results

Ovulation

The 2 primary efficacy measures in this study were number of cycles to ovulation and cumulative ovulation rate based on time to first ovulation. This reviewer also examined other measures of ovulation to further check the comparability of the 2 treatment groups; these are summarized in the following two paragraphs. A patient is counted as ovulating if the patient has at least one progesterone measurement in the luteal phase (after hCG injection and before cycle result) of ≥7 ng/mL or ≥25 nmol/L, or the patient becomes pregnant, has an ectopic pregnancy or has a miscarriage.

From Table 14, it can be seen that the percentage of patients ovulating in each cycle is comparable for the 2 treatment groups. About 20% of the ITT patients ovulated in all 3 cycles in each treatment group.

Table 14. Study 37609 Crude Ovulation Rates on Each Cycle

	ORG 32489	Metrodin
	# Ovulating/ # on Study	# Ovulating/ # on Study
Cycle 1	76/105 (72%)	42/67 (63%)
Cycle 2	45/69 (65%)	30/42 (71%)
Cycle 3	34/49 (69%)	20/29 (69%)

This reviewer found that at least half the patients (in each treatment group) ovulate in a subsequent cycle regardless of whether they ovulate in the first cycle. So it appears that failure to ovulate in the first cycle is not predictive of failure in subsequent cycles. The conditional probability of ovulating for the first time during the third cycle given one has not ovulated in the previous 2 cycles is high for both groups (75% for ORG and 80% for Metrodin). This data clearly suggests that a patient benefits from continued treatment/multiple cycles given either treatment.

The number of cycles to first ovulation is summarized in the table below. The treatment groups are clearly comparable. This can also be seen in Table 16 on the following page.

Table 15. % of Patients by Number of Cycles to Ovulation

# of Cycles to Ovulation	ORG 32489	Metrodin
0	15%	18%
1	72%	63%
2	10%	16%
3	3%	3%

Cumulative ovulation rates computed 3 different ways are presented in Table 16 below. The crude rate is computed by simply using a running sum of the number of patients ovulating for the first time. By the third cycle over 80% of the patients in each group have ovulated at least once. The life table estimates[1] and the Kaplan-Meier (KM) estimates are defined in Appendix 1 of this review. This reviewer prefers the life table estimate over the Kaplan-Meier estimate for several reasons; 1) one cannot assume that censoring is independent of treatment[2] (an assumption of the KM procedure) 2) the life table method assumes censoring uniformly throughout the cycle rather than just at the end of the cycle (see Appendix 1) and 3) times to ovulation are measured by cycle so patients do not have unique times and therefore no information is lost using the life table approach over the KM approach. Regardless of approach, the treatment groups are comparable. Confidence intervals on these estimates suggest no more than about a 10% higher rate for Metrodin over ORG 32489 (regardless of approach) which according to the applicant's definition of a clinically relevant difference (16%) is not of clinical significance. Also, no treatment difference is evident when one looks at the chance of ovulating over all 3 cycles (relative risk of 1.1; 95% confidence interval of 0.8 to 1.5 based on the proportional hazards model).

In the proposed labeling, the applicant presents the KM estimates for both ovulation and pregnancy. This reviewer suggests, instead, that the crude rates be presented in the labeling because they are easily interpretable.

Table 16. Study 37609 Ovulation Rates for Time to First Ovulation

	# on Study Who Have Not Ovulated	# Ovulating for 1st Time	Cumulative Ovulation Rates		
			Crude Rate N (%)	Life Table Estimate	KM-Estimate (Applicant's)
ORG 32489					
Cycle 1	105	76	76 (72%)	77%	72%
Cycle 2	17	10	86 (82%)	91%	89%
Cycle 3	4	3	89 (85%)	98%	95%
Metrodin					
Cycle 1	67	42	42 (63%)	67%	63%
Cycle 2	16	11	53 (79%)	91%	88%
Cycle 3	3	2	55 (82%)	97%	96%

[1]The life table estimate is the Cutler-Ederer estimate as described in Lamb, E.J. and Cruz, A.L.:Data collection and analysis in an infertility practice, Fertil Steril 23:310, 1972.

[2]For example, censoring due to hyperovulation is not independent of treatment.

Pregnancy

As expected from the ovulation data, most of the pregnancies occur in the first cycle (Table 17). Again all three estimates for cumulative pregnancy rate (based on ongoing pregnancies) are presented (see the previous section and Appendix 1 for an explanation of these rates). The treatment groups are comparable: confidence intervals do not suggest more than a 12% higher rate for Metrodin over ORG 32489. This is also supported by the hazard ratio (chance of a pregnancy); 1.2 (95% confidence interval of 0.6 to 2.3).

Table 17. Study 37609 Pregnancy Rates

	# on Study Not Pregnant	# Pregnant	Cumulative Pregnancy Rate		
			Crude Rate N (%)	Life Table Estimate	K-M Estimate (Applicant's)
ORG 32489					
Cycle 1	105	15	15 (14%)	16%	14%
Cycle 2	69	5	20 (19%)	23%	20%
Cycle 3	49	4	24 (23%)	34%	27%
Metrodin					
Cycle 1	67	7	7 (10%)	12%	10%
Cycle 2	42	5	12 (18%)	24%	21%
Cycle 3	29	1	13 (19%)	29%	24%

Length of FSH treatment (days)

The applicant presented the results for number of days of FSH treatment by cycle for patients who ovulated only. For the first 2 cycles, the duration of FSH treatment before ovulation was longer on Metrodin (about 14 days) than on ORG (about 10 days. During the third cycle, the groups were not different (about 10 days for both). Likewise, an higher number of ampules were utilized by Metrodin patients than ORG-treated patients during the first 2 cycles.

