CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

Date: July 18, 2005

Re: NDA 21-355 (Serial 000, dated March 31, 2005)
Sponsor: Berlex, Inc.
Product: Angeliq (0.5 mg Drospirenone/1 mg 17β -estradiol Tablets)
Indication: Hormone Replacement Therapy

The sponsor submits this application as a complete response to an approvable letter dated September 14, 2004 for Angeliq (0.5 mg Drospirenone/1 mg 17β -estradiol tablets), a hormone replacement therapy. The submission addresses chemistry deficiencies and unresolved labeling issues cited in the approvable letter in addition to providing a safety update for the reporting interval from January 1, 2004 to January 31, 2005.

Since the purpose of this application is to address chemistry and labeling issues cited in an approvable letter from the agency, no efficacy studies are submitted. Thus, no statistical review for efficacy is required. Instead, the Division of Reproductive and Urologic Drug Products is conducting a review of the chemistry and labeling issues and safety update.

Sonia Castillo, Ph.D.
Mathematical Statistician
HFD-715

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/s/

Sonia Castillo
7/19/05 10:38:32 AM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA:	21-355
Name of Drug:	Angeliq (Drospirenone/Estradiol)
Indication:	Hormone Replacement Therapy
Sponsor:	Berlex Laboratories, Inc.
Documents Reviewed:	Study Reports and the data submitted to Electronic Document Room: \\CDSESUB1\N21355\N_000\2001-12-14 \\CDSESUB1\N21355\N_000\2002-02-08 \\CDSESUB1\N21355\N_000\2002-03-13
Date Received:	December 17, 2001
Project Manager:	Archana Reddy, HFD-580
Clinical Reviewer:	Lesley A. Furlong, M.D., HFD-580
Clinical Team Leader:	Shelley R. Slaughter, M.D., HFD-580
Statistical Reviewer:	Sonia Castillo, Ph.D., HFD-715
Statistical Team Leader:	Michael Welch, Ph.D., HFD-715
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Key Words:	Clinical studies, NDA review, One Study Application.

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1 BACKGROUND AND INDICATION

Symptoms and conditions associated with menopause are the result of the decline of endogenous production of estrogen. Estrogen replacement therapy reduces the number of hot flushes and improves urogenital symptoms. In women who have not had a hysterectomy, however, estrogen monotherapy has been shown to be associated with an increased incidence of endometrial hyperplasia and increased risk of carcinoma. The addition of a progestin to the estrogen therapy minimizes the risk of endometrial cancer. Drospirenone (DRSP) is a progestin used in this application for combination hormone replacement.

Study 96097A was designed to determine the dose of DRSP that would prevent the development of endometrial hyperplasia when used in combination with estradiol (E2). Table 1.1 presents a brief summary of the one study submitted in this application.

Table 1.1
Brief Summary of Study 96097A

Study Number (Dates Conducted)	Number of Centers (Location)	Treatment	Sample Size (ITT)	Design	Duration of Treatment
96097A (1-22-98 to 4-28-01)	53 (USA)	1 mg estradiol 0.5 mg drospirenone + 1 mg estradiol 1.0 mg drospirenone + 1 mg estradiol 2.0 mg drospirenone + 1 mg estradiol 3.0 mg drospirenone + 1 mg estradiol	226 227 231 227 231 Total: 1142	Double Blind, Randomized, Parallel Group	Thirteen 28-day cycles

Source: Statistical reviewer's listing.

The Division of Reproductive and Urologic Drug Products agreed to accept biopharmaceutical proof of efficacy through demonstration of the bioequivalence of estradiol to estrace, an approved estrogen product. They also agreed to a one-study application. Thus, this statistical review does not address efficacy for the proposed hormone replacement therapy. Instead, this statistical review focuses on the demonstration that the addition of progestin to the estradiol component of the proposed product provides protection against endometrial hyperplasia or cancer.

The sponsor's proposed indication is:

> *ANGELIQ TABLETS is indicated in women with an intact uterus for: the treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy;* [redacted]

2 STUDY DESIGN

2.1 Study Description

Study 96097A is a multicenter (53 U.S. centers), double-blind, randomized, parallel-group study comparing 0.5 mg, 1 mg, 2 mg, and 3 mg drospirenone (DRSP) + estradiol (E2) with continuous E2 alone (active control). Postmenopausal women aged 45 to 75 years who satisfied the inclusion criteria, which included a diagnostically valid negative endometrial biopsy or, if inadequate tissue, endometrial thickness < 5 mm on vaginal ultrasound, were randomly assigned to 1 of the 5 treatment groups listed above. The study was divided into 13 28-day treatment periods or cycles. Subjects were instructed to take 1 tablet daily and evaluations for efficacy and safety were scheduled at 7 specified office visits. Endometrial biopsies were performed at the screening visit and at the final visit. Additional biopsies were performed at the discretion of the investigator. If the tissue from an endometrial biopsy was insufficient for diagnosis, then transvaginal ultrasonography was performed.

