

CLINICAL REVIEW

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: Follitropin beta for injection
Proposed Trade Name: Follistim® -AQ liquid formulation
Drug Class: Infertility
Sponsor's Proposed Indications:
1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation in the anovulatory, infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure
Dosage/Form/Strength: Sterile aqueous solution for subcutaneous or intramuscular injection: each vial contains 75IU, 150IU, [REDACTED] FSH per 0.5ml.
Dosages Regime: 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 response. In previous clinical studies it was shown that maintenance dosages range from 75 to 375 IU for six to twelve days, although longer treatment may be necessary. The maximum daily dose that Follistim®-AQ liquid formulation has been used is 600 IU.

B. State of Armamentarium for Indication(s)

There are six gonadotropin products in the United States that are used for controlled ovarian hyperstimulation and ovulation induction. Follistim®-AQ liquid formulation is one of two recombinant follicle stimulating hormone products in the United States marketplace. It is the only gonadotropin product that will have a liquid formulation. This ready to use formulation will be more convenient than previous cake formulations since it is easier to use and requires less handling.

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C. Important Milestones in Product Development

Recognition of the therapeutic potential of gonadotropins began in the 1950's with the extraction and purification of human menopausal gonadotropins (both follicle stimulating hormone and luteinizing hormone) from both human pituitaries and urine sources. Successful clinical pregnancies resulting from the use of these human derived gonadotropins were first reported in the 1960's.

Further improvement in purification resulted in separating follicle stimulating hormone (FSH) from other proteins in human menopausal urine. Purified FSH was first introduced in 1982 and continued to improve pregnancy rates after gonadotropin treatment. In the 1990's cells that are capable of producing biologically active FSH in culture produced follicle stimulating hormone (FSH). This recombinant derived FSH from *in vitro* cultured cells does not appear to be different from native human FSH clinically.

D. Other Relevant Information

The proposed label was submitted for review. Safety and efficacy data included in the labeling for Follistim®-AQ liquid formulation is identical to the labeling for the approved Follistim® lyophilized cake formulation-SRS. Efficacy for the indications of ovulation induction and multiple follicular development in an Assisted Reproductive Technology (ART) program are based on bioequivalence of Follistim®-AQ liquid formulation to the approved lyophilized cake formulation of Follistim®. Protocol [REDACTED] is supportive of one of the proposed labeling claims, namely induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. In the absence of pharmaceutical equivalence, Study 058004 alone would not provide sufficient evidence of efficacy in ovulation induction. No clinical studies were submitted to support the second indication of multiple follicular development in ART

The Division of Medication Errors and Technical Support (DMETS) re-reviewed the proprietary name, Follistim®-AQ liquid formulation. Container labels, carton and insert labeling, active ingredient, indications for use, dosing regimen, and routes of administration on March 19, 2003. DMETS had no objections to the use of the proprietary name Follistim®-AQ and recommends that the labels and labeling for Follistim® and Follistim®-AQ be clearly distinguishable.

The Division of Drug Marketing, Advertising and Communications (DDMAC) also reviewed the proposed prescribing information on March 20, 2003. The DDMAC reviewer recommends that a summary of adverse reactions to Follistim®-AQ liquid formulation preface the incidence tables for the different protocols.

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The reviewer from DDMAC also recommends that a summary statement about the experience with Follistim®-AQ liquid formulation in the beginning of the Adverse Reactions section would be useful.

E. Important Issues with Pharmacologically Related Agents

All adverse events associated with gonadotropin therapy result from ovarian stimulation, follicular development and ovulation. The two most concerning serious adverse events are ovarian hyperstimulation syndrome and thromboembolism.

Ovarian hyperstimulation syndrome is the least common complication of gonadotropin therapy, but the most serious one. The underlying pathophysiology is unknown, but results in increased vascular permeability. Ovarian hyperstimulation may occur in 0.5 to 5% of women that receive gonadotropin therapy. The treatment for this ovarian hyperstimulation is usually conservative, with management of the increased vascular permeability. Several deaths have been reported from severe ovarian hyperstimulation in the literature. The incidence of ovarian hyperstimulation syndrome using Follistim® products appears to be similar to other published studies.^{1,2} (see Appendix 1 – Table 1 (sponsor labeled Table 28))

Thromboembolism may present with or without ovarian hyperstimulation, and is usually seen in less than 1% of patients with moderate and severe ovarian hyperstimulation. The mechanism for development of thromboembolism may occur in the presence of high serum estradiol levels pre-and post-gonadotropin treatment. Worldwide experience with Follistim®-AQ liquid formulation reveals only four reported thromboembolic events and one reported case of a pulmonary embolism.

The potential for increased risk of congenital malformations with use of the assisted reproductive technologies is controversial. There is no current clinical evidence use gonadotropins increase the risk of malformations over the general population. No trends in congenital malformations were seen in the worldwide safety reports submitted by the sponsor.

Since the development of Follistim®-AQ liquid formulation, no new trends in adverse events have been identified in the worldwide safety data.

F. Foreign Approvals of Follistim®-AQ Liquid Formulation:

Follistim®-AQ liquid formulation was approved in 1999 in the European Union. The formulation of the solution in Europe is identical to the formulation

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There are no countries in which Follistim®-AQ liquid formulation has been withdrawn from marketing for any reason. No actions for safety reasons were initiated by any regulatory authority or by the sponsor for any of the Follistim® products.

G. Other Pharmacologically Related Agents Under Study:

Follistim®-AQ Cartridge is a solution for injection filled in cartridges to be administered with a pen injector. It was approved in Europe and has a pending application in the United States (NDA 21-211).

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry review of NDA 21-273 reported stability and manufacturing concerns. Certificates of analysis for the samples and reference standards, and material safety and data sheets (MSDS) of the drug substance and drug product components were requested. The chemistry review also noted that the site of stability testing and the site for manufacturing facilities needed clarification. The sponsor responded to these deficiencies on September 25, 2000 with method validation testing and confirmation of the sites where stability testing and manufacturing would occur.

The first microbiological review in March 29, 2001 resulted in questions that were conveyed to the sponsor in an Information Request Letter (by FAX April 3, 2001). Additionally inspections of the West Orange New Jersey manufacturing plant between July 17 and August 23, 2000 resulted in a Warning Letter to the facility on September 19, 2000. The inspection revealed many microbiological concerns, and resulted in a Compliance recommendation to withhold approval of the NDA on October 30, 2002. A current amendment was submitted April 20, 2001 by the sponsor to reply to the deficiencies.

The conclusion of the Team Leader on May 16, 2001 was that the application for Follistim®-AQ liquid formulation was approvable pending satisfactory resolution of remaining CMC deficiencies, Microbiology deficiencies, and satisfactory inspection reports from the Office of Compliance.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The sponsor requested a biowaiver for Follistim®-AQ liquid formulation (NDA 21-273) based on a bioequivalence (BE) study following subcutaneous administration (submitted in NDA 21-211).

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The Clinical Pharmacology and Biopharmaceutics section concluded that the main difference between the approved Follistim® lyophilized cake formulation-SRS and the current proposed Follistim®-AQ liquid formulation is in the concentration of follitropin beta. Follistim® lyophilized cake formulation-SRS results in the concentration range of 75 IU/ml to 300 IU/ml where as the proposed Follistim®-AQ liquid formulation is proposed to have a concentration range from 75 IU/0.5 ml _____/0.5 ml (i.e., 150 IU/ml _____).

There was concern that the increase in concentration in the proposed formulation may affect the bioavailability. The existing bioequivalence study between the Follistim® lyophilized cake formulation-SRS and cartridge containing the Follistim®-AQ liquid formulation injected by a pen injector (submitted in NDA 21-211) was reviewed by the Clinical Pharmacology and Biopharmaceutics section.

The Clinical Pharmacology and Biopharmaceutics section requested an additional in vitro study to compare dose losses for handling the reconstituted Follistim® lyophilized cake formulation-SRS versus handling the Follistim®-AQ liquid formulation. Because the request for waiver of bioequivalence for the liquid formulation was based on a bioequivalence study utilizing only the subcutaneous route of administration, the sponsor was requested to provide information to show that bioequivalence for the subcutaneous route of administration could be extrapolated to the intramuscular route of administration. In response, the sponsor submitted three studies that support bioequivalence of the Follistim® lyophilized cake formulation-SRS when administered subcutaneously and intramuscularly at 150IU/ _____). These studies were submitted and reviewed by the Clinical Pharmacology and Biopharmaceutics section, and the finding was that the dose/losses were similar and supports the biowaiver.

B. Pharmacodynamics

A second in vitro study was carried out to look at the FSH activity of the original formulation of Follistim® lyophilized cake formulation-SRS compared to the new Follistim®-AQ liquid formulation. The difference between the mean amount of units in the injectable volume after reconstitution of four cakes was not statistically significant from an injectable volume of a single vial of the liquid.

Since the Follistim® lyophilized cake formulation-SRS and the Follistim®-AQ liquid formulation are bioequivalent when administered subcutaneously, by extrapolation; they are bioequivalent when administered intramuscularly. Therefore, the conclusion of the Biopharmaceutics reviewer after review of these two in vitro studies was that the cake and solution are bioequivalent when administered subcutaneously. The data were considered adequate to support the sponsor's request for a biowaiver. Please refer to the Clinical Pharmacology and Biopharmaceutics review of NDA 21-273 for further information.

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IV. Description of Clinical Data and Sources

A. Overall Data

Previous clinical information:

Clinical trials (37603, 37604, 37608, 37609, 37611, 37613, and 37617) were submitted for the original product Follistim® lyophilized cake formulation-SRS (NDA 20-582) to demonstrate efficacy and safety. Follistim® lyophilized cake formulation-SRS was demonstrated to be non-inferior in efficacy compared to Metrodin® (Protocols [REDACTED]). The incidence of adverse events was similar when compared to a Metrodin® treatment group, although the rate of Ovarian Hyperstimulation Syndrome was slightly higher in the Follistim® lyophilized cake formulation-SRS.

Data in these clinical trials demonstrated no clinically relevant difference in the safety parameters between IM and SC administration of the Follistim® lyophilized cake formulation-SRS treatment. Furthermore, the route of administration of Follistim® lyophilized cake formulation-SRS did not appear to alter efficacy. [See NDA 20-582 and cross reference the original medical officer's review of the approved Follistim® lyophilized cake formulation-SRS product (NDA 20-582)] dated March 18, 1997).

There is clinical trial data for Follistim®-AQ liquid formulation from a single supportive clinical study conducted by the applicant entitled "An open-label, randomized, group-comparative, multicenter study to assess the efficacy and safety of a Follistim® solution formulation compared to a freeze-dried cake formulation, both administered subcutaneously for the induction of ovulation in clomiphene-resistant subjects with chronic anovulation (WHO group II). This clinical trial is identified as protocol [REDACTED] (see NDA 21-273)

B. Tables Listing the Clinical Trials

The tables listing the original clinical trials are contained in NDA 20-582 and 21-273 and are incorporated into this review by cross-reference. An update of current clinical trials is listed (see Appendix 1 – A. Overview of Ongoing or Completed Clinical Trials).

C. Postmarketing Experience

The sponsor reported that [REDACTED] international units of Puregon solution (tradename - Follistim®-AQ in the United States) have been sold full year 2001 worldwide. No unusual long-term adverse events or significant trends were reported in this time frame.

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An additional safety update report was submitted on October 18, 2002 containing safety data from worldwide experience with Puregon (tradename - Follistim® in the United States). Three hundred and eight total adverse events were reported. (See Appendix 1– Table 2)

Two deaths were reported in the safety data from worldwide experience. A 26 year old female patient (case report 199800041) was reported in Australia. The death occurred 9 days after Puregon use, and an autopsy was non-conclusive. In this case, there is suspicion that suicide was the actual cause, and this is also the opinion of the reporting doctor. The second death of a 29 year old female patient (case report 200100023) was reported in Vietnam. The death occurred 14 days after receiving the last dose of Puregon and both the cause of death and results of the autopsy are unknown. The directorate of the hospital and the doctors who treated the patient were contacted, but were not willing to discuss this case. The Ministry of Health for Vietnam and the physicians involved has closed this case. From the limited descriptions of the cases, the deaths do not appear to be directly related to the drug product.

Nineteen additional serious adverse events were reported worldwide, three cancers (melanoma, ovarian and thyroid carcinoma). Three deep venous thrombosis without concomitant ovarian hyperstimulation, two of occurring in the second month of pregnancy after gonadotropin treatment. One patient had a pulmonary embolism a month following an in vitro fertilization cycle using gonadotropin therapy. (See Appendix 1 – Table 3)

This worldwide experience tabulation of drug related serious adverse events are consistent with use of similar gonadotropins for infertility therapy.

D. Literature Review

See the NDA 20-582 and 21-273 for the original medical officer reviews. Additional recent references obtained from a literature search of PubMed and are listed as (Appendix 1- B. Reference List). In addition a list of references for this review are listed as (Appendix 2 – A. Published Reference List For the Review)

V. Clinical Review Methods

A. How the Review was Conducted

This review was conducted from the single supportive clinical trial report and the additional clinical information contained in an amendment submitted by the sponsor.