Reviewer's Comments on Study 37609

The ovulation and pregnancy rates for ORG 32489 were comparable to the rates for Metrodin (see Tables 16 and 17). By the third cycle, 85% of the ORG-treated patients had ovulated at least once and 23% were pregnant.

Study 37613 (Conducted 8/93 to 9/94)

Study 37613 was an open-label randomized multicenter trial designed to compare the safety and efficacy of two routes of administration of ORG 32489; subcutaneous injections and intramuscular injections.

A total of 218 patients were randomized in a 2:3 ratio to ORG IM (86 patients) and ORG SC (132 patients) at 12 centers. Eighty-nine percent of the randomized patients in each group underwent FSH-treatment (77-IM and 118-SC); 80% of the patients in each group completed the study. The treatment groups were comparable with regard to reasons for discontinuation, demographics, menstrual cycle characteristics and reasons for infertility.

The applicant's efficacy results are summarized below in Table 18. The groups are not statistically significantly different on any of these measures. The largest difference is seen for the number of recovered oocytes (9.8 for IM versus 10.4 for SC). The 95% confidence interval on the difference (IM minus SC) of -2.2 to 1.0 favors SC.

Table 18. Applicant's Efficacy Results for Study 37613

	ORG 32489 IM	ORG 32489 SC	Treatment Diff[1] (95% CI)
# FSH Ampules (mean)	30 (Range 12-62)	28 (Range 9-60)	1.6 (-0.5, 4)
# of FSH treatment days (median)	9.9 (Range 7-14)	9.7 (Range 3-16)	0.2 (-0.2, 0.6)
# of Oocytes Recovered (mean)	9.8	10.4	-0.6 (-2.2, 1.0)
# of Mature Oocytes Recovered (mean)	8.2	8.6	-0.4 (-1.8, 1.0)
Ongoing Pregnancy Rate			
Per attempt	27%	26%	1% (-12%, 14%)
Per transfer	30%	29%	1% (-13%., 15%)

To assess tolerance at the site of injection, the patient rated the degree of bruising, pain, redness, swelling and itching using a 4-point rating scale of none, mild, moderate or severe. The applicant summarized the percentage of patients having a symptom on at least one FSH-treatment day and found no treatment differences for pain, redness, swelling or itching. More bruising was reported by patients undergoing SC injections than IM injections (55% versus 39%, p=.02). The frequency of bruising (i.e. # of days observed bruising) for those patients reporting that symptom was about the same for both groups (2 days).

In conclusion, the efficacy results for Study 37613, show no statistically significant differences between the treatment groups and the confidence intervals do not suggest results that appreciably favor one route of administration over the other[2]. In addition, the tolerance data suggests no appreciable differences between the groups.

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[1] Difference = IM minus SC.

[2] The protocol did not define clinically relevant differences for any parameters. The trial was powered, however, to detect a difference in oocytes recovered of 2.6 oocytes.

Subgroup Analyses

This reviewer examined the primary efficacy results from both studies for subgroups defined by median age and by infertility type. Only the results for total number of oocytes and number of mature oocytes recovered (Study 37608, Table 19) suggest a subgroup difference based on age. These 2 measures are negatively correlated with age; this relationship is seen with both treatment groups. The results for other primary efficacy measures in both studies were generally consistent across subgroups.

Table 19. Study 37608 Mean Oocyte Results by Age Subgroups

	ORG 32489		Metrodin	
	≤32 Mean (SD)	>32 Mean (SD)	≤32 Mean (SD)	>32 Mean (SD)
# of oocytes recovered	12.2 (7.6)	9.4 (6.4)	10.1 (6.7)	7.8 (4.9)
# of mature oocytes	10.5 (7.0)	7.7 (5.9)	8.3 (6.5)	6.3 (4.8)

Reviewer's Overall Comments

1. In both studies, ORG 32489 was found to be comparable to or better than Metrodin on all efficacy measures. No clinically important differences (as defined in the protocols) in favor of Metrodin were observed.

2. The magnitudes of the responses for ORG 32489 were consistent across the 4 studies designed to support an indication for development of multiple follicles (ovarian hyperstimulation) for patients participating in ART programs (Table 20).

Table 20. Efficacy Results for ORG 32489 by Study

	37604	37608	37611	37613 IM/SC
Mean # of Oocytes Recovered				
Total	9.9	10.9	10.4	9.8/10.4
Mature	9.4	9.1	8.6	8.2/8.6
Pregnancy Rates				
Per attempt	22%	22%	30%	27%/26%
Per transfer	31%	26%	35%	30%/29%

3. In Study 37609, a higher percentage of patients in the ORG 32489 group than the Metrodin group had their cycles canceled due to an hyperovarian response (Table 13).

4. The treatment differences were consistent across subgroups defined by age, infertility

type and number of embryos transferred.

5. This reviewer recommends the following labeling revisions;

- For Study 37608 results, use the unadjusted means provided in Tables 5, 6 and 8 of this review. This reviewer thinks that the unadjusted means best reflect what can be expected, on the average, from treatment. Report pregnancy rates rounded to a whole number to be consistent with rates reported elsewhere in the labeling.

