CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-676

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-676
Drug Name:	YAZ (Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg) Tablets
Indication(s):	Prevent Pregnancy (Oral Contraception)
Applicant:	Berlex Laboratories, Inc.
Date(s):	
Submission:	Complete Response: June 16, 2005
User Fee Goal:	March 16, 2006 (Extended)
Review Priority:	Standard
Biometrics Division:	DOB2
Statistical Reviewer:	Shahla S. Farr, M. s.
Concurring Reviewers:	Mike Welch, Ph.D. – Ed Nevius, Ph.D.
Medical Division:	Division of Reproductive and Urological Drug Products (DRUDP) HFD-580
Clinical Team:	
Medical Officer:	Gerald Willett, M.D.
Medical Team Leader:	Scott Monroe, M.D.
Project Manager:	Charlene Williamson

1. EXECUTIVE SUMMARY

Originally, the Sponsor had submitted NDA 21-676 for YAZ Tablets, in a 24-day regimen for the indication of oral contraception. Consequently, the Sponsor received an approvable letter from the Agency. In response to the approvable letter and the request from the Agency, Berlex submitted a study for Follicular Inhibition or Ovulation Inhibition (Protocol # 308382). Therefore, the focus of this review is on the above mentioned Study.

1.1 Conclusions

There were several issues and problems with this study; such as no set hypothesis prior the study initiation, no statistical rational for the sample size or for the statistical methodology, the low sample size of 100, and a short duration of only 3 cycles. Nevertheless, there is an apparent trend that the 24-day treatment might have some benefit over the 21-day. The statistical methodology that the sponsor has used is reasonable; however the study results can only be considered descriptive and not confirmatory. This reviewer assessed and re-evaluated the sponsors' results. The findings were similar to that of the Sponsor's.

Comparison of the results of the recalculations of the primary efficacy endpoints with the original evaluation, show a trend toward better follicular suppression obtained with the 24 day regimen compared to the 21 day regimen.

1.2 Brief Overview of the Clinical Study

This was a single center, double-blind, randomized study to compare the effect of SH T 00186 D on follicular development (follicular size and the incidence of ovulation in normal cycles) in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3.

1.3 Statistical Issues and Findings

There were several issues and problems with this study; such as no set hypothesis prior the study initiation, no statistical rational for the sample size or for the statistical methodology, the low sample size of 100, a short duration of only 3 cycles. Thus results can only be considered to be descriptive. The 24-day treatment shows a trend that would indicate some benefit over the 21-day treatment.

2. INTRODUCTION

2.1 Overview

Originally, the Sponsor had submitted NDA 21-676 for YAZ Tablets, in a 24-day regimen for the indication of oral contraception. Consequently, the Sponsor received an approvable letter from the Agency. In response to the approvable letter and the request from the Agency, Berlex submitted a study for Follicular Inhibition or Ovulation Inhibition (Protocol # 308382). Therefore, the focus of this review is on the above mentioned Study.

The original NDA 21-676 was submitted on October 16, 2003 for YAZ Tablets, in a 24-day regimen, for the indication of oral contraception. Berlex received an approvable letter for this NDA on November 17, 2004, during the first review cycle. On June 15, 2005, Berlex responded to the approvable letter with a Resubmission.

Reference is also made to NDA 21-873 submitted on December 22, 2004 for YAZ Tablets as an oral contraceptive (OC) and for the treatment of symptoms of premenstrual dysphoric disorder. On October 21, 2005, the Division sent Berlex a clinical information request from with comments regarding Protocol 308382. The final report for this ovulation inhibition study, Report A25848, was included in the resubmission to NDA 21-6761. The clinical information request was the recalculation of the primary efficacy endpoints for the two treatment groups excluding the subjects with no progesterone level of 5ng/mL or greater during the ovulation assessment period.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This was a single center, double-blind, randomized study to compare the effect of SH T 00186 D on follicular development (follicular size and the incidence of ovulation in normal cycles) in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3.

Previously **(May 5th)** , the Sponsor had submitted data based on 99 subjects; out of which 50 were treated with the 21-day regimen and 49 were the 24-day regimen users. In that submission, Hoogland scores in cycles 2 and 3 were analyzed using a proportional odds model and an odds ratio between treatments.

