

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-992/S-016**

**STATISTICAL REVIEW(S)**

**Screening of New NDAs  
Division of Biometrics II**

**NDA #: 20-992/S-016**

**Trade Name: Cenestin® Tablets, 0.3 mg**

**Generic Name: Synthetic Conjugated Estrogens, A**

**Sponsor: Duramed Pharmaceutical, Inc.**

**Indication: Treatment of vulvar and vaginal atrophy associated with menopause women**

**No. of Controlled Studies: 1**

**User Fee Goal Date: June 17, 2002**

**Date of Submission: August 16, 2001**

**Date of 45 Day Meeting: October 9, 2001**

**Medical Reviewer : Therasa van der Vlugt, M.D. (HFD-580)**

**Project Manager: Diane Moore (HFD-580)**

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**Anticipated Review Completion Date: April 1, 2002**

**Comments: Data and analysis are included in this submission, this is fileable**

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### CHECKLIST

Item	Check (NA if not applicable)
<b>Index sufficient to locate necessary, tables, etc.</b>	Yes
<b>Original protocols &amp; subsequent amendments available in the NDA</b>	Yes
<b>Designs utilized appropriate for the indications requested</b>	Yes
<b>Endpoints and methods of analysis spelled out in the protocols</b>	Yes
<b>Interim analyses (If present) planned in the protocol and appropriate adjustments in significance level made</b>	NA
<b>Appropriate references included for novel statistical methodology (if present)</b>	NA
<b>Sufficient data listings and intermediate analysis tables to permit a statistical review</b>	Yes
<b>Data from primary studies on diskettes and/or Electronic submitted</b>	Yes
<b>Intent-to-treat analyses</b>	Yes
<b>Effects of dropouts on primary analyses investigated</b>	Yes
<b>Safety and efficacy for gender, racial, and geriatric subgroups investigated</b>	NA

### Brief Summary of Controlled Trials

<b>Study Number Date conducted Date of study completion</b>	<b>Number of Centers</b>	<b>Total Sample Size</b>	<b>Trial Design</b>	<b>Treatment Group</b>	<b>Duration</b>
DPI00-005 11/13/2000 6/15/2001	6 centers US	71	Randomized, multicenter, double-blind, placebo control, Parallel group	Cenestin N=37  Placebo N=34	16 Weeks

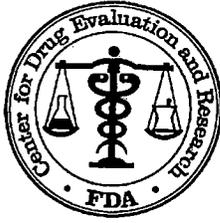
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cc. NDA 20-992/S-016  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF BIostatISTICS

# Statistical Review and Evaluation

## CLINICAL STUDIES

NDA: 20-992/S-016

Name of drug: Cenestin® Tablets (0.3 mg synthetic conjugated estrogen, A)

Applicant: Duramed Pharmaceuticals, Inc.

Indication: Treatment of vulvar and vaginal atrophy associated with the menopause

Documents reviewed: \\CDSESUB1\N20992\S\_016\2001-08-29

Project manager: Dornette Spell-LeSane

Clinical reviewer: Theresa H. van der Vlugt, M.D., M.P.H.

Dates: Received 8/17/01; user fee 6/17/02; division goal 5/17/02

Statistical reviewer: Moh-Jee Ng, M.S.

Statistics team leader: Michael Welch, Ph.D.

Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, analysis of covariance

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## 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

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### 1.1 CONCLUSIONS

The difference between 0.3 mg Cenestin® and placebo is highly significant based on the primary endpoint of change in vaginal maturation index (p-value < 0.0001). The significant improvement in the maturation index in the Cenestin group was detected as early as week 4, and maintained through weeks 8, 12 and 16. The changes from baseline in parabasal, intermediate and superficial cells were significantly different between Cenestin and placebo groups at all treatment periods except at week 16 for intermediate cells (see table 6).

At week 12, superficial cells were increased from 2.1% to 13.78% (mean changes=11.8%) in the Cenestin group and from 1.59% to 5.16% (mean change=3.6%) in the placebo group; intermediate cells were increased from 74.92% to 84.92% (mean changes=10.5%) in the Cenestin group, however intermediate cells were reduced from 78.26% to 75.63% (mean change=1.4) in the placebo group; but parabasal cells were reduced from 23% to 1.3% (mean changes=22.3%) in the Cenestin group and from 20.15% to 19.22% (mean change=2.1%) in the placebo group. Note that increases in superficial and intermediate cells and decreases in parabasal cells are beneficial effects.