- For Study 37609, use the crude rates reported in Tables 16 and 17 of this review instead of the KM estimates. Statistical comparisons should be based on life table estimates in order to account for dropouts but, for labeling, the crude rates are more easily interpretable. The labeling should clearly indicate that the rates are for number of patients ovulating for the first time.

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius 12/12/96

Dr. Kammerman 12/12/96

cc:
Archival NDA 20-582
HFD-580
HFD-580/RBennett, HJolson, LRarick
HFD-580/LPauls
HFD-715/ENevius, LKammerman, JMele, Chron
~~HFD-701/Chron~~
Mele/x3-3520/WordPerfect Windows-follitr.rev/Nov. 27, 1996
This review consists of 17 pages of text plus a 1-page appendix.

Appendix 1. Computation of Kaplan-Meier Estimates and Life Table Estimates

Kaplan-Meier Estimation of Cumulative Event Rates

Time	# at risk (n)	# of events (r)	# censored	(n-r)/n	KM estimate	Cum. Event Rate (1-KM est.)
1	105	76	12	.276	.276	.723
2	17	10	2	.411	.113	.886
3	5	3	2	.40	.045	.955

KM estimate at time (I) = [(n-r)/n at time (I)] TIMES [KM estimate at time (I-1)]
Note that censoring is assumed to occur at the end of the interval.

Life Table (Cutler-Ederer) Estimation of Cumulative Event Rates

Time	# at risk (n)	# of events (r)	# censored ©	Effective Sample Size	Prob of an Event (p)	Prob of No Event (p')	Cum No Event Rate	Cum Event Rate
1	105	76	12	99	.768	.232	.232	.768
2	17	10	2	16	.625	.375	.087	.913
3	5	3	2	4	.75	.25	.021	.978

Effective Sample Size at time (I) = $ESS_{i-1} - c_i/2 - c_{i-1}/2 - r_{i-1} = n-c/2$
For the first cycle, ESS = 105-6-0-0 = 99.

Probability of an Event (p) = r/ESS

Probability of No Event (p') = 1 - p

Cum Probability of No Event by the end of the interval = Cum-No-Event-$Rate_{i-1}$' TIMES p_i'

Cumulative Event Rate at the end of the interval = 1 - cumulative probability of no event rate

Note that censoring and events are assumed to occur uniformly over the interval. For the computations, half the total number of censored patients within an interval are assumed to be censored half-way through the interval.

Statistical Review and Evaluation
Clinical Studies

Date: DEC 12 1996

NDA #: 20-582

Applicant: Organon Inc.

Name of Drug: Follistim (follitropin beta for injection)
(The research name, ORG 32489, is used in this review)

Indication: The development of multiple follicles in ovulatory patients participating in assisted reproductive technology programs.

Documents Reviewed: Vol. 1.35, 1.54, 1.55, 1.58, 1.59

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Ridgely Bennett, M.D. (HFD-580)

Summary of Studies 37604 & 37611

Studies # 37604 and 37611 are both randomized, assessor-blind, active-control clinical trials for the indication of the development of multiple follicles in ovulatory patients participating in assisted reproductive technology programs. The eligibility criteria for subjects was the same for both studies, as were the response variables of interest. Study # 37604 was a single-center trial, with Humegon as the active-control drug, and no pituitary suppresser was used. Study # 37611 was a multi-center trial with Metrodin as the active-control drug, and with pituitary suppression (Decapeptyl) used in both treatment groups.

There is an additional controlled clinical trial, study #37608, which is included in the NDA in support of the indication of the development of multiple follicles in ovulatory patients participating in assisted reproductive technology programs. This study is reviewed in a separate document by Joy Mele (statistical reviewer in FDA's Division of Biometrics II, HFD-715). Her review also includes study #37609 which is for a second indication, specifically 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.

The 4 controlled clinical studies being considered are summarized in Table 1. The goal of these studies is to show that ORG 32489, which is recombinant human FSH, is equally effective in the treatment of fertility as urinary-extracted FSH products (Humegon and Metrodin).

Table 1: Summary of Randomized, Controlled, Assessor-blinded Comparative Studies

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms (# Randomized)	Indication	Duration of Treatment
37604 (3/92 to 12/94)	1 (Netherlands)	Follitropin (n=66) Humegon (n=43)	Ovarian hyperstimulation and induction of ovulation	1 cycle
37608 (3/92 to 1/95)	18 (18 European Countries)	Follitropin (n=615) Metrodin (n=412)	Ovarian hyperstimulation and induction of ovulation	3 cycles (only 1st cycle analyzed)
37609 (6/92 to 1/95)	12 (9 European Countries)	Follitropin (n=109) Metrodin (n=69)	Induction of ovulation in anovulatory patient.	3 cycles
37611 (8/92 to 1/95)	6 (France)	Follitropin (n=60) Metrodin (n=39)	Ovarian hyperstimulation and induction of ovulation	1 cycle

STUDY #37604

Background

Study #37604 is a randomized, assessor-blind, single-center active-control clinical trial in which the treatment for comparison is Humegon. The sample consisted of infertile female patients, ages 18-39, who were treated by in-vitro fertilization using either ORG 32489 or Humegon for induction of controlled ovarian superovulation. No pituitary suppresser was used for either treatment group. Subjects were randomly assigned to a treatment group at a ratio of 3:2 (ORG : Humegon). The treatment was administered starting on the 3rd day after menstruation began, and continued until at least 2 follicles with a diameter ≥ 15 mm were present as observed by an ultrasound. At that time, ovulation was induced by injection of hCG, oocytes were collected and fertilized, and up to 3 of the resulting embryos were transferred back to the patient to complete the in vitro fertilization process. This study had only 1 treatment cycle.

