CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-197

STATISTICAL REVIEW(S)

AUG 0 4 2000

Statistical Review and Evaluation
Clinical Studies[1]

NDA:	21-197
Applicant:	ASTA Medica
Name of drug:	Cetrotide 0.25 mg and 3 mg (cetrorelix acetate for injection)
Indication:	Prevention of premature ovulation in women undergoing controlled ovarian stimulation
Documents reviewed:	Volumes 1.156 and 1.158
Medical reviewer:	Gerald Willett, M.D. (HFD-580)

This statistical review evaluates the historical control evidence that the applicant uses to support the applicant's conclusion "cetrorelix is more effective than no treatment to prevent premature ovulation in patients undergoing ovarian stimulation for ART." The applicant claims "an appropriate historical control group has been selected[2]... ".

This review concludes the applicant has not demonstrated the appropriateness of the selected historical control group. Therefore, any comparisons between cetrorelix and the historical data are suspect.

Because the medical review of this NDA focuses on cetrorelix's ability to prevent and suppress LH surges, the impact of comparisons with the historical data is minimal. The medical review concludes LH surges occurred in only 1.4% of patients treated with cetrorelix. Suppression of LH surges in the absence of cetrorelix would not be expected.

A brief overview of the studies and the historical data, and this reviewer's statistical comments follow.

Overview of cetrorelix studies:
Three studies are used to support the efficacy of cetrorelix; see Appendix for further details. Two (3010, 3030) are randomized, active control studies, and the third (3030) evaluates cetrorelix only. The studies do not include any sites in the United States. The entry criteria were similar for the three studies.

The two randomized studies use active controls that are not approved for use in the United States. The other study (3030) is uncontrolled. To demonstrate the efficacy of

[1] Keywords: Historical control
[2] Volume 1.156, page 120

cetrorelix, therefore, the applicant compares results from the cetrorelix-treated patients with results from historical data, which are described in the following section.

Overview of historical data
The United States IVF-ET Registry was selected as the historical control group. The data are published as annual reports. The NDA uses the historical data from 1985, 1986, 1988, 1989 and 1990. These are the only years for which cancellation rates (expressed as a percentage of total treatment cycles) can be calculated; see next section. The annual reports for 1991-1996 do not summarize results according to whether women received GnRH-agonist treatment and hMG, or received hMG alone. Therefore, these years are not included in the analyses presented in the NDA.

An important feature of this registry is women who had multiple treatment cycles are counted more than once in the registry. Because no patient-level data is available, cancellation rates expressed as a percentage of total women treated cannot be calculated. Instead, results for all treatment cycles is reported.

Endpoint used for comparisons with historical data
The rate of cycles cancelled is the endpoint used to compare cetrorelix with the historical controls. A cancelled cycle is defined as premature discontinuation of the ART procedure before follicle puncture/oocyte retrieval. This endpoint was not the endpoint defined for the cetrorelix studies, which was the administration of hCG.

Results of the study:
The results are an overall cancellation rate [95% confidence interval] of 5.2% [3.7%, 7.2%] for cetrorelix treatment. The corresponding cancellation rate for the historical controls (hMG alone) is 22.7% [19.9%, 25.7%] for 1989/90 and 28.5% [27.7%, 29.4%] for all years.

The historical cancellation rates for the stimulation treatment cycles of hMG and GnRH analog are 18% (1988), 10% (1989), 13% (1990). The data for 1985, 1986, and 1991 through 1996 are not summarized by stimulation treatment. Presumably, the majority of treatment cycles in the 1990s included a GnRH agonist. The cancellation rates for 1191 through 1996, regardless of stimulation treatment, range from 14% to 20%.

Statistical review:
1. For the following reasons, the historical data are not appropriate controls:

   - The historical controls include results of multiple treatment cycles per woman.

   - Ages are not comparable. The clinical studies limited subjects to less than 40 years of age, while the historical controls include women of all ages. Therefore, the women enrolled in the clinical studies (mean age is approximately 32 years) are likely younger than the women in the historical controls.

- Other demographic characteristics may not be comparable. Demographic data for variables other than age are not available for the historical controls. Therefore, the similarity of the historical control data and the clinical studies data cannot be evaluated to determine similarity of patient populations.

- The reasons why women in the historical controls received hMG alone are unknown. The cancellation of a treatment cycle in the historical control data could be due to any reason, including premature LH surge, low or excessive response to ovarian stimulation, unsuccessful oocyte retrieval or fertilization failure.

- The study populations in the cetrorelix clinical studies are enriched relative to the historical controls. Subjects were excluded from the clinical studies if, for example, they had more than three prior IVF procedures, had a known history of low ovarian response to hMG/FSH, or had severe endometriosis. They had to have infertility cause solvable by COS and ART, and a normal uterus. The historical controls did not have these restrictions.

- Geographic location of patients is not comparable. The historical control data is limited to the United States; the clinical studies did not include any sites in the United States.

- The dates of treatment are not comparable. The historical control data are from 1988 through 1990; the clinical studies enrolled the first patient in 1995.

- Patient management may not be comparable. Patient management is likely to have changed since 1988. For example, the published reports state the number of women who have received hMG alone has declined over time. The types of ART techniques currently available are greater and more sophisticated.

- The cancellation rates for the combination of cetrorelix and hMG are less than the historical cancellation rates for women treated with the combination of GnRH-agonists and hMG. If the clinical studies population and historical control population were similar, the cancellation rates should have been similar.