For secondary endpoints, there were statistically significant differences between Cenestin® and placebo groups in vaginal pH, Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, and Total/HDL cholesterol ratio (see Table 7). There was no statistically significant difference in the LDL/HDL cholesterol ratio.

### 1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

In this submission, the sponsor has presented one clinical trial - DPI00-005. It is a multicenter, randomized, double-blind, placebo-controlled trial with two parallel treatment arms for the treatment of vulvar and vaginal atrophy. This is a 16-week trial to demonstrate the safety and efficacy of 0.3 mg Cenestin. The primary efficacy endpoint is change in vaginal maturation index from pretreatment at the end of treatment. Secondary efficacy endpoints are change in the maturation index values between pretreatment at each interim visit, change in vaginal pH from week -2 at week 16, and changes in serum lipid profiles from the average of weeks -2 and 0 at the average of weeks 12 and 16.

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## 2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

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### 2.1 INTRODUCTION AND BACKGROUND

Cenestin® has been approved by FDA at doses of 0.625 mg, 0.9 mg and 2 x 0.625 mg tablets for the treatment of moderate-to-severe vasomotor symptoms (MSVS) in a

postmenopausal population (NDA 20-992). However, a lower dose of 0.3 mg of Cenestin was not approved because of an insufficient number of patients.

In this NDA, the sponsor included a single 16-week multicenter clinical trial to demonstrate the safety and efficacy of 0.3 mg Cenestin in the treatment of vulvar and vaginal atrophy.

**2.2 DATA ANALYZED AND SOURCES**

SAS data sets were provided by the sponsor on a CD dated August 29, 2001. Additional documentation regarding the efficacy endpoints was requested on February 21, 2002 and received on February 25, 2002.

**2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY**

This was a placebo-controlled, double-blind, randomized, parallel, multicenter clinical study. Subjects were recruited from postmenopausal women at age 30-80 years, who had undergone spontaneous amenorrhea at least 12 months prior to screening or women surgically menopausal (bilateral oophorectomy, with or without hysterectomy), at least 12 weeks prior to screening, with serum FSH levels > 40 mIU/mL, vaginal mucosa maturation index score ≤ 55, endometrial thickness ≤ 5mm, non-smoker, and body mass index 18-35 kg/m<sup>2</sup>.

In this study, 72 subjects were randomized in 5 clinical sites in US; 37 subjects in Cenestin and 35 in placebo group. One subject (No. 066) in the placebo group was excluded from the study because she did not receive the study medication. There were two pretreatment visits (weeks -2 and 0) and 4 treatment visits (weeks 4, 8, 12, and 16). Table 1, summarizes the study:

**Table 1  
 Summary of Controlled Trial**

Study Number Date conducted Date of study completion	Number of Centers	Total Sample Size	Trial Design	Treatment Group	Duration
DPI00-005 11/13/2000 6/16/2001	5 centers US	71	Randomized, multicenter, double- blind, placebo control, parallel group	Cenestin N=37 Placebo N=34	16 weeks

Sixty-three subjects completed 16 weeks of treatment period. Eight subjects (3 Cenestin, 5 Control) did not complete the study. Table 2 summarizes the disposition of subjects by treatment.

**Table 2**  
**Disposition of Subjects by Treatment**

Disposition	Cenestin (n)	Control (n)	Total (n)	p-value*
Randomized	37	34	71	
Completed	34	29	63	0.467
Did Not Complete	3	5	8	
Adverse Event	1	1	2	
Non-compliance with protocol	0	1	1	
Withdrew Consent	0	1	1	
Lost to Follow-up	1	0	1	
Other	1	2	3	

\*p-value was derived from Fisher's Exact (2-tail test).

Data Source: Table 14.1.1.a-1.

The sponsor claimed that there was no statistically significant difference in dropout rate between Cenestin and placebo groups (p=0.47, Fisher Exact 2-tails tests).