Primary variables of interest were:

- Number of oocytes collected
- Ongoing pregnancy rate per attempt[1]
- Ongoing pregnancy rate per transfer[1]

Secondary variables of interest were:

- Number of FSH vials/ampoules administered
- Length of treatment (days)
- Number of mature oocytes recovered
- Max. E^2 level before hCG injection

[1] A single or multiple vital pregnancy was called ongoing when a pregnancy, after lasting at least 12 weeks beyond embryo transfer, was confirmed by the investigator.

A total of 109 patients were randomized to the two treatment groups. The 2 groups were similar with regard to demographic characteristics at baseline, as shown in Table 2. The only variable for which the differences appeared to warrant investigation was Type of Infertility (Primary vs. Secondary). However, a CMH test showed no significant differences between the 2 treatment groups (p=.21) for that variable.

Table 2: Demographic characteristics (Study #37604)

	Org 32489 (n=54)	Humegon (n=35)
mean age (years)	32.2	31.2
mean height (cm)	162.1	164.6
mean wt (kg)	59.3	62.0
mean Body Mass Index (kg/m^2)	22.5	23.0
median cycle length (days)	28.6	29.3
mean duration of flow (days)	4.6	4.3
mean duration of infertility (years)	4.3	3.5
% primary infertility	46.3	60.0
% secondary infertility	53.7	40.0
cause of infertility (%)		
tubal	57.4	48.6
endometriosis	1.9	0.0
tub/end	1.9	2.9
end/other	not classified	not classified
unknown	38.9	48.6

Source: Vol. 1.54, Tables 5. 6.

The disposition of the subjects in the 2 treatment groups was similar in terms of both the number of drop-outs at any stage and the reason for drop-outs (see Tables 3 & 4). The number of drop-outs after FSH-treatment but before the hCG injection who discontinued due to FSH too high seemed possibly unbalanced (5 in ORG32489 group, 1 in Humegon group). To investigate that possibility, this reviewer performed Fisher's Exact test which concluded there was no significant difference (p=.28).

Table 3: Disposition of subjects by group (Study #37604)

	ORG 32489		Humegon	
	n	rand. %	n	rand. %
randomized	66	100.0	43	100.0
FSH-treated	54	81.8	35	81.4
hCG-treated	48	72.7	33	76.7
Oocyte retrieval	48	72.7	32	74.4
S/O incubation *	47	71.2	32	74.4
Embryo Transfer	39	59.1	27	62.8

Source: Vol. 1.54, Figure 1.

* Sperm/Oocyte incubation after oocyte retrieval and before embryo transfer.

Table 4: Reasons for Discontinuation (Study #37604)

	ORG 32489		Humegon	
	n	% rand.	n	% rand.
After Rand. / Before FSH				
FSH too high	4	6.1	1	2.3
End of study *	3	4.5	1	2.3
Other/unknown	5	7.6	6	14.0
After FSH / Before hCG				
FSH too high	5	7.6	1	2.3
Other	1	1.5	1	2.3
Cycle cancellation after hCG				
No oocytes fertilized	7	10.6	5	11.6
Other	2	3.0	1	2.3
Total	27	40.9	16	37.2

* End of study indicates patients who were discontinued because the study was stopped due to legal issues (patent litigation).

Applicant's Analysis

The ongoing pregnancy per attempt and per transfer variables were analyzed using the Cochran-Mantel-Haenszel (CMH) test. One variable (max E^2) is measured on a continuous scale and was analyzed by standard ANOVA (GLM) methods with treatment as the only factor in the linear model. The remaining 4 response variables are counts, and were analyzed using a method proposed by Cochran (1954) which is similar to the ANOVA linear model but uses group variances to calculate weighted group means. The Cochran method was used here to be consistent with the analysis of the other studies in this application. However, in the case of only one center, the Cochran results match ANOVA results. Study 37604 is not a multi-center trial so there are no center or treatment-by-center terms in any of the models.

Point estimates for the response variables of interest are given for each treatment group below in Table 5a. The observed difference between the treatment groups was in a direction which favored ORG32489 versus Humegon for all 3 primary variables and 2 of the 4 secondary variables (see Table 5a). For the 3 primary variables, meaningful clinical differences were given in the protocol for the purpose of determining the power to detect statistically significant differences. Because the decision being considered here is that of equivalence to an active control (Humegon), instead of looking at the p-values for tests for differences we will look at the confidence intervals for the difference. Support for ORG 32489 being equivalent to Humegon is determined by the confidence interval excluding meaningful clinical differences which favor Humegon. As shown in the right-hand columns of the table below, the confidence intervals for all 3 primary variables exclude clinically meaningful values supporting Humegon.