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B. Overview of Materials Consulted in Review

This application was submitted in paper only. The protocol was originally submitted to IND 54,981. This review also contains excerpts from the original medical officer's review dated March 18, 1997, and the medical officer's review of a safety update from May 14, 1997. Additional volumes reviewed included a clinical protocol [REDACTED] submitted with NDA 21-273 submitted July 24, 2000. An additional submission (NDA 21-273 -000-AZ) dated October 18, 2002 was also included in this review and a review of the published literature to date.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

This material has been previously reviewed (see Medical Officer Reviews for NDA 20-582 and 21-273) and the Division. The appropriate DSI audits during NDA 21-273 did uncover some issues with one of the clinical sites. However, it was felt for the purposes of review that the violations did not warrant exclusion of the data from the site for the purposes of demonstrating bioequivalence.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The quality of the informed consent cannot be evaluated, as an informed consent document was not submitted for the supportive clinical trial.

E. Evaluation of Financial Disclosure

The financial disclosure statements (FDA 3454) for Follistim®-AQ liquid were reviewed previously (see Medical Officer Review NDA 21-273) and found to be acceptable.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Based on bioequivalence of Follistim®-AQ liquid formulation to Follistim® lyophilized cake formulation-SRS, it is this reviewer's opinion, Follistim®-AQ liquid formulation should be clinically equivalent in effect to the original Follistim®-AQ lyophilized cake formulation-SRS. The conclusion of clinical equivalence of Follistim®-AQ liquid formulation to Follistim® lyophilized cake formulation-SRS was also supported by the previous Medical Officer's Review (dated May 14, 2001)

B. General Approach to Review of the Efficacy of the Drug

Efficacy was claimed based on bioequivalence of Follistim®-AQ liquid formulation to Follistim® lyophilized cake formulation-SRS.

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Protocol [REDACTED] (NDA 21-273) was previously reviewed and is supportive of the indication of induction of ovulation in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

The second proposed indication is development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. No clinical study is submitted to support the second labeling claim. None is required since the new drug application is based on the demonstration of bioequivalence.

C. Detailed Review of Trials by Indication

The supportive clinical trial (Protocol [REDACTED]) was from a single clinical study conducted by the applicant entitled, "An Open-Label, Randomized, Group-Comparative, Multicenter Study to Assess the Efficacy and Safety of a Follistim® Solution Formulation Compared to a Freeze-Dried Cake Formulation, both administered Subcutaneously for the Indication of Ovulation in Clomiphene-Resistant Subjects with Chronic Anovulation (WHO Group II)".

This protocol is supportive of one of the labeling claims, induction of ovulation in anovulatory patients. The intent to treat group included 126 subjects who were randomized (64 in the Follistim® lyophilized cake formulation-SRS and 62 in the Follistim®-AQ liquid formulation) and completed the study, 123 were considered per protocol. The duration of the clinical trial was one treatment cycle (a total of 21 days maximum). The trial period was between September 1998 through September 1999.

Baseline characteristics also demonstrated differences, in parity and duration of infertility, between the two treatment arms (Follistim® lyophilized cake formulation-SRS compared to Follistim®-AQ liquid formulation). Subjects in the Follistim®-AQ liquid formulation group had a higher incidence of parity (16 subject; 25.8%) as compared to subjects in the Follistim® lyophilized cake formulation-SRS (7 subjects; 10.9%). The duration of infertility was higher in the Follistim® cake formulation-SRS group (47.9 months \pm 34.9) than in the Follistim®-AQ liquid formulation arm (31.1 months \pm 22).

The sponsor reported the primary efficacy parameter for this study as the ovulation rate. The ovulation rate was calculated as the number of subjects that experienced confirmed ovulation. Ovulation was defined as when one of two serum progesterone measurements done approximately five to ten days after human chorionic gonadotropin injection was at least 5 ng/mL. However, if this definition of ovulation was not met, but the subject later became pregnant, or had an ectopic pregnancy or miscarriage after proof of a viable fetus, ovulation was considered confirmed. No statistically significant difference was seen between Follistim® preparations for the primary efficacy parameter of overall ovulation.

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The overall ovulation rate was 82.8% for the subjects in the Intend-to Treat (ITT) Follistim® lyophilized cake formulation-SRS group and 90.3% for the subjects in the Follistim®-AQ liquid treatment group. This reviewer concurs with the previous medical officer's review that the difference between the two treatment groups was not statistically significant. (p value = 0.179) In the per protocol group, the ovulation rate was based on serum progesterone levels, and there was no statistical difference between the treatment groups.

The sponsor also described two secondary efficacy parameters: 1) Ongoing pregnancy rate and 2) Follistim® exposure (amount and duration of treatment for subjects prior to ovulation). Ongoing pregnancy rates were almost identical in both Intent to Treat Groups (17.2% in the Follistim® lyophilized cake formulation-SRS, and 17.7% in the Follistim®-AQ liquid formulation). The difference between the two treatment groups was not statistically significant. (p value = 0.934)

Follistim® exposure was sub-divided into two separate parameters: 1) Mean total amount of Follistim® administered during the treatment cycle (International Units) and 2) Duration of treatment (mean days of treatment). The mean total amount of Follistim® lyophilized cake formulation administered was 1,200.0 International Units compared to 818.2 International Units for the Follistim®-AQ liquid formulation. This difference in mean total amount of International Units was statistically significant. (p=0.006).

For the second sub-divided parameter, the mean duration of Follistim® treatment was 12 days for the subjects in the Follistim® lyophilized cake formulation-SRS compared to 9.1 days for the Follistim®-AQ liquid formulation. The difference in mean duration of Follistim® treatment was also statistically significant. (p=0.0003) The statistical differences in Follistim® exposure must be interpreted with caution as this clinical data is derived from a small, supportive clinical trial (Protocol ██████). In the protocol it was stated that 150 subjects were to be randomized in a 1:1 ratio (suggesting 75 in each arm). The actual number of subjects that completed the trial was only 126.

Reviewer's comment: The study is open-label and this may introduce bias into the results. The differences seen in the secondary efficacy parameter for Follistim® exposure for the two pharmaceutical preparations would need to be evaluated in a larger randomized, double-blind study for the purposes of the efficacy claims.

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D. Efficacy Conclusions

This reviewer concurs with the previous reviewer's conclusion that efficacy is based primarily on the bioequivalence of Follistim®-AQ liquid formulation to the approved Follistim® lyophilized cake formulation-SRS. The sponsor conducted only a single supportive open-label clinical trial (Protocol [REDACTED]) that provided some additional patient data for one of the two proposed indications, ovulation induction. Conclusions from this clinical trial (Protocol [REDACTED]) alone does not provide substantial evidence of efficacy upon which approval could be based.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Safety of Follistim®-AQ liquid formulation was primarily derived from data acquired from the studies reviewed in NDA 20-582 for the approved Follistim® lyophilized cake formulation-SRS product. Additionally, a supportive trial (protocol [REDACTED]), and worldwide safety adverse event data were also submitted to NDA 21-273 for Follistim®-AQ liquid formulation. The safety data labeling for Follistim®-AQ liquid formulation is identical to the labeling for the original Follistim® lyophilized cake formulation-SRS.

There is no evidence of new clinical safety issues with this product since the original review of the Follistim®-AQ liquid formulation. This reviewer concurs with the previous medical reviewer that there are no major safety issues to resolve with Follistim®-AQ liquid formulation.

B. Description of Patient Exposure

The company estimates that approximately [REDACTED] of the liquid solution have been sold worldwide. In the United States, 4,426,656 IU (17%) have been distributed in the conduct of clinical trials. Ongoing or completed clinical trials using Puregon® (the trade name in Europe) include 39 completed or ongoing clinical trials (with over 2500 patients per sponsor's submission). (see Appendix 1 – A. Overview of Ongoing or Completed Clinical Trials) Patient exposure is adequate and the safety profile for Follistim®-AQ liquid formulation is well defined.

C. Methods and Specific Findings of Safety Review

The safety of this drug is based primarily on data from the studies reviewed in the original NDA (20-582) for Follistim® lyophilized cake formulation-SRS. The data for adverse events for the original approved Follistim® lyophilized cake formulation-SRS product and Follistim® -AQ liquid formulation were previously reviewed.

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(See Medical Officer's original review of Follistim® lyophilized cake formulation-SRS product (NDA 20-582) dated and Medical Officer's original review of 21-273 dated May 21, 2001.

In the supportive clinical trial (protocol **██████████**), there was no significant difference in the percentage of subjects that had at least one adverse event during the trial (50% in the Follistim® lyophilized cake formulation-SRS product and 54.8% in the Follistim®-AQ liquid formulation) (see Appendix 1 – Table 1) Adverse events that occurred in both groups in greater than 5% of patients (by system-organ class) in both treatment groups were abdominal pain and cramping, headache, nausea and back pain.(see Appendix 1 – Table 1)

The incidence of three of the adverse events (abdominal pain, abdominal cramping and nausea) appears to be slightly greater in the Follistim®-AQ liquid formulation group. The sponsor noted the increased incidence of these adverse events, but did not believe the difference was significant. The difference in adverse outcomes between the treatment arms does not appear to be clinically significant for two reasons. There were no significant concomitant differences in biochemistry parameters, hematology parameters or vital signs between the two treatment arms.

Additionally, differences in adverse events between the groups did not prevent any subject from completing their treatment cycle. Therefore, these differences in adverse events did not significantly impact patient treatment or outcome measures.

Serious adverse events in protocol **██████████** were also more frequent in the Follistim®-AQ liquid formulation group (six subjects) compared to the original Follistim® lyophilized cake formulation-SRS group (no subjects). There were two cases of ectopic pregnancy, and one case of fetal demise that were unlikely to be related to the treatment.

Two cases of lower abdominal pain (one related to an ovarian cyst) and one case of ovarian hyperstimulation were reported in the Follistim®-AQ liquid formulation treatment arm. Although all six serious adverse events occurred in the Follistim®-AQ liquid formulation treatment arm, the events cannot be used to determine statistical significance because of the small number of total events. No patient deaths or thromboembolic events were reported in the supportive study.

A major concern with gonadotropins is the risk of ovarian hyperstimulation. Ovarian Hyperstimulation was reported to occur in one patient (1.6%) in the Follistim® lyophilized cake formulation-SRS group and three (4.8%) patients in the Follistim®-AQ liquid formulation group.

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One subject with ovarian hyperstimulation was also reported as a serious adverse event, however that patient (0417) was also pregnant with quintuplets. Concerns of possible ovarian hyperstimulation led to early discontinuation of the clinical trial in fourteen patients, eight in the cake formulation and six in the solution formulation.

Reviewer's comment: The risk and occurrence of ovarian hyperstimulation appear similar between the two treatment arms in this small trial from a clinical perspective. A second important consideration is that the sponsor's reported risk of ovarian hyperstimulation for Follistim®-AQ liquid formulation does not appear to be different from published reports of similar gonadotropins.^{1,2} (see Appendix 1 – Table 1)

D. Adequacy of Safety Testing

Safety data has been collected since 1997 when the original formulation of Follistim® lyophilized cake formulation-SRS was approved and in Europe since 1999 when the liquid formulation was introduced. Patient exposure is adequate, and the safety profile is well defined.

E. Summary of Critical Safety Findings and Limitations of Data

The current adverse event data from the sponsor is included in the supplement to NDA 21-273 (submitted October 17, 2002). No deaths were reported by the sponsor during the clinical trials, two deaths have been reported in the worldwide clinical experience. The adverse event data (other than the experiences listed above) are not significantly different from the other published studies. The worldwide safety experience does not appear to demonstrate any new trends or safety issues and supports the approval of this product.

VIII. Dosing, Regimen, and Administration Issues

The dosing and regimen will be identical to that for the original Follistim® lyophilized cake formulation-SRS. This is acceptable based on bioequivalence. The dosing regimen utilized in protocol [REDACTED] differs from that recommended in the approved labeling in that protocol [REDACTED], the dosage could be increased by 75 IU every 7 days (Days 8 and/or 15) if there were no evidence of an ovarian response. The approved labeling for the approved Follistim® lyophilized cake formulation –SRS (based on extensive clinical grounds) recommends that the dosage not be increased for the first 14 days and then, if needed, increased in increments of 37.5 IU.

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IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Follistim®-AQ liquid formulation is being approved for conditions that occur only in women.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Clinical studies of Follistim® lyophilized cake formulation-SRS and Follistim®-AQ liquid formulation did not include patients aged 65 and over. Follistim® lyophilized cake formulation and Follistim®-AQ liquid formulation are contraindicated in pregnancy.

C. Evaluation of Pediatric Program

Follistim®-AQ liquid formulation is not indicated for use in pediatric populations and safety and efficacy in such patients have not been established.

X. Conclusions and Recommendations

A. Conclusions

Follistim®-AQ liquid formulation differs from the original formulation in pharmaceutical presentation only. This review concurs with the previous Medical Officer review (May 14, 2001) that the benefits of taking this drug outweigh the risks.

B. Recommendations

Approval of this application is recommended pending resolution of outstanding chemistry and manufacturing issues.

