

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-273

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA/Drug Class: 21-273/3S

Name of Drug: Follistim-AQ (Follitropin Beta) 75/150/ [REDACTED] Injection

Applicant: Organon Inc.

Indication(s): Induction Of Ovulation In The Anovulatory Infertile Patients In Whom The Cause Of Infertility Is Functional And Is Not Due To Primary Ovarian Failure

Documents Reviewed: Volumes 1-3, 12-13 dated 7/24/00

Medical Reviewer: Ridgley Bennett, M.D./HFD-580

Statistical Reviewer: Shahla S. Farr, M.S./HFD-725

Introduction:

Follistim-AQ (follitropin beta injection) is a new pharmaceutical presentation of the approved Follistim, NDA 20-582. The currently approved product is formulated as a [REDACTED], to be administered after reconstitution with water for injection, whereas Follistim-AQ is an injectable aqueous solution of 75, 150, [REDACTED] IU follitropin beta per 0.5 mL, in a glass vial, to be administered with a syringe.

The primary endpoint parameter is the overall ovulation rate in the anovulatory infertile patients in whom the cause of infertility is functional and is not due to primary ovarian failure. The secondary endpoint variable is the ongoing pregnancy rates.

The sponsor has submitted one open-label, randomized, group-comparative, multi-center study to assess the efficacy and safety of Follistim Solution Formulation (FSF) compared to a Freeze-dried Cake Formulation (FCF), both administered subcutaneously for the duration 21 days.

The sponsor intends to demonstrate the comparability of the FCF to FSF using a two-sided 95% Confidence Interval (CI) around the difference between the overall ovulation rates and the overall pregnancy rates.

Reviewer's Comments: The sponsor has conducted only one study. In general, for the Phase 3 clinical trials, two adequate and well-controlled Phase 3 clinical trials are needed for approval, so that the results can be reproduced. It is difficult to confirm the results and conclusion based only on one study.

In addition, this study is open-label. This might introduce some bias in the results. Therefore, the results of this study should be interpreted with caution.

Enrollment and Discontinuations:

Site	Follistim Freeze-dried Cake Formulation (FCF) (N=64)	Follistim Solution Formulation (FSF) (N=62)
	n	n
01	12	12
03	3	3
04	13	13
05	1	2
06	6	5
07	7	7
08	9	8
10	12	11
12	1	1

One hundred and twenty six (64 in the FCF and 62 in the FSF) from 9 centers were randomized into the study. Of these, 54 subjects in the FCF and 57 patients in the solution arm completed the study. The most common reason for discontinuation in both treatment groups was risk of (ovarian) hyperstimulation: 8 subjects (12.5%) in the FCF arm and 6 subjects (9.7%) in the FSF group.

There were a total of three subjects who had a major protocol violation: two (3.1%) in the FCF treatment group and one subject (1.6%) in the FSF group.

Reviewer's Comments: In the protocol it was stated that 150 subjects were to be randomized in a 1:1 ratio (75 in each arm), from 10 centers. A minimum of 15 subjects in each center was suggested. Considering the smaller number of subjects who actually were enrolled (n=126) and finished the study, the study might be under-powered. In addition, some of the centers enrolled less than 15 subjects. The NDA did not explain these discrepancies.

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Demographics and Baseline Characteristics:

	Whole Population (N=126)	FCF (n=64)	FSF (n=62)
Age (n, %)			
18-24	8 (6.3%)	5 (7.8%)	3 (4.8%)
25-31	78 (61.9%)	42 (65.6%)	36 (58.1%)
32-39	40 (31.7%)	17 (26.6%)	23 (37.1%)
Age (mean±sd)	30.6 ± 3.8	30.1 ± 3.9	31.1 ± 3.7
Race (n, %)			
Caucasian	105 (83.3%)	52 (81.3%)	53 (85.5%)
Asia	5 (4%)	2 (3.1%)	3 (4.8%)
Black	5 (4%)	3 (4.7%)	2 (3.2%)
Other	11 (8.7%)	7 (10.9%)	4 (6.5%)
BMI (n, %)			
≤ 25 kg/m ²	77 (61.1%)	40 (62.5%)	37 (59.7%)
> 25 kg/m ²	49 (38.9%)	24 (37.5%)	25 (40.3%)
BMI (mean±sd)	24.67 ± 4.12	24.72 ± 3.7	24.6 ± 4.6
Anovulation Characteristics (n, %)			
Cycle length >35 days	120 (95.2%)	60 (93.8%)	60 (96.8%)
Amenorrhea	19 (15.1%)	11 (17.2%)	8 (12.9%)
Progesterone	6 (4.8%)	3 (4.7%)	3 (4.8%)
Fertility Characteristics (n, %)			
Early Abortion in the past	35 (27.8%)	19 (29.7%)	16 (25.8%)
Late abortion in the past	5 (4%)	2 (3.1%)	3 (4.8%)
Ectopic pregnancy in the past	3 (2.4%)	1 (1.6%)	2 (3.2%)
Duration of Infertility in months (mean±sd)	39.6 ± 30.3	47.9 ± 34.9	31.1 ± 22