Table 5a: Applicant's Results (subjects who had oocyte retrieval, n=80): (Study #37604)

Response Variables	n (ORG / Hum)	ORG 32489	Humegon	Diff.	C.I. on Diff	Meaningful Clin. Diff. (From protocol)
Primary Variables						
# oocytes collected	48 / 32	11.2	8.3	2.9 *	-1.1, 6.8	-3.7
ongoing preg. rate / attempt	54 / 35	22.2	17.1	5.1 *	-12.1, 22.2	-14.5
ongoing preg. rate / transfer	39 / 27	30.8	22.2	8.5 *	-13.4, 30.5	-17.2
Secondary Variables						
# mature oocytes recovered	48 / 32	10.6	7.5	3.1 *	-0.7, 6.9	**
Max E2 before hCG	46 / 31	3889	3145	745 *	-365, 1855	**
# FSH vials/amps used	48 / 32	18.8	18.2	0.6 •	-0.7, 1.9	**
Trmt length (days)	48 / 32	6.2	6.0	0.2 •	-0.2, 0.6	**

Source: Vol. 1.54, Tables 8, 10, 13, 19.

* A positive value for the estimated difference favors ORG 32489.
• A negative value for the estimated difference favors ORG 32489.
** No meaningful clinical difference was defined for secondary variables.

Reviewer's Analysis

The applicant's analyses for the efficacy variables, except the 2 pregnancy rate variables, were restricted to subjects who had oocyte retrieval. This excludes 9 subjects (6 ORG / 3 Hum.) who started FSH treatment but discontinued from the study prior to oocyte retrieval. This reviewer felt that the true Intent-to-Treat analysis should include those 9 subjects, and therefore repeated the analyses for the applicable variables using all subjects who received FSH treatment. The number of oocytes collected and number of mature oocytes variables were set equal to zero for the 9 subjects who did not have oocyte retrieval. The reviewer's results appear in Table 5b.

The conclusion reached with the reviewer's analysis are similar to those from the applicant's analysis. The observed difference between the treatment groups was in a direction which favored ORG 32489 versus Humegon for all 7 efficacy variables, and all the confidence intervals include the value zero. For the 3 primary variables, the confidence intervals exclude meaningful clinical values, as given in the protocol, supporting Humegon over ORG 32489.

Table 5b: Reviewer's Results (all subjects who received FSH treatment, n=89): (Study #37604)

Response Variables	n (ORG / Hum)	ORG 32489	Humegon	Diff.	C.I. on Diff	Meaningful Clin. Diff. (From protocol)
Primary Variables						
# oocytes collected	54 / 35	9.9	7.6	2.3 *	-1.2, 5.8	-3.7
ongoing preg. rate / attempt	54 / 35	22.2	17.1	5.1 *	-11.6, 21.8	-14.5
ongoing preg. rate / transfer	39 / 27	30.8	22.2	8.5 *	-12.8, 29.9	-17.2
Secondary Variables						
# mature oocytes recovered	54 / 35	9.4	6.9	2.6 *	-0.8, 5.9	**
Max E2 before hCG	46 / 32	3791	3087	704 *	-352, 1760	**
# FSH vials/amps used	54 / 35	17.4	18.1	-0.7 •	-2.6, 1.1	**
Trmt length (days)	54 / 35	5.8	6.0	-0.2 •	-0.8, 0.4	**

* A positive value for the estimated difference favors ORG 32489.
• A negative value for the estimated difference favors ORG 32489.
** No meaningful clinical difference was defined for secondary variables.

Subgroup Analyses

For descriptive purposes only, the primary efficacy results for each treatment group were compared by Age group and Infertility type.

The subjects were split into 2 groups based on age. The Age groups were defined as 32 and under, and over 32. For both studies which are included in this report, the median and mean age in both treatment groups were in the 31-33 range, so 32 was decided on as a consistent breakpoint for the age subgroup analyses. There were no study participants over 39 years of age. Comparison of the group rates and medians[2] indicated a negative correlation between pregnancy rate per attempt and age, which was consistent across the treatment groups (Table 6a).

Table 6a: Age Group Comparisons (Study #37604)

	ORG 32489		Humegon	
	Age ≤ 32	Age > 32	Age ≤ 32	Age > 32
n	25	29	22	13
Pregnancy Rate per Attempt	24.0%	20.7%	18.2%	15.4%
Pregnancy Rate per Transfer	28.6%	33.3%	23.5%	20.0%
# Oocytes Recovered (median)	8	7	7	5
# Mature Oocytes (median)	8	7	7	5

Comparing the Infertility type groups suggested that there was a positive association between Secondary type infertility and pregnancy rates, particularly in the Humegon treatment group (Table 6b).

Table 6b: Infertility Type Comparisons (Study #37604)

	ORG 32489		Humegon	
	Primary	Secondary	Primary	Secondary
n	25	29	21	14
Pregnancy Rate per Attempt	20.0%	24.1%	4.8%	35.7%
Pregnancy Rate per Transfer	29.4%	31.8%	6.3%	45.5%
# Oocytes Recovered (median)	7	8	7	6
# Mature Oocytes (median)	6	8	7	6

[2] For the subgroup analyses, medians are reported because, due to small group sizes and a few large values, the median was more representative of the data than the mean.

This reviewer wanted to check if the trends seen in the separate age group and infertility type analyses were related, so a Chi-square test was conducted to test for association between these 2 patient characteristics. There is a marginal relationship between age group and infertility type (Chi-square pvalues: .06 for ORG group; .20 for Hum. Group). Women in the 32 and under age group were more likely to be in the primary infertility category. A subgroup comparison by both these characteristics is shown in Table 6c. Among women in the 32 and under age group, the data suggest the same positive association between Secondary type infertility and pregnancy rates which was found in the analysis by infertility type only, and the association was consistent across the treatment groups. Among women in the over 32, this positive association between Secondary type infertility and pregnancy rates appears in the Humegon treatment group, but not in the ORG 32489 group.