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Appendix 1

Table 1: (Protocol ██████████ / Sponsor's Table 28 - Number (Percentage) of serious adverse events

Table 28 **Number and Percentage of Subjects with at Least One Treatment Emergent Adverse Event by WHO System-Organ Class and WHO Preferred Term by Treatment Group and Relationship to Study Drug (All-Subjects-Treated Group)**

WHO System-organ Class WHO Preferred Term	Follistim® Freeze-dried Cake Formulation (N=64)				Follistim® Solution Formulation (N=62)			
	All		Drug Related ^a		All		Drug Related ^d	
	n	%	n	%	n	%	n	%
Reproductive Disorders, Female	15	(23.4%)	7	(10.9%)	16	(25.8%)	10	(16.1%)
Abdominal Pain (Gynaecological)	8	(12.5%)	5	(7.8%)	11	(17.7%)	7	(11.3%)
Cramp Abdominal (Gynaecological)	2	(3.1%)	0		5	(8.1%)	2	(3.2%)
Ovarian Hyperstimulation Syndrome	1	(1.6%)	1	(1.6%)	3	(4.8%)	2	(3.2%)
Vaginal Bleeding	2	(3.1%)	1	(1.6%)	3	(4.8%)	1	(1.6%)
Ovarian Disorder	1	(1.6%)	1	(1.6%)	2	(3.2%)	2	(3.2%)
Dysmenorrhoea	2	(3.1%)	0		1	(1.6%)	1	(1.6%)
Menstrual Disorder	1	(1.6%)	0		1	(1.6%)	0	
Pregnancy Ectopic	0		0		2	(3.2%)	0	
Breast Pain Female	1	(1.6%)	0		0		0	
Leukorrhoea	0		0		1	(1.6%)	0	
Uterine Disorder Nos	1	(1.6%)	0		0		0	
Vaginitis	1	(1.6%)	0		0		0	
Centr & Periph Nervous System Disorders	8	(12.5%)	4	(6.3%)	8	(12.9%)	0	
Headache	8	(12.5%)	4	(6.3%)	7	(11.3%)	0	
Migraine	0		0		1	(1.6%)	0	
Gastro-Intestinal System Disorders	3	(4.7%)	0		9	(14.5%)	4	(6.5%)
Nausea	1	(1.6%)	0		9	(14.5%)	3	(4.8%)
Constipation	0		0		1	(1.6%)	1	(1.6%)
Vomiting	1	(1.6%)	0		1	(1.6%)	0	
Dyspepsia	1	(1.6%)	0		0		0	
Body As A Whole - General Disorders	8	(12.5%)	0		3	(4.8%)	1	(1.6%)
Back Pain	4	(6.3%)	0		1	(1.6%)	0	
Fever	0		0		1	(1.6%)	1	(1.6%)
Influenza-Like Symptoms	2	(3.1%)	0		0		0	
Fatigue	0		0		1	(1.6%)	0	
Leg Pain	1	(1.6%)	0		0		0	
Scar	1	(1.6%)	0		0		0	
Urinary System Disorders	3	(4.7%)	0		4	(6.5%)	2	(3.2%)
Micturition Frequency	1	(1.6%)	0		2	(3.2%)	1	(1.6%)
Dysuria	1	(1.6%)	0		1	(1.6%)	0	
Urinary Tract Infection	2	(3.1%)	0		0		0	
Urine Abnormal	0		0		1	(1.6%)	1	(1.6%)
Foetal Disorders	2	(3.1%)	0		4	(6.5%)	1	(1.6%)
Death Foetal	2	(3.1%)	0		2	(3.2%)	0	
Abortion	0		0		2	(3.2%)	1	(1.6%)
Abortion Missed	0		0		1	(1.6%)	0	
Respiratory System Disorders	2	(3.1%)	0		4	(6.5%)	0	
Upper Resp Tract Infection	0		0		3	(4.8%)	0	
Coughing	1	(1.6%)	0		1	(1.6%)	0	
Sinusitis	1	(1.6%)	0		1	(1.6%)	0	
Neoplasm	2	(3.1%)	0		2	(3.2%)	1	(1.6%)
Ovarian Cyst	2	(3.1%)	0		2	(3.2%)	1	(1.6%)
Resistance Mechanism Disorders	1	(1.6%)	0		2	(3.2%)	0	
Monilliasis Genital	0		0		2	(3.2%)	0	
Herpes Simplex	1	(1.6%)	0		0		0	

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Table 2: Sponsor's submitted Appendix 6 – Serious adverse events by WHO system class for worldwide update

Table 4: Number of (S)AEs per WHO system organ class (AP)

WHO system organ class	No. of (S)AEs
Skin and appendages disorders	22
Musculo-skeletal system disorders	8
Central & peripheral nervous system disorders	23
Autonomic nervous system disorders	1
Vision disorders	6
Hearing and vestibular disorders	2
Special senses other, disorders	1
Psychiatric disorders	15
Gastro-intestinal disorders	14
Liver and biliary system disorders	3
Metabolic and nutritional disorders	1
Endocrine disorders	1
Cardiovascular disorders, general	1
Heart rate and rhythm disorders	1
Vascular (extracardiac) disorders	4
Respiratory system disorders	11
Platelet, bleeding & clotting disorders	4
Reproductive disorders, female	29
Foetal disorders	6
Neoplasms	3
Body as a whole - general disorders	84
Application site disorders	66
Resistance mechanism disorders	2
Total	308

Table 3: Sponsor's submitted Appendix 6 – WHO serious adverse events by class for worldwide update

WHO system organ class (S)AE	<PP	PP	AP	TP
Vascular (extracardiac) disorders				
Thrombophlebitis deep			2	2
Thrombophlebitis pelvic vein			1	1
Thrombophlebitis vena cava			1	1
Platelet, bleeding & clotting disorders				
Embolism pulmonary			1	1
Reproductive disorders, female				
Ovarian disorder			1	1
Ovarian hyperstimulation syndrome			5	5
Pregnancy ectopic			2	2
*** Total ***			13	13

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A. Overview of Clinical Trials

OVERVIEW OF ONGOING OR COMPLETED CLINICAL TRIALS

Protocol	Study description	Study design	No. of subjects -planned -enrolled total	Ongoing/completed	Treatment and dose	Duration of treatment
	Efficacy and safety of two treatment schemes using Puregon in subjects with anovulatory infertility	Open-label, randomized, group-comparative, multi-center	50 57	Completed	First 7 days 50 IU, in case of insufficient follicular growth, the dose increases with 25 IU. First 7 days 50 IU, in case of insufficient follicular growth, the dose increases with 50 IU.	1 cycle
	Efficacy and safety of ovulation induction treatment schemes using Puregon and Fertinorm-P in subjects with WHO group II anovulatory infertility.	Open-label, randomized, group-comparative, multi-center trial	100 108 (53 on Puregon)	Completed	Puregon: First 7 days 50 IU, in case of insufficient follicular growth, the dose increases with 50 IU. Fertinorm-P First 7 days 75 IU, in case of insufficient follicular growth, the dose increases with 75 IU. 225 IU Puregon twice-weekly SC 150 IU Puregon three times a week SC	1 cycle
	Efficacy and safety study of Puregon in hypogonadotropic hypogonadal male subjects	Open-label, multi-center	60 49	Completed	Puregon: 150 IU/day SC Gonad-F: 150 IU/day SC	48 weeks (Puregon treatment phase) Seven days
	Pharmacodynamic and pharmacokinetic properties of Puregon and Gonad-F in healthy female volunteers	Randomised, double-blind, single-center	40 study completers (20 per group)	Completed	Org 32489 Group 1: 75 IU SC Group 2: 150 IU SC Group 3: 225 IU SC Group 4: 150 IU IM	Seven days
	Study to assess the dose-proportionality of subcutaneously administered Org 32489 and to compare the pharmacokinetics of Org 32489 administered by subcutaneous and intramuscular routes in healthy female volunteers.	Open, group-comparative, randomized, multiple-dose	48 48	Completed	150 IU SC injector pen 150 IU syringe with dissolved cake	single dose
	Efficacy and efficiency of Puregon versus Metrodin in pituitary suppressed infertile women undergoing IVF and ET	Randomized, open-label, multi-center	80 25	Completed	Group 1: 150 IU Puregon, fixed dose Group 2: 150 IU Metrodin fixed dose	1 IVF cycle
	Study to assess the relative bio-availability of Org 23489 solution for injection, given	Open-label, single dose, randomized,	48 24	Completed	150 IU	56 days

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Protocol	Study description	Study design	No. of subjects -planned -enrolled total	Ongoing/completed	Treatment and dose	Duration of treatment
	subcutaneously by a needle injection and a needle-free injection via J-TIP in healthy young female volunteers	two-way cross-over				
	Efficacy and efficiency study of a fixed daily dose treatment regimen of 100 or 200 IU of Puregon in IVF	Randomised, double-blind, multi centre	180 159	Completed	Group 1: 100 IU fixed dose Group 2: 200 IU fixed dose	1 IVF cycle
	Efficacy and efficiency study of 50 IU ampoules of Puregon compared with 75 IU ampoules of Meitrodin HP in a fixed dose treatment regimen in IVF	Randomised, open-label, multi centre	150 169	Completed	Group 1: 150 IU Puregon, fixed dose Group 2: 225 IU Meitrodin HP fixed dose	1 IVF cycle
	Study on the influence of age on the efficacy and efficiency of a fixed treatment regimen of 150 or 250 IU of Puregon in subjects between 30 and 39 years of age in IVF	Randomized, double-blind, multi center	240 141	Completed	Group 1: 150 IU fixed dose Group 2: 250 IU fixed dose	1 IVF cycle
	Study to compare local tolerance, convenience, efficacy and efficiency of Puregon solution in vials with Puregon lyospheres in ampoules in women undergoing COH	Randomized, open group-comparative, multi-center	240 186	Completed	Group 1: 150 IU solution Group 2: 150 IU lyosphere	1 or 2 cycles
	Efficacy of IVF vs ICSI in non-male factor infertility, in pituitary suppressed women	Randomized, open-label, group-comparative, multi-center	230 105	Completed	Group 1: 150 IU Group 2: 50 IU	1 IVF cycle
	Efficacy and efficiency of a fixed daily dose in pituitary-suppressed women undergoing COH and ICSI	Randomized, double-blind, multi-center, group-comparative	200 179	Completed	Group 1: 100 IU fixed dose Group 2: 200 IU fixed dose	1 IVF cycle
	Efficacy anovulation study in PCO women	Randomized, open-label, multi-center	154 86	Completed	Group 1: step up 50 IU Group 2: step down 100 IU	3 OI cycles
	Use of 50 IU and 100 IU in subjects treated for IVF, compassionate use	Open-label	No restrictions	Completed	100 IU Puregon SC for the first four days, thereafter patient-individualised	1 IVF cycle
	Use of 50 IU and 100 IU in subjects treated for IVF, compassionate use	Open-label	No restrictions	Completed	100 IU Puregon SC for the first four days, thereafter patient-individualised	1 IVF cycle
	Subjects treated for OI, compassionate use	Single centre	No restrictions 0	Completed	OI: 50 IU for the first 7 days, thereafter patient individualised	1 cycle
	Randomised, group-comparative, assessor-blind study with 100 IU or 200 IU Puregon in pituitary suppressed infertile subjects undergoing COH	Randomized, group-comparative, assessor-blind, multi-center	200 180	Completed	4 days 100 IU or 200 IU adjusted thereafter	1 cycle

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Protocol	Study description	Study design	No. of subjects -planned -enrolled total	Ongoing/completed	Treatment and dose	Duration of treatment
	Study to investigate the efficacy and efficiency of a "conventional" versus low-dose step-up protocol using a 50 IU starting dose of Puregon in subjects with WHO group II anovulatory infertility.	Randomized, open, group-comparative, multi-center	175 98	Completed	Group 1: 50 IU for 5 days, if needed, dose is increased with 50 IU per 5 days. Group 2: 50 IU for 2 weeks, if needed, dose is increased with 50 IU per week	1 OI cycle
	Study to investigate the efficacy and efficiency of a fixed daily dose treatment regimen of 100 IU or 200 IU of Puregon in pituitary suppressed infertile subject undergoing COH	Randomized, group-comparative, double-blind, single-center	60 60	Completed	100 vs 200 IU	1 IVF cycle
	Efficacy and efficiency of Puregon treatment in a fixed daily dose regimen of 100 IU vs 200 IU in pituitary-suppressed infertile Asian women undergoing COH.	Randomized, group-comparative, double-blind, multi-center	320 155	Completed	Fixed daily dose 100 IU or 200 IU until at least 3 follicles \geq 17 mm	1 cycle
	Efficacy and efficiency of a fixed daily dose of Puregon of 150 IU vs 250 IU in relation to age in pituitary-suppressed infertile women between 30 and 39 years of age undergoing COH.	Randomized, group-comparative, double-blind, multi-center	477 302	Completed	Fixed daily dose 150 IU or 250 IU until at least 2 follicles \geq 20 mm	1 cycle
	Efficacy and efficiency of 100 IU starting dose of Puregon in pituitary suppressed infertile subjects undergoing controlled ovarian hyperstimulation		35 30		Starting dose 100 IU	1 cycle
	Study to compare the local tolerance of subcutaneous injection of Puregon solution for injection and Gonat-F	Randomized, double-blind, cross-over	60 60	Completed	150 IU Puregon/150 IU Gonat-F 150 IU Gonat-F/150 IU Puregon	single dose during each treatment sequence
	Efficacy and efficiency of two treatment schemes using a 50 IU starting dose of recombinant FSH using the Puregon pen in subjects with WHO group II anovulatory infertility.	Open-label, randomized, group-comparative, multi-center	200 161	Completed	<ul style="list-style-type: none"> First seven days 50 IU, in case of insufficient follicular growth, the dose increases with 25 IU First seven days 50 IU, in case of insufficient follicular growth, the dose increases with 50 IU 	Maximum 35 days