Reviewer's Comments: The comparability of the two treatment groups with regard to demographics and baseline characteristics is not clear, since the sponsor has not provided the statistical tests and the p-values to compare and address the comparability issues. By looking at the data submitted by the sponsor, it seems that there are some differences in regards to the age category, fertility characteristics and the duration of infertility between the two treatment arms. However, one characteristic of concern is the duration of infertility since it was higher in the FCF group (47.9 months ± 34.9) than in the FSF arm (31.1 months ± 22).

Efficacy Results:

All subjects who were randomized and received at least one dose of study drug (Intend to Treat, ITT) were included in the analyses of efficacy and summaries of safety data. In cases where all dispensed study drugs were returned, the subject was considered non-treated and was not included in the ITT population.

Several sites had a small number of subjects enrolled in this study (Site 3 – six subjects, Site 5 – three subjects; and Site 12 – two subjects). The data from these three were pooled in order to balance the site data and perform statistical analyses.

The primary efficacy endpoint was based on the overall ovulation rate of the subjects.

Secondary efficacy parameter was the ongoing pregnancy rate.

Other efficacy parameters were reason for no hCG injection, number and size of follicles, and hormone levels (E2, LH, P and FSH).

Summary of Results:

Primary endpoint variable:

The overall ovulation rate was higher in the FSF treatment group (56/62=90.3%) than in the FCF treatment group (53/64=82.8%), although this difference was not statistically significant (p -value=0.179). The 95% CI, based on the ITT population, for the difference between the two proportions (FSF – FCF) was 7.5% (-4.3%, 19.3%).

Reviewer's Comments: The 95% CI indicates the true overall ovulation rate could be as much as 19.3% higher or as much as 4.3% lower for FSF relative FCF. A margin for non-inferiority was not pre-defined.

Secondary efficacy parameter:

The ongoing pregnancy rates in the two treatment groups were almost identical (11/62=17.7% for the FSF treatment group and 11/64=17.2% for the FCF treatment group; p -value=0.934). The 95% CI for the difference between these two rates was 0.6% (-12.7%, 13.8%).

Reviewer's Comments: The 95% CI indicates the true ongoing pregnancy rate could be as much as 13.8% higher or as much as 12.7% lower for FSF relative FCF. A margin for non-inferiority was not pre-defined.

Thirteen subjects (20.3%) in the FCF treatment group and 9 subjects (14.5%) in the FSF treatment group did not receive a HCG injection. The most common reason for no HCG injection was hyperovarian response.

Subjects in the FSF arm had a slightly larger number of follicles (10.5 follicles) than the subjects in the FCF arm (9.2 follicles). The mean number of follicles when categorized by size was similar between the two treatment groups.

Conclusion:

1. The overall ovulation rate was 90.3% in the FSF treatment group, and 82.8% in the FCF treatment group. The 95% CI indicates the true overall ovulation rate could be as much as 19.3% higher or as much as 4.3% lower for FSF relative FCF. A margin for non-inferiority was not pre-defined.
2. The observed ongoing pregnancy rates in the two treatment groups were almost identical (17.7% for the FSF treatment group and 17.2% for the FCF treatment group). The 95% CI indicates the true ongoing pregnancy rate could be as much as 13.8% higher or as much as 12.7% lower for FSF relative FCF. A margin for non-inferiority was not pre-defined.

3. The above results should be interpreted with caution, since there was some concern regarding the comparability of the two treatment arms based on the duration of infertility at baseline. Furthermore, the non-inferiority margin was not defined.

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cc:

Archival NDA 21-273

HFD-580

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/s/

Lisa A. Kammerman

5/11/01 04:32:45 PM

BIOMETRICS

Signing on behalf of Shahla Farr, the primary statistical reviewer

S. Edward Nevius

5/14/01 11:35:56 AM

BIOMETRICS

Concur with review.