The likely implications of the differences between the historical control population and the clinical studies population are (1) an overestimate of the historical control cancellation rates, and (2) an underestimate of the historical control pregnancy rates. A conclusion that cetrorelix is better than no treatment could be reached, when there is actually no difference between cetrorelix and no treatment.

2. The major statistical analysis issue is the correlation of results of treatment cycles in the historical control data. The published reports for the historical controls assume the results of treatment cycles as reported in the historical control database are independent events. This is clearly not the case, because women with multiple

treatments in a calendar year are counted more than once in the registry. The within-patient correlation is not accounted for in the published reports.

The degree of correlation, and its impact on the reported cancellation rates and pregnancy rates are unknown. In other clinical settings, individuals who are at higher risk for failing are usually the ones who are re-enrolled into a study. If that is the case for these historical data, then the implications are (1) an overestimate of the historical control cancellation rates, and (2) an underestimate of the historical control pregnancy rates.

3. Of interest is the pregnancy rates reported for the historical control data in comparison with the rates reported for the clinical studies. The per cycle and per embryo transfer pregnancy rates for the historical control data are[3]:

Year	1985	1986	1988	1989	1990
Pregnancy % per cycle	8.6	10	8.2	4.7	18.1
Pregnancy % per ET	14.1	16.9	18.1	14.8	26.5

The pregnancy rates for 1990 are much higher than for previous years, and are similar to the combined results reported for the cetrorelix studies (25% per cycle, 27% per ET)[4]. The NDA does not explore possible reasons for why the results for 1990 appear different from earlier years.

Moreover, the year 1990 is five years earlier than 1995, when the first cetrorelix-treated patient was enrolled in the clinical studies. Potentially, the pregnancy rates in 1995 and later for women receiving hMG alone could be higher than those reported for 1985 through 1990.

Conclusion:
The historical control data used in this submission are not "an appropriate historical control group" as claimed by the applicant. Had a more comparable historical control population with single treatment cycles been used, the reported cancellation rates and the reported pregnancy rates would have been closer to those reported for the cetrorelix-treated subjects. Therefore, based on the comparisons with the historical controls, cetrorelix has not been demonstrated to be better than no treatment.

[3] From Volume 1.156, page 130, Table 2
[4] Volume 1.156, page 131, Table 3.

/S/

Lisa A. Kammerman, Ph.D.
Team Leader, DB II

Concur: E. Nevius, Ph.D. (HFD-715) /S/ 8-4-00

cc:
Archival NDA# 21-197
HFD-580/GWillett, JBest, SSlaughter
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APPEARS THIS WAY
ON ORIGINAL

APPENDIX
Overview of Studies 3010, 3020, and 3030

Study Number	Number Of Centers	Total Sample Size	Type of Control	Design	Duration Of Treatment
3010	7 (UK, B, NL, DK)	Cetrorelix .25mg: 188 Buserelin: 86	Active (buserelin; not approved in US)	Open, randomized	Cetrorelix : 1 to 19 days Buserelin: 19 to 38 days
3030	8 (France)	Cetrorelix 3mg: 115 Triptorelin: 39	Active (triptorelin; not approved in US)	Open, randomized	Cetrorelix: one dose Triptorelin: one dose
3020	13 (Europe)	Cetrorelix .25mg: 346	Uncontrolled	Open	1 to 15 days

P.C.T

Screening of New NDAs
Division of Biometrics II

Date: DEC 1 4 1999

NDA #: 21-197

Trade Name: Cetrotide

Generic Name: Cetrorelix acetate

Priority Classification: 1S

Applicant: Asta Medica, Inc.

Indication: Prevention of premature ovulation in patients undergoing controlled ovarian stimulation

No. of Controlled Studies: 2

Date of Submission: October 29 ,1999

User Fee Goal Date: 8/29/00

Medical Reviewer: G. Willett, M.D.

Project Manager: Jeanine Best

Volume numbers in statistical section: 1.1, 1.132-1.161

Date of 45 Day Meeting: December 6, 1999

Screened by: Lisa Kammerman, Ph.D.

Anticipated Review Completion Date: A statistical review is not anticipated. Statistical reviewers, however, will be available to address any issues that arise during the clinical review of this application.

Comments:

1. See Vol. 1.58 (ISE) for analyses not included in the individual study reports. This volume discusses the historical control data and the analyses performed with these data.
2. One-sided 95% confidence intervals are given for endpoints within treatment groups. Two-sided 95% confidence intervals are used for comparisons of endpoints between the Cetrorelix-treated patients and the historical control data.

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	No. Used historical controls rather than an accepted active control.
Endpoints and methods of analysis spelled out in the protocols	Yes, for the studies as designed; but not for comparison with historical controls
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	N/A
Appropriate references included for novel statistical methodology (if present)	Yes
Sufficient data listings and intermediate analysis tables to permit a statistical review	Yes
Data from primary studies on diskettes and/or CANDA submitted	No
Intent-to-treat analyses	Yes
Effects of dropouts on primary analyses investigated	No
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes

BRIEF SUMMARY OF CONTROLLED TRIALS

Study Number	Number Of Centers	Total Sample Size	Type of Control	Design	Duration Of Treatment
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3030	8 (France)	Cetrorelix 3mg: 115 Triptorelin: 39	Active (triptorelin; not approved in US)	Open, randomized	Cetrorelix: one dose Triptorelin: one dose
3020	13 (Europe)	Cetrorelix .25mg: 346	Uncontrolled – sponsor claims this is a confirmatory study	Open	1 to 15 days

/S/ 12/14/99

Statistical Reviewer

cc:
Archival NDA 21-197
HFD-580
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APPEARS THIS WAY
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