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Protocol	Study description	Study design	No. of subjects -planned -enrolled total	Ongoing/completed	Treatment and dose	Duration of treatment
	ovarian hyperstimulation for IVF or ICSI.					
	Compare local tolerance of two SC injections with recombinant FSH: Puregon Pen and Gonal-F.	Randomized, double-blind, cross-over, single center	60 60	Completed	follicular growth as assessed by ultrasonography (USS). 150 IU Puregon/150 IU Gonal-F 150 IU Gonal-F/150 IU Puregon	Single dose during each treatment sequence
	Efficacy and safety study of a low dose of Puregon in ovulation induction (Japanese Phase II trial)	Open, multi-center, joint controlled	40 17	Completed	25 IU Puregon IM for the first 14 days, thereafter adapted according to response. 50 IU Puregon IM for the first 14 days, thereafter adapted according to response.	2 OI cycles
	Efficacy and safety study of Puregon compared with Humegon in ovulation induction in patients with second grade amenorrhoea (Japanese Phase III trial)	Randomized, double-blind	105 38	Completed	Group 1: 100 IU Puregon IM Group 2: 75 IU Humegon IM Fixed dose for first 2 weeks, thereafter dose may be doubled	1 OI cycle
	Study to assess the efficacy and safety of infertile Japanese women undergoing in vitro fertilization and embryo transfer	Open-label, multi-center (5 centers)	150 156	Completed	150 IU or 225 IU daily for the first 4 days, dose adjusted to individual response	1 IVF cycle
	Study to assess the efficacy and safety of a Puregon solution formulation compared to a freeze-dried cake formulation, both administered subcutaneously for the induction of ovulation in Clomiphene resistant subjects with chronic anovulation (WHO group II)	Open-label, randomized, group-comparative multi-center	150 126	Completed	Day 1-7: 75 IU / day SC Day 8-14: 150 IU / day SC Day 15-21: 225 IU / day SC	1 OI cycle
	Pilot study to compare single subcutaneous administration of Puregon and oral clomiphene citrate as treatment for anovulation in chronic anovulatory infertile women.	Randomized, open, cross-over, single-center	40 14	Completed	Seq 1: Clomiphene 50mg/day po for 5 days, followed by Puregon 300IU sc, once Seq 2: Puregon 300IU sc, once followed by Clomiphene 50mg/day po for 5 days	single dose

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Protocol	Study description	Study design	No. of subjects -planned -enrolled total	Ongoing/completed	Treatment and dose	Duration of treatment
	Study to investigate the effects of recFSH (Puregon) and uFSH (Fertinex) on oocyte and embryo quality	Assessor-blind, randomized, group-comparative, single-center	20 3	Completed	Puregon: 75 IU FSH bioactivity Lupron: 2.8 ml Fertinex: 75 IU FSH activity Pregnyl (hCG): 10000 USP of hCG Not applicable	
	Pregnancy and delivery follow-up of Protocol nr. 058-004	Open-label, randomized, group-comparative multi-center	25 25	Completed	Not applicable	Not applicable
	Tolerance, safety, kinetics and dynamics after single and multiple dose IM injection	Open, multi-center	Enrolled: Single dose: 5 Multi dose: 4	Completed	Single dose: 300 IU Multiple dose (for 7 days): 75/150/225 IU	Multiple dose 7 days
	Efficacy, safety and optimum dose in patients with hypothalamic and pituitary amenorrhea.	Open, multi-center		Completed	50/75/100/150 IU for 14 days, thereafter adapted according to response	1 OI Cycle

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Clinical Review Section

B. Reference List: Current Published Clinical Trials from 2000-2003:

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B. Reference List: Current Published Clinical Trials from 2000-2003 (continued):

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Appendix 2

A. Published Reference List For the Review:

1. Devigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 2002; 8(6):559-77.
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/s/

Audrey Gassman
7/16/03 04:22:14 PM
MEDICAL OFFICER

Shelley Slaughter
7/16/03 04:32:41 PM
MEDICAL OFFICER
I concur.

Medical Officer's Safety Review

NDA: 21273
Reference NDA: 20582
Drug Name: Follistim® -AQ (Follitropin beta for injection)
Sponsor: Organon, Inc.
Indications: 1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation in the anovulatory, infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure

**Dosage/Form/
Strength:** Sterile aqueous solution for subcutaneous or intramuscular injection: each vial contains 75IU, 150IU, ██████████ FSH per 0.5ml.

Original Submission Date: July 21, 2000
Original Review Completed: May 14, 2001
Date of Request: December 23, 2002
Date Completed: January 29, 2003

Background

This review is to reexamine the clinical safety information presented in NDA 21273 for Follistim®-AQ. This data was submitted July 21, 2000. Because of outstanding chemistry, manufacturing and control deficiencies (CMC), the NDA received an Approvable action on May 24, 2001. Follistim® -AQ is a new presentation (liquid formulation) of Follistim® (NDA 20582). The current Follistim® product is a lyophilized powder cake administered after reconstitution with water for injection.

NDA 20-582 for Follistim® was approved by the Agency on September 29, 1997 for the indications of development of multiple follicles (controlled ovarian stimulation) in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

Previous clinical information:

Clinical trials (37603, 37604, 37608, 37609, 37611, 37613, and 37617) were submitted in the final NDA to demonstrate efficacy and safety of Follistim®. Follistim® was demonstrated to be non-inferior in efficacy compared to Metrodin® (Protocols ██████████). The incidence of adverse events was similar when compared to a Metrodin® treatment group, although the rate of Ovarian Hyperstimulation Syndrome was slightly higher in the Follistim® group.

Study 37613 was unique in that it has primary objective of safety and local tolerance. In this study, 218 subjects treated with Follistim® were evaluated, including 118 patients with subcutaneous injection and 77 with intramuscular injection. The incidence of markedly abnormal laboratory values also was not different between subcutaneous and intramuscular injection groups. In both treatment groups, a decreased value was found for total protein, hemoglobin, hematocrit and lymphocytes. Upward shifts for leukocytes and neutrophils were found in greater than 10% of both groups. This data demonstrated no clinically relevant difference in the safety parameters between IM and SC administration of the Follistim® treatment. Further, there was no clinically relevant difference in efficacy.

Follistim -AQ liquid background:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) determined that the human pharmacokinetics and biopharmaceutics section of NDA 21-273 for the new formulation, Follistim® -AQ was acceptable to support approval. The Office of Compliance issued a "Withhold:" recommendation on October 30, 2002 following a WARNING LETTER issued on September 19, 2000 by the New Jersey

Follistim –AQ liquid background (continued):

District after inspection of the West Orange, NJ manufacturing plant between July 17 and August 23, 2000. Because of this recommendation and other outstanding CMC deficiencies, NDA 21-273 received an Approvable action.

Trial design and objectives:

Protocol [REDACTED] was submitted as supportive to the bioequivalence study for consideration of approvability. This data comes from a single clinical study conducted by the applicant. The clinical trial was titled “An Open-Label Randomized, Group-Comparative, Multicenter Study to Assess the Efficacy and Safety of a Follistim® Solution Formulation Compared to a Freeze-Dried Cake Formulation, both Administered Subcutaneously for the Induction in Clomiphene-Resistant Subjects with Chronic Anovulation (WHO Group II). This clinical trial was identified as protocol [REDACTED] and recruited 126 patients that were randomized to either Follistim® AQ (liquid formulation) or to Follistim® (cake formulation) and treated. This clinical trial was designed to give information on the safety, efficacy and local tolerance of Follistim® when administered subcutaneously as a solution formulation and in the cake formulation.

Overall adverse events:

Twenty-two patients had early discontinuation in the trial, thirteen in the cake formulation group and nine in the solution group. No deaths were noted during the study. Overall, there were six subjects that had seven serious adverse events. Six of these serious adverse events occurred in the Follistim® AQ arm: two ectopic pregnancies, two cases of abdominal pain (one patient was reported to have an ovarian cyst), one fetal demise, one ovarian hyperstimulation. No serious adverse events of pelvic inflammatory disease, endometritis or cellulitis were documented using either formulation. Eighteen total adverse events were reported, six in the cake formulation and twelve in the solution formulation. Both serious adverse events and total adverse events were higher in the Follistim® solution group.

The adverse events that occurred in greater than 5% of patients in both treatment groups were abdominal pain and cramping, headache, nausea and back pain. These overall adverse event incidences are similar to other fertility medication used for this indication such as Repronex® SC¹ (Table 1). The exception to these similarities was gastrointestinal disorders. Nausea was seen in nine patients in the Follistim® solution group and only one patient in the Follistim® cake formulation group. This adverse event, nausea, is higher in the solution group than in other published studies of similar fertility medications² (Table 2). All subjects recovered without further adverse events.

Ovarian hyperstimulation:

Ovarian Hyperstimulation was reported to occur in one patient (1.6%) in the Follistim® cake formulation and three (4.8%) patients in the Follistim® Solution Formulation. Early discontinuation of the clinical trial occurred in fourteen patients, eight in the cake formulation and six in the solution formulation for concern of ovarian hyperstimulation. The Follistim® preparations do not appear to demonstrate a clinically significant different in risk or occurrence of ovarian hyperstimulation. The risk of ovarian hyperstimulation does not appear to be different from other published studies looking at the number of ovarian hyperstimulation cases secondary to fertility treatment.^{1,2}

Laboratory safety data: Hematology

Laboratory safety data for protocol [REDACTED] contained nineteen cases with at least one clinically significant abnormal value. Nine subjects had hematologic abnormalities using the cake formulation (14%) and four subjects in the solution group had similar abnormalities (8%). These trends are similar to data derived from the original safety trials, although original trial data for Follistim® reported observing an upward trend of

Laboratory safety data: Hematology (continued)

leukocytes in study patients. The most common abnormal hematologic abnormality documented in this clinical trial was a decreased value of lymphocytes (Sponsor submitted table 29). This abnormality is not statistically different between treatment groups: five patients in the cake formulation (7.8%) versus three patients in the solution formulation (4.8%) (Table 29). The number of subjects with significantly abnormal hematology laboratory values was similar for both Follistim® cake and Follistim® solution in terms of hemoglobin, hematocrit, white blood cells count and lymphocytes. The summary statistics of the three red blood cell parameters (hemoglobin, hematocrit, and red blood cell count) showed very slight decreases in the parameters from baseline to last assessment. These parameter shifts were not considered clinically significant (less than 3% change from baseline). Red blood cell parameter decreases have been documented in previous trials using Follistim® products, and do not appear to be clinically significant. No other trends of hematology parameters were noted in or between treatment groups.

Laboratory safety data: Chemistry

Blood chemistry was drawn at baseline, day of hCG injection, and day of last assessment. No statistically significant differences in biochemistry parameters were noted when comparing Follistim® cake and Follistim® solution groups. Thirty-eight cases of abnormal laboratory values were documented: ten subjects in the cake formulation (15%) and eighteen subjects in the solution formulation (29%). The most common abnormal values reported were abnormalities in total cholesterol and bicarbonate (Sponsor submitted table 30). Adverse changes in bicarbonate and cholesterol values were noted as significant events in both formulation groups. Bicarbonate level abnormalities occurred at a similar incidence in both groups, and total cholesterol values appeared to decrease in select patients treated using Follistim®. In comparing treatment groups, however, the solution formulation had a higher incidence of appreciably different cholesterol levels during the clinical trial (Table 30).

Two patients in the Follistim® AQ solution group had laboratory results that were considered significant. One patient had elevated ALT levels documented at screening visit that became significantly increased after treatment (293 U/L). A second patient had a mild elevation of ALT level during the trial which was 1.5 x the upper limit of normal (93 U/L). Both patients completed their treatments without otherwise noted complications. The comparisons of AST and ALT parameters were not statistically different between treatment groups (three patients having abnormal ALT levels after treatment in each group). There were no significant differences between the treatment groups in urinalysis abnormalities.

Other safety issues:

- Vital signs (blood pressure, heart rate, body weight and temperature) were similar between the treatment groups at baseline and remained unchanged through the study. Three patients in the Follistim® solution group did report > 10% weight gain, although the sponsor did not consider this data statistically significant.
- Local responses of the patients in each treatment group. The symptoms were categorized into bruising, pain, redness, swelling, itching and overall. The differences in tolerance of the solution formulation and the cake formulation were not statistically significant. Local tolerance symptoms were classified into a pain scale in this clinical trial. The use of a pain scale causes difficulty in comparing this data to other published studies. Severe pain and a significant overall reaction were noted in three patients (4.9%) in the Follistim® solution group. The local reactions are comparable to the European and Israeli study group. This trial demonstrated that approximately 3% of patients using recombinant FSH experienced significant inflammation and pain at the injection site². Although the sponsor's data documented a significant number of patients in the Follistim® solution group had a reaction to injection (70%), a majority of these reactions were mild (54%) (Table 33).