A central reading laboratory, [redacted] was used for all endometrial biopsy specimens. Lab pathologists performed the safety read and three independent pathologists, who are blinded to

treatment, performed the efficacy read. One of the pathologists who performed the safety read ( ) was also one of the primary pathologists who performed the efficacy read. Table 2.1 presents the 10 endometrial biopsy diagnoses used for both reads. Per protocol, the pathologists met to discuss the criteria for hyperplasia prior to reading any slides for the efficacy read. If the two primary pathologists do not provide an identical diagnosis, the third pathologist acted as an arbitrator. The majority opinion is binding. If the arbitrator does not agree with either of the principal readers, the three pathologists will meet to jointly re-evaluate the slides to achieve consensus.

Table 2.1
Study 96097A: Ten Endometrial Biopsy Diagnoses

Endometrial Biopsy Diagnoses	
Tissue insufficient for diagnosis	Menstrual type endometrium
Strips of benign surface & glandular lining epithelium	Simple hyperplasia without cytological atypia
Inactive / atrophic endometrium	Complex hyperplasia without cytological atypia
Proliferative endometrium	Atypical hyperplasia
Progestational secretory endometrium	Cancer

2.2 Primary Objective and Efficacy Variable

The primary objectives of this study are to evaluate the efficacy and safety of thirteen, 28-day cycles of 4 E2-DRSP (estradiol-drospirenone) combinations compared with E2 by analysis of protection against hyperplasia in postmenopausal women. The occurrence of endometrial hyperplasia was the primary efficacy variable.

2.3 Statistical and analytical plans

For each group, the incidence of endometrial hyperplasia/cancer was estimated as a binomial proportion. A 95% one-sided confidence interval was computed for the incidence of hyperplasia/cancer for each treatment group. In addition, responses from the subjects who withdrew from the study without having a post-baseline biopsy or with insufficient sample if biopsy was attempted, were imputed using a computer simulation method and then data were analyzed using a life table method. Use of this imputation method leads this statistician to conclude that the imputed hyperplasia data is questionable; thus these results will not be presented.

3 STUDY RESULTS

3.1 Subject Enrollment, Randomization, Disposition, and Demographics

Table 3.1 presents a summary of the subject enrollment, randomization, and disposition. A total of 1147 subjects were enrolled and randomized at 53 study sites. Most study sites (n=41) randomized between 11 and 30 patients, 1 had more than 51 patients, and 11 sites had between 1 and 10 patients. There were 1142 subjects who were treated and made up the ITT population because 5 subjects were dispensed study medication but no information could be obtained regarding how much study medication was taken. Of the 1142 subjects in the ITT population, 297 (26%) subjects did not complete the study and 845 subjects completed the study. Each group had about 150 or more completed subjects, the number specified in the protocol.

Table 3.1
Study 96097A: Summary of Subject Disposition

Population	E2 1 mg	E2 + 0.5 mg DRSP	E2 + 1 mg DRSP	E2 + 2 mg DRSP	E2 + 3 mg DRSP	Total
Number of Subjects Randomized	227	228	231	228	233	1147
Number (%) of Subjects in ITT Efficacy Population*	226 (99.6)	227 (99.6)	231 (100.0)	227 (99.6)	231 (99.2)	1142 (99.6)
Number (%) of Subjects Who Completed Study	149 (65.9)	179 (78.8)	169 (73.2)	173 (76.2)	175 (75.8)	845 (74.0)
Number (%) of Subjects Who Did Not Complete Study	77 (34.1)	48 (21.2)	62 (26.8)	54 (23.8)	56 (24.2)	297 (26.0)
Reasons for Not Completing:						
Adverse Event	53 (23.5)	29 (12.8)	35 (15.2)	39 (17.2)	33 (14.3)	189 (16.6)
Lack of Efficacy	1 (0.4)	0	0	0	0	1 (0.1)
Protocol Deviation	6 (2.7)	4 (1.8)	9 (3.9)	6 (2.6)	5 (2.2)	30 (2.6)
Withdrawal of Consent	10 (4.4)	11 (4.9)	9 (3.9)	3 (1.3)	11 (4.8)	44 (3.9)
Other	7 (3.1)	4 (1.8)	9 (3.9)	6 (2.6)	7 (3.0)	33 (2.9)

Source: Text Tables 8 and 9, page 43.
Note: All percentages are relative to the number of ITT subjects except as noted otherwise.
* Percentages are relative to the number of subjects randomized.