May 5th (Based on 99 Subjects)
Estimated odds ratio for having a lower Hoogland score by cycle - FAS , PPS

Cycle	**Analysis sets**	**Estimated odds ratio**	**95% CI**
2	FAS	6.91	[2.67; 20.49]
	PPS	6.01	[2.29; 17.94]
3	FAS and PPS	3.06	[1.44; 6.65]

In response to the Division's October 21, 2005 request, additional analysis was performed and submitted by the Sponsor. The evaluation of the primary efficacy variables was redone, excluding 21 subjects (11 subjects from the 24-day regimen and 10 subjects from the 21-day regimen) specified by the FDA.

Odds ratios for treatment effect in cycles 2 and 3 - **FAS excluding the 21 subjects** specified by the FDA:

Cycle	**Estimated Odds ratio**	**95% CI**
2	7.65	[2.82 ; 23.57]
3*	2,35	[1.03 ; 5.47]

* The results of the cycle 3 were the same for FAS as well as PPS

Based on another request from the Division to exclude subjects with progesterone levels not higher than 1.57 ng/ml in the baseline cycle, the evaluation of the primary efficacy variables was repeated.

Odds ratios for treatment effect in cycles 2 and 3 – **PPS excluding the 8 subjects** with all baseline progesterone levels below 1.57 ng/ml:

Cycle	**Odds ratio**	**95% CI**
2	6.55	[2.46 ; 19.78]
3*	2.68	[1.24 ; 5.92]

* The results of the cycle 3 were the same for FAS as well as PPS

Odds ratios for treatment effect in cycles 2 and 3 - **FAS excluding the 8 subjects** with all baseline progesterone levels below 1.57 ng/ml:

Cycle	**Odds ratio**	**95% CI**
2	7.56	[2.88 ; 22.68]
3	2.68	[1.24 ; 5.92]

4. CONCLUSIONS

This study lacked a prospective statistical analysis plan and can only be considered to be descriptive. There is an apparent trend that the 24-day regimen might have some benefit over the 21-day regimen. The statistical methods that the sponsor has used seems to be reasonable. This reviewer assessed and re-evaluated the sponsors' results. The findings were similar to that of the Sponsor's.

Comparing the results of three different recalculations of the primary efficacy endpoints with the original evaluation, better follicular suppression is indicated with the 24 day regimen compared to the 21 day regimen.

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/s/

Mike Welch
1/18/2006 04:32:36 PM
BIOMETRICS
Submitted for Shahla Farr. Concur with review.

S. Edward Nevius
1/18/2006 05:04:48 PM
BIOMETRICS
Concur with review.

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-676
Drug Name:	YAZ (Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg) Tablets
Indication:	Prevention of Pregnancy (Oral Contraception)
Applicant:	Berlex Laboratories, Inc.
Dates:	
Submission:	October 16, 2003
Filing:	December 16, 2003
User Fee Goal:	August 17, 2004
Ext. User Fee Goal:	November 17, 2004
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Shahla S. Farr, M.S.
Statistical Team Leader:	Mike Welch, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products, HFD-580
Clinical Team:	
Medical Officer:	Gerald Willett, M.D.
Medical Team Leader:	Scott Monroe, M.D.
Project Manager:	Charlene Williamson

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1. EXECUTIVE SUMMARY

The sponsor had submitted the results of one open-label, one-arm, multi-center, multi-national and uncontrolled pivotal, Phase 3 clinical study to evaluate the safety and efficacy of Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets in a 24-day regimen (Study A12007) for prevention of pregnancy in women. However, due to potential safety concerns regarding the length of the 24-day regimen, the clinical review team asked that Study A15129 which used a 21 day regimen, also be reviewed. This review addresses the efficacy outcomes for both studies.

1.1 Conclusions

Based on the data provided by the sponsor, Study A12007 for Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets, 24-day regimen, shows a Pearl index of 1.41 (95% CI: 0.73 to 2.42) based on 12 pregnancies. For Study A15129, for the 21-day regimen, the Pearl index is 0.35 (95% CI: 0.06 to 1.02) based on 3 pregnancies.

1.2 Overview of Clinical Studies

Table 1 summarizes the studies for this review.

Table 1: Overview of Studies

Study # (N) Regimen Duration	Study Design	# of Centers	Location	Age	Total # of Cycles	# of Pregnancies
A12007 (1027) 24-day Regimen for 13 Cycles	One Arm, Uncontrolled, open-label	35	Europe South America United States	17 - 36	11,036	12
A15129 (516) 21-day Regimen for 26 Cycles	One Arm, Uncontrolled, open-label	33	Germany Switzerland	18 - 36	11,219	3

The primary efficacy parameter for both of the studies is the Pearl index (rate). The pregnancy rate and cumulative rate based on a life table analysis are used as supportive outcomes. In this review, each study will be examined and reported individually.