Table 6c: Age Group & Infertility Type Comparisons (Study #37604)

	ORG 32489				Humegon			
	Age ≤ 32		Age > 32		Age ≤ 32		Age > 32	
	Prim.	Sec.	Prim.	Sec.	Prim.	Sec.	Prim.	Sec.
n	15	10	10	19	15	7	6	7
Pregnancy Rate per Attempt	20.0%	30.0%	20.0%	21.1%	6.7%	42.9%	0.0%	28.6%
Pregnancy Rate per Transfer	25.0%	33.3%	40.0%	30.8%	10.0%	42.9%	0.0%	50.0%
# Oocytes Recovered (median)	9	8	3.5	8	7	8	7	4
# Mature Oocytes (median)	9	8	3.5	8	7	7	7	4

Conclusions - Study #37604

This study compares ORG 32489 to Humegon as the active-control drug, with no pituitary suppression used. Confidence intervals for all 3 primary variables exclude clinically meaningful values (as specified in protocol) favoring Humegon over ORG 32489, and the direction of the difference favored ORG 32489 versus Humegon. With 95% confidence, the population number of oocytes collected is not more than 1.2 oocytes less than the true rate for Humegon, and could be as much as 5.8 oocytes better than Humegon.

The applicant's results for the 3 primary and 4 secondary variables of interest (shown in Table 5a) appear in the proposed labeling. The applicant's results for the 2 pregnancy rate variables (both are primary variables) match those in the reviewer's results (Table 5b) because the same set of subjects were used to calculate those values. However, for the other 5 efficacy variables, the applicant eliminated some subjects who had received treatment. This is not the appropriate Intent-to-treat analysis for those variables. The reviewer's analysis (Table 5b) includes the correct subjects for the Intent-to-treat analyses. Although the conclusions reached from the 2 analyses are the same, the treatment group means are slightly lower in the reviewer's analysis than in the applicant's analysis. Therefore we may want to consider changing the values listed in the label to reflect the true intent-to-treat subject group, as shown in the reviewer's results in Table 5b.

STUDY #37611

Background

Study # 37611 is a randomized, assessor-blind, multi-center active-control clinical trial in which the treatment for comparison is Metrodin. The sample consisted of infertile female patients, ages 18-39, who were treated by in-vitro fertilization using either ORG 32489 or Metrodin for induction of controlled ovarian hyperstimulation after pituitary suppression with Decapeptyl. Subjects were randomly assigned to a treatment group at a ratio of 3:2 (ORG : Metrodin). Administration of Decapeptyl was started on the 1st day after menstruation began. The FSH treatment was started 10 to 18 days after Decapeptyl had been started, once blood tests determined the Decapeptyl had resulted in a hypogonadotropic state. Treatment with FSH continued until at least 3 follicles with a diameter ≥ 17 mm were present as observed by an ultrasound. At that time, ovulation was induced by injection of hCG, oocytes were collected and fertilized, and up to 5 of the resulting embryos were transferred back to the patient to complete the in vitro fertilization process. Subjects were enrolled for only 1 treatment cycle.

Primary variables of interest were:

Number of oocytes collected
Ongoing pregnancy rate per attempt[3]
Ongoing pregnancy rate per transfer[3]

Secondary variables of interest were:

Number of FSH vials/ampoules administered
Length of treatment (days)
Number of mature oocytes recovered

One secondary response variable which was included in the analysis of the other studies in this application but was not analyzed for study # 37611 was Maximum E^2 level before hCG injection. This was not measured consistently across all the centers in this study, and the different procedures used were not compatible, thus making it impossible to compare or combine data from all the centers.

[3] A single or multiple vital pregnancy was called ongoing when a pregnancy, after lasting at least 12 weeks beyond embryo transfer, was confirmed by the investigator.

A total of 99 patients were randomized to the two treatment groups. The 2 groups were similar with regard to demographic characteristics at baseline, as shown in Table 7.

Table 7: Treatment Group Comparison of Demographic Variables (Study #37611)

Demographics	Study 37611	
	ORG 32489 (n=57)	Metrodin (n=33)
Mean age (years)	32.2	31.2
Mean height (cm)	162.1	164.6
Mean weight (kg)	59.3	62.0
Mean Body Mass Index (kg m^2)	22.5	23.0
Median cycle length (days)	28.6	29.3
Mean duration of flow (days)	4.6	4.3
Mean duration of infertility (years)	5.4	3.7
% primary infertility	33.3	33.3
% secondary infertility	66.7	66.7
Cause of infertility (%)		
tubal	61.4	66.7
endometriosis	10.5	6.1
tub/end	3.5	6.1
end/other	1.8	0.0
unknown	22.8	21.2

Source: Vol. 1.57, Tables 5, 6.

The subjects were not well balanced across the 6 centers. The majority of the subjects in this study were enrolled in 2 of the 6 centers, Montpelier and Bondy, as shown in Table 8 below.