Of the 1142 ITT subjects, the mean age is 56 years and the majority (92%) of subjects are Caucasian. Treatment groups are comparable in race and age.

3.2 Sponsor's Efficacy Results and Conclusion

The ITT population included all subjects randomized to the study and known to have taken at least 1 dose of study medication. Of the 1142 subjects included in the ITT population, 226 subjects received E2 alone, 227 subjects received 0.5 mg DRSP + E2, 231 subjects received 1 mg DRSP + E2, 227 subjects received 2 mg DRSP + E2, and 231 subjects received 3 mg DRSP + E2.

A total of 806 subjects were included in the analysis of the incidence of endometrial hyperplasia at any time for the ITT population. This analysis did not include subjects who withdrew before completing 1 year of treatment with no evidence of endometrial hyperplasia.

Table 3.2 presents the proportion of subjects with endometrial hyperplasia and/or cancer at any time during the study. Endometrial hyperplasia was diagnosed for 19 subjects who received E2 alone and 1 subject who received 0.5 mg DRSP + E2. No subjects in the other 3 E2 +DRSP combination treatment groups had endometrial hyperplasia. There were no subjects who had endometrial cancer. None of the upper bounds of the one-sided 95% confidence interval for the incidence of hyperplasia exceeds 4%, as documented in the 1995 Hormone Replacement Therapy (HRT) Guidance (draft).

Table 3.2
Study 96097A: Incidence of Endometrial Hyperplasia and/or Cancer within 1 Year for Each Treatment Group Using Efficacy Readings

Treatment	n [1]	Estimate of Incidence of Hyperplasia or Worse [2] (n)	Upper bound of one-sided 95% confidence interval for Incidence of Hyperplasia or Worse [3]
Estradiol Alone	155	0.123 (19)	0.175
Estradiol + 0.5 mg Drospirenone	171	0.006 (1)	0.027
Estradiol + 1 mg Drospirenone	157	0.000 (0)	0.019
Estradiol + 2 mg Drospirenone	161	0.000 (0)	0.018
Estradiol + 3 mg Drospirenone	162	0.000 (0)	0.018

Source: Text Table 16 and Table 15, pages 53 and 510, respectively. An exact one-sided Clopper-Pearson 95% confidence interval was calculated by the statistical reviewer using the data in Table 15 because the sponsor instead computed an exact two-sided 95% confidence interval.
[1] Subjects with endometrial hyperplasia at baseline were excluded from the analysis. Subjects without diagnosis of hyperplasia who did not complete 1 year of treatment were excluded.

Based on the above results, the sponsor concludes that DRSP in combination with E2 was efficacious in protecting against endometrial hyperplasia in postmenopausal women.

3.3 Reviewer's Efficacy Analyses

Two problems were identified in the blinded read procedure used in this study. On occasions when the three pathologists gave different diagnoses, a consensus read was performed. The Division does not view a consensus read as acceptable. Instead, if there is no agreement among the three pathologists, the most severe pathological diagnosis should be used. Also, a training session for the blinded readers before evaluation of the biopsy slides was performed in the study, which is also not acceptable to the Division.

The following analyses used cases that were identified using only the three pathologists' diagnoses. Two of the three had to agree; and if none agreed, then the most severe pathological diagnosis was selected. The dataset used in the following analyses removed those patients who entered the study with hyperplasia, did not take study medication, only had a screening biopsy, had no biopsies, or had a 3 month or greater lag between the last dose taken and the last biopsy performed. This was done per the Medical Reviewer. Table 3.3 presents the numbers of removed patients.

Table 3.3
Study 96097A: Patients Removed from Statistical Reviewer's Analyses

Treatment	Entered study with hyperplasia	No Drug	Only screening biopsy	No Biopsies	≥ 3 months between last dose and last biopsy	Total
Estradiol Alone	0	1	24	5	10	40
Estradiol + 0.5 mg Drospirenone	0	1	27	9	5	42
Estradiol + 1 mg Drospirenone	1	0	31	9	3	44
Estradiol + 2 mg Drospirenone	0	1	24	8	6	39
Estradiol + 3 mg Drospirenone	0	2	30	8	4	44

Source: Statistical reviewer's listing.