Two deaths occurred in the United States site for Study A12007. According to the sponsor, these deaths were not related to the study medication. No deaths were reported for Study A15129.

1.3 Statistical Issues and Findings

For Study A12007, the sponsor reported a total of 11 pregnancies. However, the medical reviewer counted one additional pregnancy. The Pearl index, pregnancy rate, and associated two-sided 95% confidence intervals (CI) based on 12 pregnancies are shown in Table 2 for all cycles and for cycles with no other form of contraception. The results based on 11 pregnancies are shown in Section 3 of this review.

Table 2: Study A12007 - Pregnancy Rates, Pearl Indices and Associated Two-Sided 95% CI's for All Cycles (All) and Cycles with No Other Form of Contraception Use (NOCON)

Study A12007 (N=1027)					
	Total Number of Cycles	Pregnancy (n=12)		Pearl index	
		Rate	95% CI	Rate	95% CI
All	12,746	0.012	(0.006, 0.020)	1.22	(0.63, 2.09)
NOCON	11,036			1.41	(0.73, 2.42)

The cumulative life table estimate of pregnancy rate is 0.01 with 95% CI (0.005, 0.018).

In Study A15129, according to the sponsor, 2 pregnancies were considered as having occurred during treatment period. However, according to the clinical reviewer, there were a total of 3 pregnancies in this trial. The pregnancy rates, Pearl indices and the associated two-sided 95% CI's based on 3 pregnancies are shown in Table 3 for all cycles and for cycles with no other form of contraception. The results based on 2 pregnancies are shown in Section 3 of this review.

Table 3: Study A15129 - Pregnancy Rates, Pearl Indices and Associated Two-Sided 95% CI's for All Cycles (All) and Cycles with No Other Form of Contraception Use (NOCON)

Study A15129 (N=516)					
	Total Number of Cycles	Pregnancy (n=3)		Pearl index	
		Rate	95% CI	Rate	95% CI
All	12,712	0.0058	(0.001, 0.017)	0.31	(0.05, 0.90)
NOCON	11,219			0.35	(0.06, 1.02)

The cumulative life table estimate of pregnancy rate is 0.006 with 95% CI (0.000, 0.012).

2. INTRODUCTION

2.1 Overview

Study A12007 (24-day regimen)

A 24-day regimen, uncontrolled, open-label clinical study that includes data from 35 centers in Europe, South America and the United States (1 site) to evaluate the safety and efficacy of Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets for prevention of pregnancy in women 17 to 36 years of age. The duration of treatment was 13 cycles. A total of 1027 women were instructed to take one tablet daily for 24 days in sequence, followed by 4 days of 1 inert tablet daily.

A total of 11 pregnancies were reported by the sponsor, where 7 of them had occurred in Brazil, 2 in Austria, one in Argentina and one is the USA. There were no pregnancies in Poland. Seven of the pregnancies were among the Caucasians, 3 in the Black and one in the Hispanic group. However, based on the Medical Officer's findings, there were a total of 12 pregnancies in this trial. The pregnancy rates, Pearl indices and associated confidence intervals, based on both 11 and 12 pregnancies, are reported for all the subjects as a whole and for subjects who did not use any other form of contraception.

Two deaths occurred in the United States site, which, according to the sponsor, were not related to the study medication.

The clinical team expressed concerns regarding potential safety of the 24-day regimen for this drug, and the team asked that the other study (based on a 21-day regimen) be reviewed as well, although this latter study was not considered a principal study by the sponsor.

Study A15129 (21-day regimen)

A 21-day regimen, uncontrolled, open-label clinical study that includes data from 33 centers in 2 countries, Germany (27) and Switzerland (6) to evaluate the safety and efficacy of Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets for prevention of pregnancy in women 18 to 36 years of age. The duration of treatment was 26 cycles. A total of 516 subjects were instructed to take one tablet daily for 21 days in sequence, followed by 7 days of tablet-free interval.

In Study A15129, according to the sponsor, 2 pregnancies were considered as having occurred 'during treatment period'. However, the Medical Officer counted one additional pregnancy. In this review, both 2 and 3 pregnancies are assessed and reported.

No deaths were reported for this study.