The primary efficacy endpoint is the change in vaginal maturation index from pretreatment at the end of treatment. The secondary efficacy endpoints are the changes in the maturation index value from pretreatment at each interim visit, changes in vaginal pH, vaginal microbiology and lipid profiles. All efficacy analyses are based on an intent-to-treat (ITT) population, with last observed carried forward (LOCF). The intent-to-treat is defined as all subjects randomized who completed at least one post-randomization assessment of vaginal cytology during the treatment period. The last observation carried forward (LOCF) approach was used for any missing time points after the first week. Analysis of variance models were used to assess differences between treatment groups for the change from week -2 at week 16 in the maturation index score.

Vaginal cytology was assessed by counting the number of parabasal, intermediate, and superficial cells and calculating the percentages of each cell type according to the equation:

$$\text{Maturation Index Score} = (\% \text{ Parabasal cell} \times 0.0) + (\% \text{ Intermediate cells} \times 0.5) + (\% \text{ Superficial cell} \times 1.0)$$

Table 3 lists the primary and secondary endpoints.

**Table 3**  
**Efficacy Endpoints**

<b>Primary</b>
• The change in the Maturation index from week -2 to week 16
<b>Secondary</b>
• The change in the maturation index values between week -2 and weeks 4, 8, and 12
• The change in vaginal pH from week -2 to week 16
• The change in vaginal microbiology
• The change in lipid profiles

### 2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The primary efficacy endpoint was the change in the Maturation Index score from baseline at week 16. Because the data were not normally distributed, the sponsor performed tests of the hypothesis that the medians, rather than the means are equal.

The analysis of variance showed that there was a statistically significant difference between the treatment groups at each visit ( $p < 0.0001$ ). The variables site effect and the treatment-by-site interaction were not statistically significant, therefore the final model considered only treatment effect in accordance with the protocol. The sponsor concluded that there was a significant difference between the Cenestin and the placebo groups based on the primary efficacy endpoint. A significant improvement in the maturation index in the Cenestin group was detected at week 4, and maintained through weeks 8, 12 and 16.

At week 16, superficial cells were increased from 1% to 12% (median change=11%) in the Cenestin group and from 0% to 2% (median change=1%) in the placebo group; and parabasal cells were reduced from 14% to 0% (median change=14%) in the Cenestin group and from 14.5 to 7% (median change=3.5 %) in the placebo group. Median change in maturation index was 14.5 in the Cenestin group compared to 3.8 in the placebo group. These results are shown in Table 4.

**Table 4**  
**Sponsor's Primary Efficacy Results**

Cell Type	Study Week	Cenestin® N=37		Placebo N=34		p-values
		Median	Median change from baseline	Median	Median change from baseline	
Parabasal (%)	-2	14		14.5		
	16	0	-14	7	-3.5	0.004
Intermediate(%)	-2	83		84		
	16	87	6	82	-1	0.2314
Superficial (%)	-2	1		0		
	16	12	11	2	1	0.0001
Maturation Index	16		14.5		3.8	<0.0001*

Source: Table 11.4.1.1-1 Maturation Index score: Statistical summary of the median change from week -2 to 16

Table 11.4.1.2-3 Parabasal, Intermediate, and Superficial cells: Statistical Summary

\* Primary efficacy endpoint

The sponsor performed an analysis on the change in the vaginal pH from week -2 at week 16. The mean change in vaginal pH decreased by 0.97 in the Cenestin as compared to an increase of 0.1 in the placebo group. For the lipid profiles endpoints, the sponsor performed an analysis on the change from the average of weeks -2 and 0 at the average of weeks 12 and 16. The sponsor concluded that there were significant differences between the Cenestin and the placebo groups for all variables except the triglycerides. Total cholesterol, calculated LDL cholesterol, the total/HDL cholesterol ratio, and the LDL/HDL cholesterol ratio decreased in the Cenestin group, compared to the placebo group, by 7.6%, 17.1%,

11.9%, and 21.0%, respectively. HDL cholesterol increased by 4.9% in the Cenestin group as compared to placebo group (see Table 5).