Study efficacy:

Efficacy data in the study showed no statistically significant difference in pregnancy rate between liquid and cake formulations. The most significant difference between Follistim® preparations was in the difference in treatment duration (p=0003). Questions arose whether the two treatment groups had comparability with regard to demographics and baseline characteristics. The duration of infertility was statistically different between the two treatment arms. Furthermore, given the small number of subjects enrolled (n=126), the study was underpowered. The original reviewer (Dr. Bennett) commented that, "Protocol [redacted] alone, does not provide substantial evidence of safety and efficacy upon which approval could be recommended."

Conclusions:

- No evidence of an obvious clinical safety issue can be derived from this data.
- A subset of patients may demonstrate increased weight after use of Follistim® AQ solution with the mechanism of this response somewhat unclear.
- The Follistim® AQ solution group may increase nausea in a subset of patients who use the medication.
- The absolute number of patients experiencing significant ALT elevation after use of Follistim®-AQ solution was higher than the Follistim® cake group, but was not statistically significant.
- The risk of ovarian hyperstimulation was somewhat higher in the Follistim® AQ treatment group, but it is unclear if this is secondary to patient selection issues, the size of the trial, or directly related to the formulation.
- More overall serious adverse events occurred in the Follistim®-AQ arm, but it is unclear if the liquid formulation was directly responsible or if this was a result of poor trial design.
- No other significant differences in adverse events in the study using Follistim®-AQ when compared to other current published studies of fertility therapy with menopausal gonadotropins.

References:

1. Nichols J, Knochenhauer E, Fein SH, Nardi RV, Marshall DC. Subcutaneously administered Repronex® in oligoovulatory female patients undergoing ovulation induction is as effective and well tolerated as intramuscular human menopausal gonadotropin treatment. *Fertil Steril* 2001 Jul; 76(1): 58-66.
2. Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial. The European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating. *Fertil Steril* 2002 Sep; 78(3): 520-8.

Table 1: Summary of safety data for 36 patients, who received Repronex SC, 36 patients who received Repronex IM and 36 patients who received Pergonal IM¹.

Patients	Repronex SC (n = 36)	Repronex IM (n = 36)	Pergonal IM (n = 36)
With adverse events (%)	13 (36.1)	13 (36.1)	19 (52.8)
With serious adverse events ^a (%)	1 (2.8)	1 (2.8)	1 (2.8)
With most frequently reported Adverse events ^b (%)			
Headache	2 (5.6)	3 (8.3)	7 (19.4)
Ovarian enlargement ^c	4 (11.1)	2 (5.6)	4 (11.1)
Abdominal pain/cramping	6 (16.7)	4 (11.1)	5 (13.8)
OHSS ^d	3 (8.3)	1 (2.8)	3 (8.3)
Abdominal enlargement	0	3 (8.3)	3 (8.3)

^a Involved hospitalization.

Table 2: Number of patients with adverse events (possible and probably related to study drug) by body system and preferred term in the APT population.²

Symptom	HP-hMG (n = 373) n (%)	rFSH (n = 354) n (%)
Central and peripheral nervous system disorders		
Headache	14 (3.8)	10 (2.8)
Gastrointestinal system disorders		
Abdominal pain	24 (6.4)	25 (7.1)
Nausea	7 (1.9)	1 (0.3)
Enlarged abdomen	10 (2.7)	2 (0.6)
Female reproductive disorders		
Ovarian hyperstimulation	26 (7.0)	18 (5.1)
Application site disorders		
Inflammation at injection site	18 (4.8)	12 (3.4)
Pain at injection site	17 (4.6)	13 (3.7)
Reaction at injection site	5 (1.3)	3 (0.8)

Table 3: (from Sponsor Submitted Table 29)

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Table 29 Number of Subjects with at Least One Clinically Significant Abnormal Hematology Laboratory Value (All-Subjects-Treated Group)

Parameter (units)	Criterion for CSALV	Follistim® Freeze-dried Cake Formulation (N=64)		Follistim® Solution Formulation (N=62)	
		n	%	n	%
Hemoglobin (g/L)	<97 >200	3	(4.7%)	1	(1.6%)
Hematocrit (L/L)	<0.32 >0.60	2	(3.1%)	1	(1.6%)
RBC Count (x 10 ¹² /L)	<3 >6	0		0	
WBC Count (x 10 ⁹ /L)	<2.8 >16	0		0	
Basophils (%)	>6	0		0	
Eosinophils (%)	>10	1	(1.6%)	0	
Lymphocytes (%)	<15 >65	5	(7.8%)	3	(4.8%)
Monocytes (%)	>15	1	(1.6%)	0	
Neutrophils (%)	<15 >90	0		0	
Platelet Count (x 10 ⁹ /L)	<75 >700	0		0	
RBC Morphology		0		0	

Note: Information in this table was derived from Appendix G-22.

Table 4: (from Sponsor Table 30)

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Table 30 Number of Subjects with at Least One Clinically Significant Abnormal Biochemistry Laboratory Value (All-Subjects-Treated Group)

Parameter (units)	Criterion for CSALV	Follistim® Freeze-dried Cake Formulation (N=64)		Follistim® Solution Formulation (N=62)	
		n	%	n	%
Sodium (mmol/L)	<0.9 x LLN >1.1 x ULN	0		0	
Potassium (mmol/L)	<0.9 x LLN >1.1 x ULN	1	(1.6%)	0	
Chloride (mmol/L)	<0.9 x LLN >1.1 x ULN	0		0	
Bicarbonate (mEq/L)	<21 >33	4	(6.3%)	4	(6.5%)
Glucose (mmol/L)	<0.8 x LLN >1.2 x ULN	1	(1.6%)	2	(3.2%)
BUN (mmol/L)	>10.7	0		0	
Creatinine (µmol/L)	>177	0		0	
AST (SGOT) (U/L)	>3 x ULN	0		1	(1.6%)
ALT (SGPT) (U/L)	>3 x ULN	0		1	(1.6%)
Alkaline Phosphatase (U/L)	>3 x ULN	0		0	
LDH (U/L)	>3 x ULN	0		0	
Total Bilirubin (µmol/L)	>34	0		1	(1.6%)
Total Protein (g/L)	<0.8 x LLN >1.2 x ULN	0		0	
Albumin (g/L)	<25.6 >60.0	0		0	
Calcium (mmol/L)	<0.9 x LLN >1.1 x ULN	0		0	
Phosphorus (mmol/L)	<0.9 x LLN >1.1 x ULN	2	(3.1%)	1	(1.6%)
Total Cholesterol (mmol/L)	<0.8 x LLN >1.2 x ULN	5	(7.8%)	10	(16.1%)
Triglycerides (mmol/L)	>5.65	1	(1.6%)	1	(1.6%)
Uric Acid (µmol/L)	>500	1	(1.6%)	0	

LLN = lower limit of the normal range.

ULN = upper limit of the normal range.

Note: Information in this table was derived from Appendix G-22.

Table 5: (from Sponsor Table 33) Overall Local Tolerance: Number of Subjects with the Responses None, Mild, Moderate, and Severe by Symptom (All Subjects-Treated Group)

Symptom Classification	Statistic	Follistim® Freeze-Dried Cake Formulation	Follistim® Solution Solution Formulation
Pain	None	36 (56.3%)	33 (56.1%)
	Mild	18 (28.1%)	20 (32.8%)
	Moderate	9 (14.1%)	5 (8.2%)
	Severe	1 (1.6%)	3 (4.9%)
Overall	None	18 (28.1%)	18 (29.5%)
	Mild	30 (46.9%)	33 (54.1%)
	Moderate	15 (23.4%)	7 (11.5%)
	Severe	1 (1.6%)	3 (4.9%)

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/s/

Audrey Gassman
1/28/03 10:44:52 AM
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Shelley Slaughter
1/30/03 10:55:04 AM
MEDICAL OFFICER
I concur.

NDA 21-273

Re: Response to Approvable Letter

From: Gerald D. Willett MD, DRUDP

Sponsor submission date: October 17, 2002

CDER receipt date: October 18, 2002

Summary:

The sponsor's response to the approvable letter is mainly related to chemistry issues. From a clinical perspective approval was previously recommended based on an acceptable demonstration of bioequivalence. In addition to chemistry information, this submission also includes a periodic safety update detailing adverse events from other countries where the product is approved. The sponsor has also included labeling in this submission.

Recommendation:

This application is acceptable for filing from a clinical perspective.

Gerald Willett MD

12-6-02

cc: Shames D, Slaughter S

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/s/

Gerald Willett
12/6/02 10:42:13 AM
MEDICAL OFFICER

Shelley Slaughter
12/13/02 12:39:39 PM
MEDICAL OFFICER
I concur.

**Follistim®-AQ
Team Leader Review**

NDA: 21-273

Drug: Follistim®-AQ (Follitropin beta for injection)

Indication:

1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

Dosage/Form/Strength: Sterile aqueous solution for subcutaneous or intramuscular injection; each vial contains 75 IU, 150 IU, FSH per 0.5 ml.

Applicant: Organon, Inc

Original Submission Date: July 21, 2000

Primary Clinical Review Completed: May 14, 2001

Date of Memorandum: May 16, 2001

Background

NDA 20-582 for Follistim® was approved by the Agency on 9/29/97 for the indications of development of multiple follicles (controlled ovarian stimulation) in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure. Follistim® is a freeze-dried cake formulation for reconstitution with sterile water. On March 18, 1999 Organon, the Sponsor, met with the Agency in a pre-NDA guidance meeting to discuss a completed bioequivalence study of Follistim® vs. a new pharmaceutical presentation, Follistim®-AQ-Cartridge. The bioequivalence study was proposed as the basis for an NDA submission. The completed bioequivalence study compared a single dose of 150 IU of Follistim® (2-vials of 75 IU dissolved in 1 ml of diluent) administered subcutaneously with a syringe to a single dose of 150 IU of Follistim®-AQ Cartridge administered subcutaneously with a pen-injector. The results were non-equivalent; the pen injector dose had a higher bioavailability. In this BE study it was noted that the handling of the lyophilized cake during the injection process resulted in dose losses. The Sponsor was requested to provide to the Agency information regarding the comparison of dose losses in handling the cake formulation versus the solution to support accepting the solution formulation as bioequivalent to the cake formulation. This information was acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). Based on the BE study, the Sponsor made a

biowaiver request to substantiate that the increase in concentration in the proposed solution formulation of Follistim®-AQ (the subject of this NDA) does not affect the bioavailability. Because the BE study was conducted following subcutaneous administration and the solution formulation is proposed for IM as well as SC administration, the Sponsor was asked to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. No clinical trials were proposed or conducted by the Sponsor to demonstrate safety and efficacy. The Sponsor had conducted one open-label comparative study for another purpose and the Agency requested that this study be included as supporting data for the BE study.

The NDA for Follistim®-AQ was submitted on July 21, 2000 and filed on September 22, 2000. The Sponsor proposes that the ready-to-use presentation of Follistim®-AQ is more convenient and requires less handling than the approved product. Approvability of the NDA will be determined on the basis of a BE study, an in vitro study of comparative dose losses and a supportive clinical trial.

Chemistry/Manufacturing

The following summary addresses the major issues identified in the chemistry review.

The drug substance is manufactured, packaged and tested by [REDACTED]. A letter of authorization was provided to allow for the cross-referencing of DMF [REDACTED]. The DMF was reviewed and determined to be adequate to support NDA 20-582 for Follistim® (lyophilized powder for injection). The updated DMF was reviewed and determined to be adequate to support this NDA. The Sponsor has also cross-referenced the drug substance information provided in NDA 20-582.

The drug product is a new presentation of the previously approved Follistim®. Follistim® is a sterile lyophilized drug product to be reconstituted with water for injection. The new presentation is a ready-for-use formulation of follitropin beta solution in 75 IU, 150 IU, 225 IU and 300 IU of FSH per 0.5 ml, filled into 2 ml vials. The solution drug product contains L-methionine as an anti-oxidant to stabilize the protein in solution. The drug product is manufactured by Organon, Inc., West Orange, NJ and packaged by Organon, Inc., Allentown, PA. Three facilities are involved in the quality control testing: Organon, Inc., West Orange, NJ; NV Organon, Netherlands; [REDACTED].

The proposed shelf life of [REDACTED] was determined not to be acceptable based on the primary and supporting stability data. It was further determined that a [REDACTED] expiry at [REDACTED] could be granted, during which time it can be stored at controlled room temperature [REDACTED] for up to three months. In addition, the Sponsor was asked to revise the subunit content stability specifications to NMT [REDACTED]. The Sponsor was also asked to revise the total oxidation specification to be expressed as the oxidation of the alpha subunit alone and to revise the L-Methionine content stability specification to [REDACTED].

The Office of Compliance issued a "Withhold" recommendation on October 30, 2000 following a WARNING LETTER issued on September 19, 2000 by the New Jersey District after inspection of the West Orange, NJ manufacturing plant between July 17 and August 23, 2000.

From a Chemistry, Manufacturing and Controls perspective, the NDA is considered approvable pending satisfactory resolution of deficiencies listed in the CMC and Microbiology IR letters and satisfactory inspection reports from the Office of Compliance.