Table 4 summarizes the main features of the two studies.

Table 4: Overview of Studies

Study # (N) Regimen Duration	Study Design	# of Centers	Location	Age	Total # of Cycles	# of Pregnancies
A12007 (1027) 24-day Regimen for 13 Cycles	One Arm, Uncontrolled, open-label	35	Europe South America United States	17 - 36	11,036	12
A15129 (516) 21-day Regimen for 26 Cycles	One Arm, Uncontrolled, open-label	33	Germany Switzerland	18 - 36	11,219	3

2.2 Data Sources

For the review of this application, the electronic study reports of the two Phase 3 studies (Study A12007 & Study A15129) were reviewed. In addition, the electronic SAS data sets submitted by the sponsor were analyzed and evaluated individually. The electronic data sets include:

\\CDSESUB1\N21676\N_000\2003-10-16 (Study A12007)
\\CDSESUB1\N21676\N_000\2003-11-18 (Study A12007)
\\CDSESUB1\N21676\N_000\2004-06-29 (Study A12007)
\\CDSESUB1\N21676\N_000\2004-03-18 (Study A15129)
\\CDSESUB1\N21676\N_000\2004-08-23 (Study A15129)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study A12007: Based on the sponsor's report, a total of 1027 subjects received at least 1 dose of study medication and had at least 1 post-treatment observation. These women were between the ages of 18 and 35, except one who was 17 and another one 36 years of age. These subjects were not excluded from the analysis of efficacy. The mean age and standard deviation were 24.7 ± 4.4. The majority of the subjects (88%) were Caucasian. Thirty five investigators from 5 countries: Argentina (n=169, 16%), Austria (n=472, 46%), Brazil (n=190, 19%), Poland (n=120, 12%) and USA (n=76, 7%) had participated in this trial, with each enrolling between 5 and 80 subjects. Due to some problems handling the data in one of the sites in Brazil, with the agreement of the Medical Division, the sponsor had excluded that center from the analyses. . At the end of the study, there was a small decrease in the weight of the subjects from their baseline; on average, 61.06 kilograms at baseline vs. 60.97 kilograms at the last cycle, a loss of about 0.1 kilograms.

Based on the sponsor's report, a total of 11 pregnancies had occurred, where 7 of them were in Brazil, 2 in Austria, one in Argentina and one in the USA. There were no pregnancies in Poland. Seven of these pregnancies were among the Caucasians, 3 in the Black and one in the Hispanic group.

During the study, two deaths occurred at the United States site. According to the sponsor, these deaths were not related to the study medication.

Study A15129: A total of 516 subjects from 33 centers in 2 countries; Germany (27) and Switzerland (6) between the ages of 18 to 36 were instructed to take one tablet daily for 21 days in sequence, followed by 7 days of tablet-free interval. The duration of treatment was 26 cycles. Each site had enrolled between 6 and 30 volunteers. Germany had enrolled 429 (83%) women and Switzerland entered a total of 87 (17%) subjects into the study. The mean age and standard deviation were 24.6 ± 4.5. A total of 3 subjects were 36 years old, these subjects were not excluded from the study. A total of 6 subjects had notified the investigators that they are not sexually active. These subjects were not disqualified by the sponsor. These subjects were included in this reviewer's analyses, as well. The majority of the subjects (98%) were Caucasian. At the end of the study, there was a small increase in the weight of the subjects from their baseline; on average, 63.24 kilograms at baseline vs. 63.61 kilograms at the last cycle, a gain of about 0.4 kilograms.

In Study A15129, according to the sponsor, 2 pregnancies were considered as having occurred 'during treatment period'. Both these events occurred in Germany. However, based on the Medical Officer, there were a total of 3 pregnancies in this trial. The pregnancy rates, Pearl indices and the associated confidence intervals, based on both 3 and 2 pregnancies are reported in this review for all cycles and for cycles with no other form of contraception.

Primary Efficacy Endpoint:

The primary efficacy endpoint for both studies is based on calculation of pregnancy rates using the Pearl index in women aged 18 to 36 years, excluding any cycles where other birth control methods was used. The Pearl index for each group is defined as follows: The Pearl index is to be calculated as the number of pregnancies per 100 women-years of exposure, where the numerator is the number of failures (pregnancies) and the denominator is a sum of each woman's total number of cycles of exposure.