**Table 5**  
**Sponsor's Secondary Efficacy Results**

	Weeks	Cenestin (N=36)		Placebo (N=31)		* Mean Difference	** P-Values
		Mean (SD)	Mean change from baseline	Mean (SD)	Mean change from baseline		
Vaginal pH	-2	6.2 (0.9)		6.0 (0.8)			
	16	5.19 (0.8)	-0.97 (1.0)	6.1 (0.8)	0.1 (0.6)	-17.1 %	0.0001
		Cenestin (N=34)		Placebo (N=29)			
Total Cholesterol (mg/dL)	-2	227.5 (30.6)		231.2 (31.1)			
	Avg 12+16	210.6 (30.7)	-16.6 (20.9)	233.1 (26.2)	-0.3 (20.4)	-7.6%	0.0022
HDL Cholesterol (mg/dL)	-2	61.6 (14.0)		62.4 (11.4)			
	Avg 12+16	64.8 (15.9)	4.2 (6.0)	62.9 (11.3)	0.7 (7.3)	4.9%	0.043
LDL Cholesterol (mg/dL)	-2	141.5(28.6)		142.3(29.1)			
	Avg 12+16	119.8 (28.3)	-22.1 (21.2)	145.5 (24.5)	0.2 (20.1)	-17.1%	<0.0001
Triglycerides (mg/dL)	-2	122.8 (56.0)		131.5 (58.1)			
	Avg 12+16	131.9 (57.8)	6.6 (38.6)	125.8 (61.8)	-2.7 (38.2)	7.7%	0.3400
Total/HDL Cholesterol	-2	3.9 (0.9)		3.9 (0.9)			
	Avg 12+16	3.4 (0.8)	-0.5(0.5)	3.8 (0.9)	-0.04 (0.6)	-11.9%	0.0025
LDL/HDL Cholesterol	-2	2.4 (0.7)		2.4 (0.7)			
	Avg 12+16	2.0 (0.6)	-0.5 (0.5)	2.4 (0.7)	-0.02 (0.5)	-21.0%	0.0002

Source: Tables 14.2.4.a-1, 14.1.5-1, and 14.4.1.2-5 Vaginal pH  
 Table 11.4.1.2-6 Serum Lipid Profile: Statistical Summary for the change from the average of weeks -2 and 0 to the average of weeks 12 and 16  
 \* mean difference derived through natural log-transformation  
 \*\*P-values for secondary endpoints are not confirmatory

The sponsor concluded that the 0.3 mg Cenestin is efficacious in the treatment of vulvovaginal atrophy in postmenopausal women.

### 2.3.2 STATISTICAL REVIEWER'S FINDINGS

The primary efficacy endpoint presented in the submission is the median change in the maturation index score from baseline at week 16. However, this is not in accordance with the revised 1995 Hormone Replacement Therapy (HRT) Guidance where a 12 week treatment period of the mean difference in the Maturation Index from baseline at week 12 was recommend for the treatment of vulvar and vaginal atrophy indication. For this reason this reviewer's primary efficacy endpoint was the mean change in the Maturation Index score from baseline at week 12. The two-sample t-test, with LOCF in the ITT population was used in this analysis. This reviewer also analyzed the following secondary efficacy endpoints: changes in the maturation index values from pretreatment at each interim visit, changes in vaginal pH, and serum lipid profiles from week -2 at week 16. Tables 6 and 7 summarize the primary and secondary efficacy results.