Microbiology

The following deficiencies were noted in the Microbiology reviews (see review 1 and 2):

- a. The Sponsor was asked to describe the storage and distribution systems for Water for Injection in the facility. The WFI system was described and the explanation was acceptable. The _____

b. _____

c. _____

- d. In response to an inquiry concerning the relationship of the _____ validation data, the Sponsor indicated the _____ has been used in other facilities and is to be used as an alternate. Since the intended use of this _____ was not identified in the manufacturing process description in the original submission, it has not been reviewed and is not approved. A supplement may be provided for this change after approval or this _____ may be added to the manufacturing process description in an amendment. The Sponsor was requested to provide appropriate references or resubmit the validation data to speed the review. _____

- e. The description of the container and closure integrity test did not identify the growth medium, culture preparation, culture density, immersion conditions, incubation parameters and control tests. The Sponsor's response was acceptable

f. _____



From the Microbiology perspective, the NDA is approvable pending satisfactory resolution of the remaining deficiencies.

Product Name

The tradename Follistim®-AQ was recommended for acceptance by OPDRA on October 17, 2000.

Pre-Clinical Pharmacology and Toxicology

Based on the structural and functional similarities of Follistim®-AQ with natural and approved urinary FSH and recombinant FSH, as well as extensive clinical experience with these types of products, the Pharmacology reviewer has recommended that from a pre-Clinical and Pharmacology view point the NDA should be approved.

Biopharmaceutics

A comparative bioavailability study with Follistim®-AQ Cartridge vs. Follistim® was previously conducted and the results of this study were submitted to NDA 21-211. The study design was an open-label, single-center, single dose, crossover study in 22 female subjects comparing the bioavailability of a single dose of Follistim®-AQ (150 IU) with Follistim® (reconstituted-150 IU). Follistim®-AQ resulted in 20% higher AUC and C_{max} than Follistim® and the two formulations were found not to be bioequivalent. In this same study, the Sponsor weighed the syringes for Follistim® before and after the injection to each patient to determine the actual dose delivered. It was found that the conventional syringe delivered a lower amount than the nominal dose. The Sponsor calculated a correction factor for the dose administered to each patient by dividing the maximum (theoretical) weight of the syringe content by the actual weight administered. The mean correction factor was 18%. The Sponsor applied this 18% correction factor to the AUC and C_{max} values for Follistim® delivered with the conventional syringe and with this correction factor, the Pen-Injector was bioequivalent to Follistim®. The Office of Clinical Pharmacology and Biopharmaceutics accepted this approach.

The concentration of FSH in Follistim®-AQ is double that of the cake formulation. The Sponsor requested a biowaiver for this NDA based on the earlier BE study. In this BE study it had been shown that the bioavailability of FSH was not influenced by the concentration in the range of 150 IU/ml to 833 IU/ml of FSH. This concentration range includes the maximum concentration of the solution formulation (600 IU/ml) and, therefore, the BE study results can be extrapolated to the solution formulation. The Sponsor was requested to provide comparative data regarding the loss of dose during handling and injection preparation for the solution formulation compared to the cake formulation. From that comparison, the mean injectable FSH was 285 IU for the cake formulation and the mean injectable FSH was 296 IU for the solution formulation. The mean injectable FSH activity from the solution formulation compared to the cake formulation was 104%, with a 95% confidence interval of 99%-109%. This difference in mean injectable FSH

activities was statistically insignificant and it is concluded that the two formulations will result in similar doses being injected into the body. Therefore, based on the BE study from NDA21-211 and the in vitro comparative data on loss of dose during handling and injection, the request for waiver of a BE study for the solution formulation is acceptable.

Because the BE study, referenced for the waiver of bioequivalence, was conducted following subcutaneous administration, the Sponsor was requested to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. In response the Sponsor submitted synopses of 3 pharmacokinetic studies that supported bioequivalence of 150 IU/ml Follistim® by the intramuscular or subcutaneous route of administration in ██████████ total injections. A safety and efficacy study submitted to the original NDA, 20-582, also showed comparable safety and efficacy between the subcutaneous and intramuscular routes of administration. Based on this information, the bioequivalence via the subcutaneous route of administration can be extrapolated to the intramuscular route of administration.

OCPB find that the human pharmacokinetics and biopharmaceutics section of NDA 21-273 is acceptable.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

DSI audits were conducted at three clinical sites (Austin, TX, Grand Rapids, MI and La Jolla, CA). Two of the 3 sites were judged as compliant with regulations and meeting good clinical practices. The Grand Rapids, MI site was cited for failure to adhere to the protocol and inadequate and inaccurate record keeping. These serious violations as well as the failure to also have adequate drug accountability and adequate patient consent would mandate deletion of the contribution of the data from this clinical site had the clinical study been relied upon to demonstrate the safety and efficacy of the drug.

Clinical Efficacy and Safety

The data from a single clinical trial was submitted as supportive to the BE study for consideration of approvability. This study was an open-label, multicenter, randomized, group comparison study of Follistim®-AQ (solution formulation) to Follistim® (cake formulation) for induction of ovulation in clomiphene-resistant subjects with chronic anovulation (WHO Group II). Each subject received 75 IU of Follistim solution formulation or cake formulation on treatment days 1-7. If the investigator judged that no ovarian response had occurred by day 8, then the dose was increased to 150IU on days 8-14. If no ovarian response had occurred by day 15, the dose was increased to 225 IU on days 15-21. No increase to the Follistim® dosage was made if an ovarian response was noted, however, the dose could be decreased if warranted in the investigator's judgement. Each subject received treatment for only one cycle and the maximum duration of treatment was 21 days. One hundred twenty six (126) subjects were randomized. A total of 22 subjects (9 on solution formulation and 13 on the cake formulation) discontinued the study early. Of these 22 early discontinuations, 14 were for risk of ovarian hyperstimulation syndrome (OHSS) and 3 were for insufficient ovarian response.

The primary efficacy parameter was the percentage of subjects who ovulated. In the intent-to-treat analysis, the ovulation rate for the solution formulation was 90.3% compared to 82.8% for the cake formulation. The difference between the two treatment groups was not statistically significant. Ongoing pregnancy rate was a secondary efficacy parameters. The ongoing pregnancy rate was 17.7% with the solution formulation and 17.2% with the cake formulation. This difference was not statistically significant.

There were no deaths in this study. There were 7 serious adverse events in 6 subjects. All six were in the solution formulation arm. The serious adverse events included three adverse pregnancy outcomes (two ectopics and one fetal demise) which were judged to be unrelated to study drug administration. Two cases of lower abdominal pain and one case of ovarian hyperstimulation syndrome were considered as related to study drug administration. All subjects completed treatment and recovered from the serious adverse event.

This study was submitted as supportive of the BE data. It was not intended to provide the safety and efficacy data to support approval. While this single open label study is not acceptable to provide the sole safety and efficacy data to support approval, it does satisfy its intent as supportive of the BE data.

Discussion and Conclusions

The Sponsor supports this application with bioequivalence information comparing Follistim®-AQ with Follistim® submitted to NDA 21-211. After adjusting for losses in the handling and preparation for injection with the syringe and needle for the cake formulation, it was accepted that Follistim®-AQ Cartridge and Follistim® were bioequivalent. A biowaiver for bioequivalence for Follistim®-AQ and Follistim® was accepted based on the original BE study and the in vitro comparative data on loss of dose during handling and injection for Follistim® solution formulation versus Follistim® cake formulation. In addition, the Sponsor provided information that was accepted as demonstrating that the bioequivalence via the subcutaneous route of administration can be extrapolated to the intramuscular route of administration.

I concur with the recommendation of the clinical reviewer that this NDA for Follistim®-AQ can be approved based on biopharmaceutical equivalence to the approved drug product Follistim®. However, outstanding chemistry, manufacturing and control deficiencies must be satisfactorily addressed before an approval action can be taken.

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 21-149
S. Allen, MD
D. Shames, MD
R. Bennett, MD
L. Kammerman, Ph.D.
D. Spell-Lesane
S. Slaughter, M.D., Ph.D.
V. Jarugula, Ph.D.

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/s/

Shelley Slaughter
5/17/01 02:26:54 PM
MEDICAL OFFICER

Daniel A. Shames
5/24/01 01:39:04 PM
MEDICAL OFFICER

Safety Update

Amendment dated May 11, 2001 is a response to our telephone request of May 9, 2001 for a safety update.

The response notifies us that there have been no additional reports of adverse events for study 058-004 beyond those originally submitted in the NDA.

It is recommended that the applicant should submit a report of postmarketing experience obtained from all countries where the drug product is marketed in the form of a safety update when such information becomes available to them.

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

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/s/

Ridgely C. Bennett
5/22/01 09:55:00 AM
MEDICAL OFFICER

Shelley Slaughter
5/22/01 04:10:40 PM
MEDICAL OFFICER

Medical Officer's Original Clinical Review

NDA Number: 21-273

Applicant: Organon, Inc.

375 Mount Pleasant Avenue

West Orange, New Jersey 07052

Date of Submission: July 21, 2000

Date Submission Received: July 24, 2000

Date Review Completed: May 14, 2001

EXECUTIVE SUMMARY:

I. Recommendations:

- A. Approval of this application is recommended from a clinical perspective based on the acceptable demonstration of bioequivalence of this drug to that of an approved and marketed drug. Clinical studies were not submitted to demonstrate safety and efficacy. However, the results of one open-label, randomized, group-comparative, multicenter study was submitted as supportive data since the study had been completed. This study was reviewed and evaluated and does provide supportive evidence for the safety and efficacy of the Follistim®-AQ, the new formulation of an already approved Follistim® product. The approved product is a freeze-dried cake to be reconstituted with water for injection while Follistim®-AQ is formulated as an injectable solution. An acceptable benefit/risk relationship was demonstrated for the already approved drug product and applies equally as well to the new drug product which differs from it only in its pharmaceutical presentation.
- B. Phase 4 studies are not required. As a part of risk management, the applicant should submit a report of postmarketing experience obtained from all countries where the drug is marketed including the seven countries where it has been marketed since 1999.

II. Summary of Clinical Findings:

A. Brief Overview of Clinical Program:

1. Name of Product: Follistim®-AQ (follitropin beta)
2. Therapeutic Class of Product: Infertility
3. Routes of Administration: S.C. and I.M.
4. Clinical Trial: The results of one multicenter trial for one indication (induction of ovulation) involving 126 subjects randomized to either Follistim® (the approved product) or to Follistim®-AQ (the subject of this application) is submitted for supportive information only and not as the basis for approval of this application.

B. Efficacy:

Efficacy was demonstrated on the basis of bioequivalence with an approved drug product and the one clinical study supported this finding. The indications claimed are induction of ovulation and for use in assisted reproductive technologies, the same indications for the approved drug product.

C. Safety:

As Follistim®-AQ differs from the approved Follistim® in its pharmaceutical presentation only, data on clinical safety contained in NDA 20-582 for Follistim® and pertinent annual reports for Follistim® are the basis for the determination of safety of Follistim®-AQ. The safety data included in the labeling for Follistim® is the identical data in the draft labeling for Follistim®-AQ.

D. Dosing:

Dosage and administration are the same for Follistim®-AQ as for Follistim®, based on bioequivalence evaluation. This is acceptable. The dosage regimen utilized in protocol [REDACTED] differs from that recommended in the approval labeling in that in protocol [REDACTED], the dosage could be increased by [REDACTED].

labeling (based on extensive clinical grounds) recommends that the dosage not be increased for the first 14 days and then, if needed, increased in increments of 37.5 IU.

E. Special Populations:

This drug is being approved for conditions that occur only in women. This drug is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established. Clinical studies of Follistim® did not include subjects aged 65 and over. This drug is contraindicated in pregnancy.

REVIEW:

I. Introduction and Background:

- A. Established Drug Name: Follitropin beta
- B. Proposed Trade Name: Follistim®-AQ
- C. Laboratory Code Name: Org 32489
- D. Therapeutic Class: Infertility
- E. 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 sialylation, 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 transected 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.

F. Proposed Indications:

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

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

G. Dosages Recommended:

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 with patients who are responding, 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. However, in patients that were low or poor responders, maintenance doses of 375 to 600 IU were administered according to individual response. This later category comprised approximately 10% of evaluated women. The maximum, individualized, daily dose of Follistim®-AQ 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 is 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®-AQ therapy; this will reduce the chance of developing OHSS.

Ovulation Induction:

Treatment usually starts with a 75 IU daily dose of Follistim®-AQ which is continued for up to 14 days. If there is no ovarian response, the daily dose will then be increased by 37.5 IU of Follistim®-AQ at weekly intervals until

follicular growth and/or serum estradiol levels indicate an adequate response. The maximum, individualized, daily dose of Follistim®-AQ 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 preovulatory 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®-AQ therapy, hCG must be withheld during this course of treatment; this will reduce the chances of developing OHSS.

During treatment with Follistim®-AQ 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®-AQ 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.

H. Age Groups Studied:

Most studies included women 18-39 years of age.

I. Active Ingredient:

Follicle stimulating hormone (recombinant)

J. Routes of Administration:

Subcutaneous and Intramuscular

K. Armamentarium for Indications:

There are many drugs already marketed for these indications including Follistim®.