Pearl index: (# of pregnancies × 13 cycles/year × 100) / Total # of cycles under treatment)

The primary efficacy analysis includes calculation of two-sided 95% confidence intervals for the Pearl index.

The cumulative life table pregnancy rates are also calculated as supportive evidence.

This review will focus only on the results of the primary efficacy objective, contraception, in woman 18 to 36 years of age who did not use any other method of contraception in the cycles under the study. For these analyses, the specific cycles when subjects had missing information regarding use of other barriers or had, in fact, used other method of contraception, were deleted. The data for the rest of the cycles for that subject was used.

The pregnancy rates, Pearl indices and associated confidence intervals for all cycles and for cycles with no other form of contraception are shown in Tables 5.1 and 5.2 for Study A12007 and Tables 6.1 and 6.2 for Study A15129.

Table 5.1: Study A12007 - Pregnancy Rates, Pearl Indices and Associated Two-Sided 95% CI's for All Cycles (All) and Cycles with No Other Form of Contraception Use (NOCON) - Based on 12 Pregnancies

Study A12007 (N=1027)					
	Total Number of Cycles	Pregnancy (n=12)		Pearl index	
		Rate	95% CI	Rate	95% CI
All	12,746	0.012	(0.006, 0.020)	1.22	(0.63, 2.09)
NOCON	11,036			1.41	(0.73, 2.42)

The cumulative life table estimate of pregnancy rate was 0.01 with 95% CI (0.005, 0.018).

Table 5.2: Study A12007 - Pregnancy Rates, Pearl Indices and Associated Two-Sided 95% CI's for All Cycles (All) and Cycles with No Other Form of Contraception Use (NOCON) - Based on 11 Pregnancies

Study A12007 (N=1027)					
	Total Number of Cycles	Pregnancy (n=11)		Pearl index	
		Rate	95% CI	Rate	95% CI
All	12,746	0.011	(0.005, 0.020)	1.12	(0.52, 1.99)
NOCON	11,036			1.30	(0.60, 2.30)

The above results are comparable to the sponsor's: Pearl index=1.29, upper 97.5% CI=2.30.

The reviewer's cumulative life table estimate of pregnancy rate is: 0.010 with 95% CI (0.004, 0.017). The sponsor's estimate for the life table estimate is: 0.013, with 95% CI (0.005, 0.020).

Table 6.1: Study A15129 - Pregnancy Rates, Pearl Indices and Associated Two-Sided 95% CI's for All Cycles (All) and Cycles with No Other Form of Contraception Use (NOCON) - Based on 3 Pregnancies

Study A15129 (N=516)					
	Total Number of Cycles	Pregnancy (n=3)		Pearl index	
		Rate	95% CI	Rate	95% CI
All	12,712	0.0058	(0.001, 0.017)	0.31	(0.05, 0.90)
NOCON	11,219			0.35	(0.06, 1.02)

The life table estimates of pregnancy rate were 0.006 with 95% CI (0.000, 0.012).

Table 6.2: Study A15129 - Pregnancy Rates , Pearl Indices and Associated Two-Sided 95% CI's for All Cycles (All) and Cycles with No Other Form of Contraception Use (NOCON) - Based on 2 Pregnancies

Study A15129 (N=516)					
	Total Number of Cycles	Pregnancy (n=2)		Pearl index	
		Rate	95% CI	Rate	95% CI
All	12,712	0.0039	(0.001, 0.014)	0.20	(0.05, 0.74)
NOCON	11,219			0.23	(0.06, 0.84)

The above results are similar to the sponsor's: Pearl index=0.23, upper 97.5% CI=0.84

The reviewer's cumulative life table estimate of pregnancy rate is: 0.004 with 95% CI (0.000, 0.009). The sponsor's estimate is: 0.004, with 95% CI (0.000, 0.010).

3.2 Evaluation of Safety

For information regarding the safety of this medication, please refer to the Medical Officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No subgroup analysis was deemed necessary.

5. SUMMARY AND CONCLUSIONS

5.1 Conclusions

Based on the data provided by the sponsor, Study A12007 for Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets, 24-day regimen, shows a Pearl index of 1.41 (95% CI from 0.73 to 2.42) based on 12 pregnancies. For Study A15129, for the 21-day regimen, the Pearl index is 0.35 (95% CI from 0.06 to 1.02) based on 3 pregnancies.

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/s/

Mike Welch
11/16/04 01:54:32 PM
BIOMETRICS
Submitted for reviewer. Concur with review.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)