**Table 6**  
**Summary of Maturation Index Analyses**  
**Intent-to-Treat Population**

Cell Type	Study Week	Cenestin® N=37		Placebo N=34		p-values
		Mean (SD)	Mean change from baseline to subsequent week	Mean (SD)	Mean change from baseline to subsequent week	
<b>Parabasal (%)</b>	-2	23.0 (22.2)		20.2 (20.7)		
	4	5.4 (13.5)	-18.8 (21.0)	18.9 (19.9)	-1.3 (17.5)	0.002
	8	1.4 (4.5)	-22.9 (22.0)	17.7 (19.2)	-5.7 (13.2)	0.0011
	12	1.3 (3.4)	-22.3 (21.9)	19.2 (20.8)	-2.1 (17.4)	0.0001
	16	1.6 (1.6)	-21.5 (22.9)	15.7 (19.6)	-4.5 (15.0)	0.0004
<b>Intermediate (%)</b>	-2	74.9 (21.6)		78.3 (20.0)		
	4	81.5 (14.2)	7.7 (18.7)	76.3 (18.2)	-2.1 (17.0)	0.0207
	8	85.5 (10.9)	11.7 (21.1)	77.4 (17.5)	1.3 (14.8)	0.0410
	12	84.9 (13.7)	10.5 (22.7)	75.6 (20.3)	-1.4 (19.5)	0.0248
	16	82.5 (13.8)	7.6 (23.7)	79.0 (17.3)	0.7 (15.13)	0.1166
<b>Superficial (%)</b>	-2	2.1 (2.52)		1.6 (2.8)		
	4	13.0 (11.87)	11.1 (11.3)	4.8 (8.0)	3.4 (7.6)	0.0019
	8	13.1 (11.04)	11.2 (10.3)	4.9 (5.7)	5.7 (9.1)	0.0053
	12	13.8 (14.05)	11.8 (12.9)	5.2 (8.5)	3.6 (7.9)	0.0116
	16	15.9 (13.94)	13.8 (13.4)	5.3 (7.3)	3.8 (7.4)	0.0002
<b>Maturation Index</b>	-2	39.5 (11.6)		40.7 (10.9)		
	4	53.8 (10.51)	14.6 (14.9)	42.9 (12.1)	2.3 (10.5)	<0.0001
	8	55.9 (6.41)	16.7 (13.6)	43.6 (11.2)	3.5 (8.3)	=0.0002
	#12	<b>55.6 (7.56)</b>	<b>17.0 (13.9)</b>	<b>42.98 (12.3)</b>	<b>2.8 (19.4)</b>	<b>&lt;0.0001 *</b>
	16	57.2 (7.4)	17.7 (14.5)	44.8 (11.9)	4.1 (9.1)	<0.0001

Source: SAS data

\* Statistically significant at 0.05 level

#Indicates the primary efficacy endpoint

The difference between 0.3 mg Cenestin® and placebo is highly significant based on the primary endpoint (p-value < 0.0001). The significant improvement in the maturation index in the Cenestin group was detected as early as week 4, and maintained through weeks 8, 12 and 16. The changes from baseline in parabasal, intermediate and superficial cells were significantly different between Cenestin and placebo groups (p< 0.05) at all treatment periods except at week 16 for intermediate cells (see table 6).

At week 12, superficial cells were increased from 2.1% to 13.78% (mean change=11.8%) in the Cenestin group and from 1.59% to 5.16% (mean change=3.6%) in the placebo group; intermediate cells were increased from 74.92% to 84.92% (mean changes=10.5%) in the Cenestin group, however intermediate cells were reduced from 78.26% to 75.63% (mean change=-1.4) in the placebo group; but parabasal cells were reduced from 23% to 1.3% (mean changes=22.3%) in the Cenestin group and from 20.15% to 19.22% (mean change=-2.1%) in the placebo group. Note that increasing in the superficial and intermediate cells and decreasing parabasal cells are beneficial effects.

This reviewer also performed an analysis of the median change in the Maturation index score from baseline at week 12. Parabasal cells were significantly reduced in the Cenestin group

from 14% to 0% (median decrease of 13%). Superficial cells were significantly increased in the Cenestin group from 1% to 11% (median increase of 9%). The result is consistent with the mean change from baseline at week 12 which shows that the test of mean change from baseline is sufficiently robust even when the condition of normality is not met.

		Cenestin® N=37	Cenestin ®	Control N=34	Control	
Cell Type	Study Week	Median (SD)	change from baseline	Median (SD)	change from baseline	p-values
Parabasal (%)	-2	14		14.5		
	12	0	-13	10.5	-2	0.001
Intermediate(%)	-2	83		84		
	12	87	4	81.5	0	0.0242
Superficial (%)	-2	1		0		
	12	11	9	1.5	0	0.0002