Follistim®-AQ (follitropin beta injection) is a new pharmaceutical presentation of the approved Follistim® (follitropin beta for injection), NDA No. 20-582. The currently approved product is formulated as a freeze-dried cake, to be administered after reconstitution with Water for Injection (WFI), whereas Follistim®-AQ (follitropin beta for injection) is an injectable aqueous solution of 75, 150, ██████████ IU follitropin beta per 0.5mL, in a glass vial, to administered with a syringe.

A ready-to-use presentation is considered to be more convenient than the approved product since its use requires less handling. The use of the vial presentation facilitates self administration by patients.

The concentration of follitropin beta in the Follistim®-AQ (follitropin beta injection) solution ranges from 75 IU/0.5mL to 300IU/0.5mL (i.e., from 150 IU/mL to 600 IU/mL). After reconstitution, the concentration of the approved product ranges from 75 IU/mL to 300 IU/mL. (In line with the approved labeling, up to 4 cakes may be reconstituted in _____ of WFI.

L. Prior FDA Reviews and Issues:

In Organon's Request for Biowaiver submitted January 11, 2000, it was shown that the concentration difference between the approved product and Follistim®-AQ is not considered to impact bioavailability. However, in the same biowaiver request it was shown that differences may be caused by the various ways in which the different Follistim® presentations are handled and administered.

Therefore, during the teleconference between DRUDP and Organon on March 31, 2000 (minutes issued by the Division April 28, 2000), the decision was reached that supportive data from in-vitro tests to show volume/dose losses from liquid and cake formulations to support the waiver should be provided.

Based on this decision, an in vitro study was carried out (Comparison of In Vitro Activity of FSH in Follistim® (Cake) and Org 32489 Solution in Vial (Liquid) by EIA Method; (Document No. PDTSR-050.00). The report is included in this submission under 314.50(d)(1)(ii) Drug Product; Investigational Formulations, and under 314.50(d)(3) Human pharmacokinetics and bioavailability section.

This study shows that the mean amount of units in the injectable volume of a single vial of Follistim®-AQ (follitropin beta injection) 300 IU/vial is 104% as compared to the injectable volume obtained after reconstitution of 4 cakes of the approved product Follistim® (follitropin beta for injection) 75 IU. This difference is not statistically significant.

In line with the conclusions reached during the March 31, 2000 teleconference, this in vitro study was submitted to substantiate the request for a biowaiver as submitted January 11, 2000.

Under Follistim® IND No. 54,981, an open-label, randomized group-comparative multicenter study was carried out to assess the efficacy and safety of Follistim® solution formulation compared to a freeze-dried cake formulation, both administered subcutaneously for the induction of ovulation in clomiphene-resistant subjects with chronic anovulation (WHO group II); Protocol No. [REDACTED]

During the above-referenced meeting, the Division requested that the data from this study be submitted. The Clinical Report for Study 058-004 is included in this submission under 314.50(d)(5) Clinical data section.

As Follistim®-AQ (follitropin beta injection) differs from the approved Follistim® (follitropin beta for injection) in its pharmaceutical presentation only, data on Clinical Efficacy and Safety contained in NDA No. 20-582 and pertinent Annual Reports are incorporated into NDA 21-273 by cross-reference.

M. Foreign Approvals of Follistim®-AQ:

Follistim®-AQ was approved April 26, 1999 in Austria, Belgium, Denmark, Ireland, Finland, France, Germany, Greece, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and United Kingdom. It was also approved in New Zealand April 29, 1999, Iceland October 28 1999, Norway February 3, 2000 and Australia February 17, 2000. In addition, applications for approval have been submitted to Argentina, Brazil, Canada, Cyprus, and Switzerland. There are no countries in which Follistim® has been withdrawn from marketing for any reasons related to safety or efficacy.

N. Other Pharmacologically Related Agents Under Study:

Follistim®-AQ Cartridge is a solution for injection filled in cartridges to be administered with a pen injector device. It is approved in Europe.

II. Clinically Relevant Findings from the Biopharmaceutics Review:

Follistim®-AQ is a new formulation of an already approved Follistim® product. The approved product is a freeze dried cake to be reconstituted with water for injection. Approval was for 75 IU per vial and 150 IU per vial. Only the 75 IU per vial preparation is currently marketed. Follistim®-AQ is formulated as an injectable solution of 75, 150, [REDACTED] IU per 0.5 mL in glass vials which equates to 150-600 IU per mL.

The applicant submitted a request for a biowaiver for this product based on the results of an existing bioequivalence study between the freeze dried cake and

injectable solution injected with a pen injector that was evaluated by our clinical pharmacology and biopharmaceutics review team in their review of NDA 21-211. In that bioequivalence study it was shown that the concentration of follitropin in the range of 150 IU/mL to 833 IU/mL did not affect the bioavailability. Since the maximum concentration of the current formulation is 600 IU/mL, the bioequivalence study supports this concentration.

The results of an in vitro study comparing dose losses for handling the freeze dried cake versus handling the solution were submitted to this application. The volume/dose losses were similar.

The freeze dried cake formulation has been shown to be bioequivalent when administered subcutaneously and intramuscularly at 150 IU/mL (300 IU/2mL). Since the cake formulation and solution are bioequivalent when administered subcutaneously, by extrapolation, they are bioequivalent when administered intramuscularly.

III. Human Pharmacokinetics and Pharmacodynamics:

Based on FDA's recommendations, an in vitro study was carried out to compare volume and FSH activity losses from Follistim®-AQ (Liquid), in reference to those of the approved product, Follistim® (follitropin for injection) Cake. The result of this study is intended to substantiate Organon's request for a Biowaiver submitted January 11, 2000.

In line with FDA's recommendations, the clinical situation was mimicked and the "worst case scenario" was considered, in which the volume and the activity losses after reconstitution of 4 vials of Follistim® (Cake), 75 IU/vial were compared with 1 vial of Org 32489 Solution in Vial (Liquid), 300 IU per 0.5 mL. The findings focus on injectable volume, and the extracted FSH activity as determined by enzyme immunoassay (EIA).

This study shows that the particular handling of Follistim®-AQ (300 IU per 0.5 mL) leads to an actual injectable volume of [REDACTED]. Expressed in EIA units the actual dose ranges from [REDACTED].

To reconstitute the first Follistim® 75 IU/vial cake, in clinical practice approximately [REDACTED] of WFI is extracted from the vial of diluent with a [REDACTED] syringe. The actual amount proved to be higher, as the injectable volume after reconstituting 4 Follistim® cakes proved to be [REDACTED]. The actual amount of FSH in the injectable volume, as determined by EIA ranged from [REDACTED].

The mean extracted FSH EIA activity from Follistim® - AQ 300 IU as compared to four Follistim® 75 IU cakes was 104%, ranging from 84% to 130%, with a 95%

confidence interval ranging from 99-109%. This difference is not statistically significant ($\alpha=0.05$).

Relating the data on volume or dose losses during handling obtained in this in vitro study to similar data from other studies is not considered to give additional information. From the nature of the methodology, inter-study differences will be highly dependent on experience of personnel, syringes and needles used, adherence to instructions, etc.

The data of the in vitro study are considered to substantiate Organon's request for Biowaiver, as submitted on January 11, 2000.

As Follistim®-AQ (follitropin beta injection) differs from the approved Follistim® (follitropin beta for injection) in its pharmaceutical presentation only, Human Pharmacokinetics and Bioavailability Data contained in NDA No. 20-582 are incorporated into NDA 21-273 by cross-reference.

IV. Description of Clinical Data and Sources:

A. Overall Data:

The data come from a single clinical study conducted by the applicant entitled "An Open-Label, Randomized, Group-Comparative, Multicenter Study to Assess the Efficacy and Safety of a Follistim® Solution Formulation Compared to a Freeze-Dried Cake Formulation, both Administered Subcutaneously for the Induction of Ovulation in Clomiphene – Resistant Subjects with Chronic Anovulation (WHO Group II)". This clinical trial is identified as Protocol

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B. Disposition of Subjects:

Table 1
(Applicant's Table 10)
Disposition of Subjects

Number of	Follistim® Freeze-dried Cake Formulation (N=64)	Follistim® Solution Formulation (N=62)	Total (N=126)
	n	n	n
Subjects Randomized	64	62	126
Subjects Treated	64	62	126
Subjects Completing the Study	54	57	111

Overall, 168 subjects were screened. Each subject received 75 IU of Follistim® on treatment days 1-7, then, if no ovarian response by day 8, the dose was increased to 150 IU on days 8-14, and, then, if no ovarian response by day 15, the dose was increased to 225 IU on days 15-21. Treatment was for one cycle and the maximum duration of treatment was 21 days.

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Table 2
Applicant's Table 11
Reasons for Early Discontinuation

Reasons for Early Discontinuation	Follistim® Freeze-dried Cake Formulation (N=64)	Follistim® Solution Formulation (N=62)
	n (%)	n (%)
Risk of Hyperstimulation ^a	8 (12.5%)	6 (9.7%)
Insufficient Ovarian Response ^b	2 (3.1%)	1 (1.6%)
Other Reasons	3 (4.7%)	2 (3.2%)
Total Discontinued	13 (20.3%)	9 (14.5%)

^a Hyperstimulation is defined as having more than four follicles ≥ 15 mm and no hCG administered.

^b Insufficient ovarian response is defined as follicles too small and/or too few (0-1 follicle ≥ 15 mm in diameter), and less than 21 days of Follistim® treatment.

There were seven subjects who discontinued from the study that were followed up and ended up meeting the criteria for study completion. Four subjects were discontinued because of OHSS, but were pregnant at the end of the study. Three subjects were discontinued because of insufficient ovarian response, but actually had completed 21 days of therapy.

The majority of all subjects were Caucasian (83.3%) and were between 25 and 31 years of age (61.9%). There were more 25-31 year olds in the Follistim® Freeze-dried Cake Formulation treatment group (65.6%) than in the Follistim® Solution Formulation treatment group (58.1%), and more 32-39 year olds in the Follistim® Solution Formulation treatment group (37.1%) than the Follistim® Freeze-dried Cake Formulation treatment group (26.6%). BMI, height, and weight were similar between treatment groups.

Anovulation, fertility characteristics, and duration of infertility were generally similar between treatment groups. The only notable differences between groups were the incidence of parity (deliveries that occurred ≥ 28 weeks of gestation) and the duration of infertility. Subjects in the Follistim® Solution Formulation treatment group had a higher incidence of parity (16 subjects; 25.8%) as compared to subjects in the Follistim®

Freeze-dried Cake Formulation treatment group (7 subjects; 10.9%). Subjects in the Follistim® Freeze-dried Cake Formulation treatment groups had a longer duration of infertility (47.9 months) than subjects in the Follistim® Solution Formulation treatment group (31.1 months).

Reviewer's Comment:

The differences in parity and duration of infertility both favor the Follistim® Solution Formulation.

C. Postmarketing Experience:

None submitted in this original submission. This information should be supplied by the applicant in the Safety Update when it is submitted.

D. Literature Search:

None.

V. Clinical Review Methods:

A. The single clinical trial report submitted was reviewed in its entirety.

B. This application was submitted in paper only. The protocol was originally submitted to IND 54, 981. The sponsor felt confident that they could demonstrate an acceptable "step up" dose regimen of administration.

C. Data Quality and Integrity:

DSI audits were conducted at the three sites with the most subjects. These sites were located in Austin, Grand Rapids, and La Jolla. Two of the three investigators generally adhered to all U.S. regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. The third investigator did not. This investigator failed to adhere to the protocol and maintained inadequate and inaccurate records. These are serious violations which would mandate deleting this investigator's contribution from the applicant's summary report if the applicant wished to use this study for any purpose other than its intended purpose in this application, which is simply to support the bioequivalence of the solution formulation (Follistim®-AQ) with the cake formulation (Follistim®). This investigator also had a problem with inadequate drug accountability and a lesser problem with inadequate patient consent.

D. Ethical Issues:

The quality of informed consent cannot be evaluated because an informed consent document was not submitted to the IND or the NDA.

E. Financial Disclosure:

Form FDA 3454 has been completed and certified by the applicant.

VI. Review of Efficacy:A. Findings in Light of Proposed Labeling Claims:

Protocol [REDACTED] supports one of the proposed labeling claims, namely, induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. The second proposed indication is development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. No clinical study is submitted to support this second labeling claim. None is required since the new drug application is based on the demonstration of bioequivalence.