Table 8: Subjects by Centers (Study #37611)

	FSH-treated Subjects		Subjects with Oocyte Retrieval	
Center	ORG 32489	Metrodin	ORG 32489	Metrodin
1 (Nantes)	2	1	2	0
2 (Montpelier)	20	11	20	10
3 (Paris) *	2	1	1	1
4 (Bondy) *	20	12	19	12
5 (Sevres)	4	1	4	1
6 (Amiens) **	9	7	9	7
Total	57	33	55	31

Source: Vol. 1.57, Tables 2.

The original protocol listed 3 centers: Nantes, Montpelier, and Sevres.

* Paris and Bondy centers were added via a protocol amendment (dated 3 mths. prior to start of study).

** Amiens was added without a protocol amendment (no date given for start at this center).

The disposition of the subjects in the 2 treatment groups is shown in the following table. While the percentage of each sample which resulted in an embryo transfer is similar, the pattern of the time points when subjects dropped from the 2 groups is not. All the subjects who dropped from the Metrodin group did so prior to administration of hCG or attempted oocyte retrieval, and at that stage the Metrodin group had a higher dropout percentage than the ORG 32489 group. In the ORG 32489 group, 6 subjects discontinued due to cycle cancellation after administration of hCG and attempted oocyte retrieval.

Table 9: Disposition of subjects by group (Study #37611)

	ORG 32489		Metrodin	
	n	% rand	n	% rand
randomized	60	100.0	39	100.0
FSH-treated	57	95.0	33	84.6
hCG-treated	55	91.7	31	79.5
Oocyte retrieval	55	91.7	31	79.5
S/O incubation *	54	90.0	31	79.5
Embryo Transfer	49	81.7	31	79.5

Source: Vol. 1.57, Figure 1.

* Sperm/Oocyte incubation after oocyte retrieval and before embryo transfer.

Table 10: Reasons for Discontinuation (Study #37611)

	ORG 32489		Metrodin	
	n	% rand.	n	% rand.
After Rand. / Before FSH				
End of study *	2	3.3	2	5.1
Other	1	1.7	4	10.3
After FSH / Before hCG				
Insuff. Therapeutic effect	1	1.7	1	2.6
Other	1	1.7	1	2.6
Cycle cancellation after hCG				
No oocytes fertilized	4	6.7	0	0.0
Other	2	3.3	0	0.0
Total	11	18.3	8	20.2

* End of study indicates patients who were discontinued because the study was stopped due to legal issues (patent litigation).

Applicant's Analysis

The ongoing pregnancy per attempt and per transfer variables were analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for multiple centers. The overall rates are calculated as weighted averages of the rates in the individual centers. The remaining 4 response variables are counts, and were analyzed using a method proposed by Cochran (1954) which is similar to an ANOVA linear model but uses variances by center to calculate overall weighted means.

The applicant provided output for both the Cochran method and SAS-GLM for the variables using ANOVA linear models, but reported the results from the Cochran method in their summary report. The SAS-GLM results indicate an adequate model fit, so it wasn't necessary to use Cochran's approach for that reason. The Cochran method was reported for this study to be consistent with the analysis of the other studies in this application. These results for the Cochran method appear below in Table 11a.

In the applicant's results, the difference between the treatment group means for the 3 primary variables and 2 of the 3 secondary variables is in the direction favoring ORG 32489, and all 6 confidence intervals include the value zero. A meaningful clinical difference was defined by the applicant in the protocol for only one variable, # oocytes collected, and for this variable the confidence interval excludes any values which would indicate support in favor of Metrodin.

Table 11a: Applicant's Results (subjects who had oocyte retrieval, n=84): (Study #37611)

Response Variables	n (ORG / Met)	ORG 32489	Metrodin	Diff.	C.I. on Diff	Meaningful Clin. Diff.
Primary Variables						
# oocytes collected	53/31	9.7	8.9	0.8 *	-1.7, 3.2	-3.8
ongoing preg. rate / attempt	57/33	30.2	17.4	12.8 *	-6.4, 31.9	**
ongoing preg. rate / transfer	48/31	34.0	18.8	15.2 *	-5.5, 35.9	**
Secondary Variables						
# mature oocytes recovered	53/31	8.1	6.9	1.2 *	-1.1, 3.4	**
# FSH vials/amps used	53/31	30.2	29.6	0.6 •	-3.2, 4.4	**
Trmt length (days)	53/31	10.2	10.3	-0.1 •	-0.8, 0.7	**

Source: Vol. 1.57, Tables 8, 13, 20.

* A positive value for the estimated difference favors ORG 32489.

• A negative value for the estimated difference favors ORG 32489.

** No meaningful clinical difference was defined for these variables.

Reviewer's Analysis

This reviewer has 2 concerns about the applicant's analyses. The first is that the subset of subjects included in the applicant's analyses was restricted to those who had oocyte retrieval, rather than the Intent-to-Treat group of subjects who had received FSH treatment. Four subjects (2 ORG / 2 Met.) were excluded from their analyses for this reason. Also, the program the applicant used to generate the Cochran method results excluded any center which did not have at least one subject in both of the treatment groups. At the Nantes center, 2 subjects in the ORG 32489 group had oocyte retrieval, but no subjects in the Metrodin group had oocyte retrieval. Therefore the 2 subjects from the Nantes center were excluded from the applicant's analyses.