Source: SAS data

**Table 7**  
**Summary of Secondary Efficacy Analyses**  
**Intent-to-Treat Population**

	Weeks	Cenestin (N=36)		Placebo (N=34)		P-Values
		Mean (SD)	Mean change from baseline	Mean (SD)	Mean change from baseline	
Vaginal pH	-2	6.2 (0.9)		6.0 (0.8)		
	16	5.2 (0.8)	-0.93 (1.0)	6.1 (0.8)	0.09 (0.6)	<0.0001
		Cenestin (N=34)		Placebo (N=29)		
Total Cholesterol (mg/dL)	-2	226.4 (35.2)		228.1 (30.3)		
	16	211.3 (33.0)	-17.0 (29)	230.0 (30.3)	1.3 (24.8)	0.0005
HDL Cholesterol (mg/dL)	-2	61.0 (14.2)		62.7 (13.8)		
	16	65.8 (17.9)	5.2 (9.1)	61.3 (13.2)	-1.9 (10.9)	< 0.0001
LDL Cholesterol (mg/dL)	-2	140.0(31.7)		140.7 (27.8)		
	16	119.8 (28.3)	-22.8 (26.5)	144 (29)	4.0 (22.1)	0.0124
Triglycerides (mg/dL)	-2	127.3 (67.8)		129.4 (63.9)		
	16	128.8 (62.6)	3.4 (63)	127.4 (65)	-0.4 (53.8)	0.0078
Total/HDL Cholesterol	-2	3.9 (0.9)		3.9 (1.0)		
	16	3.4 (0.8)	-0.6(0.7)	3.9 (1.2)	0.2 (0.9)	<0.0001
LDL/HDL Cholesterol	-2	2.4 (0.7)		2.4 (0.8)		
	16	2.0 (0.6)	-0.5 (0.5)	2.4 (1.0)	0.2 (0.7)	0.8072

Source: SAS data

The reviewer performed the analysis of the change in the vaginal pH and lipid profile from week -2 at week 16 instead of average of weeks of -2 and 0 at the average of weeks 12 and 16. Vaginal pH decreased significantly from week -2 at week 16.

This reviewer's lipid profiles results were consistent with the sponsor's results except triglycerides and HDL/LDL cholesterol. There were statistically significant differences between Cenestin and placebo groups in Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and Total/HDL cholesterol ratio (see Table 7). There was no statistically significant difference in LDL/HDL cholesterol ratio.

Subjects enrollment was not evenly distributed across the sites. In particular, sites 3 and 5 enrolled relatively small numbers of subjects (7 and 3, respectively). The sponsor claimed that there was no statistically significant treatment by site interaction. Therefore, in the final model of the analysis of variance, the sponsor only included the treatment effect; stating that site and the treatment-by-site effects were not statistically significant.

These two centers should have been pooled in the analysis when testing for the interaction term on the ANOVA model. However, such pooling should have been proposed in the protocol.

	Cenestin	Placebo	Total
<b>Randomized</b>	37	34	71
1. Chicago Center for Clinical Research	10 (14%)	9 (13%)	19 (27%)
2. Phoenix Center for Clinical Research	11 (15%)	11 (15%)	22 (31%)
3. Pharmacology Research Clinic, Las Vegas	4 (6%)	3 (4%)	7 (10%)
4. San Antonio Center for Clinical Research	10 (14%)	10 (14%)	20 (28%)
5. South Ease Research Associate	2 (3%)	1 (1%)	3 (4%)

Source: SAS

#### 2.4 CONCLUSIONS

The difference between 0.3 mg Cenestin® and placebo is highly significant based on the primary endpoint in vaginal maturation index (p-value < 0.0001). Significant improvement in the maturation index in the Cenestin group was detected as early as week 4, and maintained through weeks 8, 12 and 16. The changes from baseline in parabasal, intermediate and superficial cells were also significantly different between Cenestin and placebo groups at all treatment periods except at week 16 for intermediate cells (see table 6).

For secondary endpoints, there were statistically significant differences between Cenestin® and placebo groups in vaginal pH, Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, and Total/HDL cholesterol ratio (see Table 7). There was no statistically significant difference in the LDL/HDL cholesterol ratio.

#### 2.5 LABELING COMMENTS

In accordance with the revised 1995 Hormone Replacement Therapy (HRT) Guidance Report, Tables 3 and 4 in the labeling should be recalculated to express the results in terms of mean values rather than medians. P-values for secondary outcomes should not be reported in the label.

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/s/

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Moh-Jee Ng  
5/28/02 09:48:32 AM  
BIOMETRICS

Mike Welch  
5/28/02 02:40:33 PM  
BIOMETRICS  
Concur with review.

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