B. Review of Protocol [REDACTED]1. Title of the Study:

An Open-Label, Randomized Group-Comparative, Multicenter Study to Assess the Efficacy and Safety of Follistim® Solution Formulation Compared to a Freeze-Dried Cake Formulation, both Administered Subcutaneously for the Induction of Ovulation in Clomiphene-Resistant Subjects with Chronic Anovulation (WHO Group II)

2. Investigators and Study Sites:Site Principal Investigators

01	Young, JE, MD, Michigan Reproductive and IVF Center, Grand Rapids, MI
02	Maxon, WS, MD, Northwest Center for Infertility and Reproductive Medicine, Margate, FL*
03	Penzias, AS, MD, Boston IVF, Brookline, MA
04	Silverberg, KM, MD, 3705 Medical Parkway Austin, TX

- 05 Garcia, JE MD, Johns Hopkins University School of Medicine, Baltimore, MD
- 06 Klein, NA, MD, University of Washington, Seattle, WA
- 07 Steinkampf, MP, MD, University of Alabama at Birmingham School of Medicine, Birmingham AL
- 08 Odem, RR, MD, Washington University in St. Louis School of Medicine, St. Louis, MO
- 09 Cardone, VRS, MD, Fertility Center of New England, Reading, MA**
- 10 Kettel, LM, MD, San Diego Fertility Center, La Jolla, CA
- 11 Doody, K, MD, Center for Assisted Reproduction, Bedford, TX*
- 12 Young, P, MD, San Diego Medical Center, San Diego, CA

* Indicates that site did not participate in the study

** Indicates that site did not enroll any subjects in the study.

3. Objectives of the Study:

To obtain information on the efficacy, safety and local tolerance of Follistim® when administered subcutaneously as the solution formulation and in the freeze-dried cake formulation in clomiphene-resistant subjects with chronic anovulation (WHO Group II)

4. Rationale for the Study:

Follistim®-AQ (follitropin beta injection) is a new pharmaceutical presentation of the approved Follistim® (follitropin beta for injection), NDA No. 20-582. The currently approved product is formulated as a freeze-dried cake, to be administered after reconstitution with WFI, whereas Follistim®-AQ (follitropin beta injection) is an injectable aqueous solution of 75, 150, ██████████ IU follitropin beta per 0.5mL, in a glass vial, to be administered with a syringe.

5. Method of Assignment to Treatment:

Women who were identified as potential subjects by the clinic staff were to meet with the investigator for an explanation of the study and entry requirements, and a review of the informed consent. The subject must have signed the informed consent before undergoing any screening assessments. If all inclusion criteria were met and none of the exclusion criteria were present, the subject was to receive a study number from the Randomization Schedule and was to be randomly assigned to one of the two treatment groups.

6. Number of Subjects:

126 (64 in the Follistim® Freeze-dried Cake Formulation and 62 in the Follistim® Solution Formulation) were randomized. This was 24 subjects less than the protocol required.

7. Duration of Treatment:

One cycle, maximum treatment of 21 days.

8. Inclusion Criteria:

Subjects were eligible for enrollment in the study if they met the following criteria:

- a. Subjects were to be infertile women with ovulatory dysfunction, between the ages of 18-39 years, inclusive (treatment had to have begun before 40th birthday), and wishing to conceive.
- b. Subjects were to be healthy, as determined by the investigator's judgment of her ability to undergo fertility treatment.
- c. Subjects were to be anovulatory as defined by cycle length > 35 days, or if subject was amenorrheic (no more than two periods per year), anovulation was presumed, and historical data confirming anovulation was to be provided. If cycle length ≤ 35 days, documentation to demonstrate that two serum progesterone (P) levels, measured between approximately Days 21 and 28 of the menstrual cycle did not exceed 3 ng/mL had to be provided.
- d. Subjects were to have failed to conceive despite apparent ovulation induced by clomiphene citrate (CC) for a period equal to or greater than three cycles or failed to ovulate at a maximum dose of 150 mg of CC per day for five days.
- e. Subjects were to have had patency and apparent normalcy of fallopian tube(s) and uterine cavity as documented by hysterosalpingography or laparoscopy within three years.
- f. Subjects were to have spontaneous menses or a positive response to progesterone withdrawal.

- g. Subject's male partner or semen donor was to have semen analysis, done within three months prior to initiation of Follistim® treatment, showing normalcy by criteria which were adapted from WHO guidelines and were at least as strict as ≥ 20 million/mL, $>50\%$ motile, and $\geq 30\%$ normal morphology. Kruger Criteria ($>4\%$ normal morphology) may alternatively have been applied for the morphology assessment.
- h. Subjects were to have a body mass index (BMI) less than or equal to 32kg/m^2 .
- i. Subjects were to agree to participate in Study 058007 (pregnancy follow-up of subjects who became pregnant as a result of treatment in this study).
- j. Subjects were to be willing to give written informed consent.

9. Exclusion Criteria:

Subjects were excluded from the study if they had any of the following conditions.

- a. Subjects had any clinically significant abnormal hematology, clinical chemistry, or urinalysis parameters or endocrine and/or metabolic abnormalities (pituitary, hypothalamus, thyroid, adrenal, pancreas, liver, or kidney) at screening based on the investigator's judgment.
- b. Subjects had serum FSH >20 mIU/mL.
- c. Subjects had used any investigational drugs within three months prior to screening.
- d. Subjects had an ovarian cyst with a diameter >25 mm which had persisted for more than one cycle or ovarian endometrioma on ultrasound (done within one month prior to screening).
- e. Subjects had a history of substance abuse in the 12 months prior to screening.
- f. Subjects refused or were unable to comply with the requirements of the protocol, for any reason, including attending scheduled clinic visits and laboratory tests.

- g. Subjects were breast feeding, pregnant, or had a contraindication for pregnancy.

10. Trial Period:

September 1998 to September 1999.

11. Dosage and Mode of Administration:

Each subject was to initially receive 75 IU of Follistim®/day for up to seven days. If an ovarian response, defined as an increase in the size of a follicle over baseline size as measured by ultrasound, was observed on Day 8 prior to the Follistim® injection, this dose was to be continued. If there was no ovarian response (i.e., no follicular growth was observed on Day 8), the dose of Follistim® was to be increased to 150 IU on Day 8 until Day 14. If no response was observed on Day 15, prior to Follistim® injection, the dose was to be increased to 225 IU of Follistim® on Day 15 through Day 21. If an increase in dose was indicated, the increase was to be to the next higher dose, in 75 IU increments. The maximum treatment period was not to exceed 21 days. The maximum dose was 225 IU.

It should be noted that if an ovarian response was observed, the dose of Follistim® was not to be increased. However, the dose could have been decreased, if appropriate in the investigator's judgment (i.e., to regulate the number and size of developing follicles).

All subjects and individuals of the subject's choosing were to receive instructions from the investigator as to the proper method of drug administration. Subcutaneous injections were to be administered in the abdominal wall by the subject or a properly trained individual. If a subject or the trained individual were unable to administer the drug or if the trained individual was unavailable, the subject was to report to the study site for daily injections.

12. Primary Efficacy Assessment:

Ovulation rate was the primary efficacy parameter. As can be seen in Table 3 the overall ovulation rate was 82.8% for the subjects in the ITT Follistim® Freeze-dried Cake Formulation treatment group and 90.3% for the subjects in the Follistim® Solution Formulation treatment group. The difference between the two treatment groups for the overall ovulation rate was not statistically significant (p-value=0.179).

In the PP Group, the ovulation rate was based on the progesterone level. There was no statistical difference between the treatment groups.

Table 3
Applicant's Table 20
Ovulation Rate (Intent-to-Treat Group)

Ovulation	Follistim® Freeze-dried Cake Formulation (N=64)	Follistim® Solution Formulation (N=62)
Based on progesterone	51 (79.7%)	54 (87.1%)
Based on pregnancy	1 (1.6%)	1 (1.6%)
Based on Ectopic pregnancy	0	1 (1.6%)
Based on miscarriage after proof of a vital fetus	0	0
Based on spontaneous ovulation	1 (1.6%)	0
Overall	53 (82.8%)	56 (90.3%)

Ongoing pregnancy rate and Follistim® exposure (amount and duration of treatment for subjects with ovulation) were secondary efficacy parameters.

Table 4 shows that the ongoing pregnancy rates were almost identical in both Intent-to-Treat groups: 17.2% in the Follistim® Freeze-dried Cake Formulation treatment group and 17.7% in the Follistim® Solution Formulation treatment group. The difference between the two treatment groups for ongoing pregnancy rate was not statistically significant (p-value=0.934).

The ongoing pregnancy rates were slightly higher in the PP Groups than in the ITT/AST Groups: 21.7% in the Follistim® Freeze-dried Cake Formulation treatment group and 18.4% in the Follistim® Solution Formulation treatment group.

Table 4
(Applicant's Table 21)

Parameter	Follistim® Freeze-dried Cake Formulation (N=64)	Follistim® Solution Formulation (N=62)
Ongoing Pregnancy	11 (17.2%)	11 (17.7%)

The extent of exposure to Follistim® for the subjects who ovulated was measured in terms of total amount of Follistim® administered and duration of Follistim® treatment. The mean total amount of Follistim® administered was 1,200.0 IU for the subjects in the Follistim® Freeze-dried Cake Formulation treatment group and 818.2 IU for the subjects in the Follistim® Solution Formulation treatment group. The difference between the two treatment groups for the amount of Follistim® administered was statistically significant (p-value=0.006).

The mean duration of Follistim® treatment was 12.0 days for the subjects in the Follistim® Freeze-dried Cake Formulation treatment group and 9.1 days for the subjects in the Follistim® Solution Formulation treatment group. The difference between the two treatment groups for the duration of Follistim® administration was statistically significant (p-value=0.0003).

Table 5
Follistim® Exposure for Subjects with Ovulation (ITT)

Number of Subjects	Dried Cake	Solution
	N=64	N=62
Total IU Administered (mean)	1200.0	818.2
Treatment Duration (days) (mean)	12.0	9.1

C. Comments from the Statistician's Evaluation:

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.

In the protocol it was stated that 150 subjects were to be randomized in a 1:1 ratio (75 in each arm). 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.

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 Follistim® cake formulation group (47.9 months \pm 34.9) than in the Follistim® solution formulation arm (31.1 months \pm 22).

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 Follistim® solution formulation relative Follistim® cake formulation. A margin for non-inferiority was not pre-defined.

Medical Reviewer's Comments: The medical reviewer agrees with the statistician's comments. The study results provide some supporting data for the recommended approval of the new drug application based on bioequivalence of the Follistim®-AQ to the approved Follistim® freeze-dried cake formulation. Protocol [REDACTED] alone, does not provide substantial evidence of safety and efficacy upon which approval could be recommended.

VII. Integrated Review of Safety:

A. Findings as Reflected in Proposed Labeling:

Safety is based, primarily on the data from the studies reviewed in NDA 20-582 for Follistim®, approved December 9, 1998. The safety data included in the labeling for Follistim®-AQ is identical to the labeling for Follistim®.

B. Adequacy of Patient Exposure and Safety Assessment:

Patient exposure is adequate and the safety profile for Follistim® has been adequately defined.

C. Safety Parameters in Protocol 058004:

There were no deaths in this study. Three subjects in the solution group and one subject in the freeze-dried cake group were discontinued because of OHSS. Six subjects experienced seven serious adverse events. All six subjects were in the Follistim®-AQ treatment arm. There were two cases of ectopic pregnancy and one case of fetal demise which were unlikely related to the study drug. Two cases of lower abdominal pain (one with an ovarian cyst) and one instance of ovarian hyperstimulation syndrome were related to the study drug. All subjects completed treatment and recovered from the serious adverse event.

VIII. Assessment of Dosing/Regimen/Administration Issues:

Dosage and administration are the same for Follistim®-AQ as for Follistim®, based on bioequivalence evaluation. This is acceptable. The dosage regimen utilized in protocol [REDACTED] differs from that recommended in the approved labeling in that in protocol [REDACTED], the dosage could be increased by [REDACTED] if there were no evidence of an ovarian response while the approved labeling (based on extensive clinical grounds) recommends that the dosage not be increased for the first 14 days and then, if needed, increased in increments of 37.5 IU.

IX. Use in Special Populations:

- A. This drug is being approved for conditions that occur only in women.
- B. This drug is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established.
- C. Clinical studies of Follistim® did not include subjects aged 65 and over.
- D. This drug is contraindicated in pregnancy.

X. Conclusions and Recommendations:

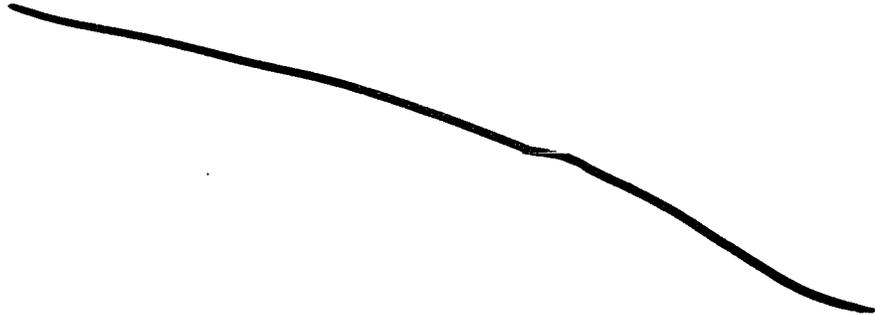
A. Overall Risk-Benefit Analysis:

Follistim®-AQ differs from the approved Follistim® in its pharmaceutical presentation only. The benefits of the drug outweigh its risks.

B. Remaining Unresolved Issues:

None.

C. Major Issues Regarding Draft Package Insert:



D. Approval of this application is recommended.

E. Post-Marketing Risk Management Studies Recommended:

None. The applicant should submit a report of postmarketing experience obtained from all countries where the drug product is marketed in the form of a safety update.

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

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/s/

Ridgely C. Bennett
5/16/01 08:41:48 AM
MEDICAL OFFICER

Shelley Slaughter
5/16/01 12:30:30 PM
MEDICAL OFFICER
I concur