This reviewer felt it was important to check the impact of dropping these 6 subjects from the analyses by repeating the analyses using the true Intent-to-treat group. First, as a preliminary step, I compared the results of a GLM model with all the Intent-to-Treat subjects to a GLM model without these 6 subjects to check that the linear model was appropriate. (The SAS-GLM procedure was used because the applicant's program for the Cochran method was not designed for PC-SAS.) The conclusions reached by these 2 analyses matched each other, as well as the conclusions from the applicant's Cochran model, for all 4 response variables which used an ANOVA model. Specifically, there were no significant treatment-by-center interactions, and no significant treatment main effects. However, since this an active-control study, we are interested in the confidence intervals on the difference between the treatment groups.

The applicant's treatment group means, differences, and confidence intervals, as shown in Table 11a, were calculated using weights based on the variance for each center from the Cochran method. This method could not be duplicated for the full Intent-to-treat set of subjects because of programming incompatibility, so this reviewer calculated unweighted treatment group means for the differences and confidence intervals.

The results of unweighted treatment group means along with confidence intervals of the difference appear below in Table 11b. These results are similar in magnitude and direction to the applicant's results (Table 11a) and indicate similar conclusions. All confidence intervals include the value zero, and the direction of the difference favors ORG 32489 for all 6 variables. A meaningful clinical difference was defined by the applicant in the protocol for only one variable, # oocytes collected, and for this variable the confidence interval excludes any values which would indicate support in favor of the comparative drug (Metrodin). With 95% confidence, the population number of oocytes collected is not more than 1.0 oocytes less than the true rate for Metrodin, and could be as much as 4.3 oocytes better than Metrodin.

Table 11b: Reviewer's Results (all subjects who received FSH treatment, n=90): (Study #37611)

Response Variables	n (ORG / Met)	ORG 32489	Metrodin	Diff.	C.I. on Diff	Meaningful Clin. Diff.
Primary Variables						
# oocytes collected	57/33	10.4	8.8	1.6 *	-1.0, 4.3	-3.8
ongoing preg. rate / attempt	57/33	29.8	18.2	11.6 *	-6.1, 29.4	**
ongoing preg. rate / transfer	49/31	34.7	19.4	15.3 *	-3.9, 34.6	**
Secondary Variables						
# mature oocytes recovered	57/33	8.6	6.8	1.8 *	-0.5, 4.1	**
# FSH vials/amps used	57/33	30.6	32.1	-1.5 •	-7.0, 4.0	**
Trmt length (days)	57/33	10.1	10.2	-0.1 •	-1.0, 0.7	**

* A positive value for the estimated difference favors ORG 32489.
• A negative value for the estimated difference favors ORG 32489.
** No meaningful clinical difference was defined for secondary variables.

Subgroup Analyses

For descriptive purposes only, the results for each treatment group were compared by Age group and Infertility type. A comparison by infertility type indicated efficacy results were consistent across the subgroups and treatments, and a check for a relationship between age group and infertility type found no significant association (Chi-square pvalues: .57 for ORG group; .44 for Met. group). Therefore the subgroup analysis by infertility type is not presented in this report. Also, there were no significant treatment-by-center interactions in any of the analyses, so sub-group breakdown by center is not included here.

The Age groups are defined as 32 and under, and Over 32. There were no study participants over 39 years of age. Comparison of the group means indicated that all 4 efficacy variables listed below are negatively correlated with age. This trend was consistent across the 2 treatment groups.

Table 12: Age Group Comparisons (Study #37611)

	ORG 32489		Metrodin	
	Age ≤ 32	Age > 32	Age ≤ 32	Age > 32
n	27	30	21	12
Pregnancy Rate per Attempt	40.7%	20.0%	19.0%	16.7%
Pregnancy Rate per Transfer	52.4%	21.4%	21.1%	16.7%
# Oocytes Recovered (median)	12	7	8	6
# Mature Oocytes (median)	9	7	6	5.5

Conclusions - Study #37611

This study compares ORG 32489 to Metrodin as the active-control drug, with pituitary suppression (Decapeptyl) used. Based on the true Intent-to-treat analysis conducted by this reviewer, the direction of the difference in treatment group means favors ORG 32489 for all 6 variables, and all confidence intervals include the value zero. A meaningful clinical difference was defined by the applicant in the protocol for only one variable, # oocytes collected, and for this variable the confidence interval excludes any values which would indicate support in favor of the comparative drug (Metrodin) over ORG 32489. With 95% confidence, the population number of oocytes collected is not more than 1.0 oocytes less than the true rate for Metrodin, and could be as much as 4.3 oocytes better than Metrodin.

This study was included in the submission in support of the indication for the development of multiple follicles in ovulatory patients participating in assisted reproductive technology programs. The conclusions reached from the reviewer's true Intent-to-treat analysis are the same as those from the applicant's analysis. However, the results of this study are not listed or included in the clinical data for the labeling, so the reviewer's analysis of this study does not indicate the need to make any changes in the proposed labeling.

Summary (37604 & 37611)

The goal of each of these studies was to show equivalence of ORG 32489 (Follistim) to the respective active-control product. Therefore, a comparison of confidence intervals for the observed difference between ORG 32489 and the comparative treatment for the 3 primary response variables of interest was used to assess whether this goal was met. In both studies, the observed differences in treatment group means favored ORG 32489, and the confidence intervals on the differences excluded large values favoring the active-control product, for all 3 primary efficacy variables.

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Concur: Dr. Nevius 8 EN 12/12/96

Dr. Kammerman LdK 12/12/96

cc:
Archival NDA 20-582
HFD-580
HFD-580/RBennett, HJolson, LRarick
HFD-580/LPauls
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