Table 3.4 presents the proportion of subjects with endometrial hyperplasia and/or cancer at any time during the study using the efficacy readings. Endometrial hyperplasia was diagnosed for 25 subjects who received E2 alone, 1 subject who received 0.5 mg DRSP + E2, and 1 subject who received 1 mg DRSP + E2. No subjects in the other 2 DRSP combined with E2 treatment groups had endometrial hyperplasia. There were no subjects in the efficacy read who had endometrial cancer. None of the upper bounds of the one-sided 95% confidence interval for the incidence of hyperplasia exceeds 4%, as documented in the 1995 HRT Guidance (draft).

Table 3.4
Study 96097A: Incidence of Endometrial Hyperplasia and/or Cancer within 1 Year for Each Treatment Group Using Efficacy Readings

Treatment	n [1]	Estimate of Incidence of Hyperplasia or Worse [2] (n)	Upper bound of one-sided 95% confidence interval for Incidence of Hyperplasia or Worse [3]
Estradiol Alone	186	0.134 (25)	0.183
Estradiol + 0.5 mg Drospirenone	185	0.005 (1)	0.025
Estradiol + 1 mg Drospirenone	187	0.005 (1)	0.025
Estradiol + 2 mg Drospirenone	188	0.000 (0)	0.016
Estradiol + 3 mg Drospirenone	187	0.005 (1)	0.025

Source: Statistical Reviewer's listing from sponsor SAS data sets
[1] Subjects who took drug and had a biopsy at either end of study or when they withdrew from study are included.
[2] Includes categories of simple hyperplasia without cytological atypia, complex hyperplasia without cytological atypia, atypical hyperplasia, and cancer.
[3] Upper limit based on exact Clopper-Pearson confidence interval.

An analysis which removed those women with insufficient tissue for diagnosis and >5 mm endometrial thickness was performed per a request from the Medical Reviewer. Since there were few of these women in 3 of the 5 groups, there was no difference in results as seen in Table 3.4.

Table 3.5 presents the proportion of subjects with endometrial hyperplasia and/or cancer at any time during the study using data from the unblinded safety readings. The safety read results are presented because the Medical Reviewer wanted to compare the efficacy read results with the safety read results. Endometrial hyperplasia was diagnosed for 22 subjects who received E2 alone, 4 subjects who received 0.5 mg DRSP + E2, 1 subject who received 1 mg DRSP + E2, 3 subjects who received 2 mg DRSP + E2, and 2 subjects who received 3 mg DRSP + E2. There are no subjects in the safety read who had endometrial cancer. The upper bounds of the one-sided 95% confidence interval for the incidence of hyperplasia exceeds 4% in the 0.5 mg DRSP + E2 and 2 mg DRSP + E2 groups.

Table 3.5
Study 96097A: Incidence of Endometrial Hyperplasia and/or Cancer within 1 Year for Each Treatment Group Using Safety Readings

Treatment	n [1]	Estimate of Incidence of Hyperplasia or Worse [2] (n)	Upper bound of one-sided 95% confidence interval for Incidence of Hyperplasia or Worse [3]
Estradiol Alone	186	0.118 (22)	0.165
Estradiol + 0.5 mg Drospirenone	185	0.022 (4)	0.049
Estradiol + 1 mg Drospirenone	187	0.005 (1)	0.025
Estradiol + 2 mg Drospirenone	188	0.016 (3)	0.041
Estradiol + 3 mg Drospirenone	187	0.011 (2)	0.033

Source: Statistical Reviewer's listing from sponsor SAS data sets
[1] Subjects who took drug and had a biopsy at either end of study or when they withdrew from study are included.
[2] Includes categories of simple hyperplasia without cytological atypia, complex hyperplasia without cytological atypia, atypical hyperplasia, and cancer.
[3] Upper limit based on exact Clopper-Pearson confidence interval.

3.4 Conclusions

From a statistical standpoint, the sponsor has provided one study that is well controlled and adequate for demonstrating the protective effect of 1 mg and 3 mg drospirenone in combination with estradiol against the development of endometrial hyperplasia and/or cancer in patients receiving ANGELIQ as hormone replacement therapy.

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/s/

Sonia Castillo
9/18/02 02:21:20 PM
BIOMETRICS

Mike Welch
9/19/02 03:30:34 PM
BIOMETRICS
Concur with review.

NDA 21-355
Drug: Angeliq™ (drospirenone/17β-estradiol)

Statistical Review/Dissolution Stability

A statistical review of dissolution stability is not required.

AR 6/15/02