CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

NDA/Serial Number:	21-788 / 000
Drug Name:	Bijuva™ (SCE-A: synthetic conjugated estrogens, Cream) 1 g, 2 g Strength
Indication(s):	Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy Associated with the Menopause
Applicant:	Duramed Pharmaceuticals, Inc.
Date(s):	Letter Date: September 26, 2008 PDUFA Date: Nov. 29, 2008
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Biometrics Team Leader:	(acting) Sonia Castillo, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products
Clinical Team:	Phill Price, M.D., Medical Reviewer Shelley Slaughter, M.D., Team Leader
Project Manager:	George Lyght
Key Words:	Class 1 labeling resubmission

Recommendations on Labeling: The Statistical review of the NDA submission dated 3-12-08 was entered into DFS on September 2, 2008. The label in this Class 1 labeling resubmission is acceptable from a statistical perspective.

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/s/

Sonia Castillo
11/25/2008 10:04:21 AM
BIOMETRICS
Signing off as acting team leader for Mahboob Sobhan

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-788
Drug Name:	Bijuva™ (SCE-A: synthetic conjugated estrogens, Cream) 1 g, 2 g Strength
Indication(s):	Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy Associated with the Menopause
Applicant:	Duramed Research, Inc.
Date(s):	
Submission:	March 12, 2008
User Fee Goal:	September 13, 2008
Review Priority:	P
Biometrics Division:	Division of Biometrics III
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Keywords:
NDA Review, Clinical Trial, Multi-Center, Randomization

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Bijuva™ 1g and 2g Vaginal Cream (containing 0.625 mg and 1.25 mg SCE-A respectively), applied once daily for the first 7 days and then two times/week, was statistically significantly superior to placebo with respect to the following endpoints: vaginal maturation index (decreasing parabasal cells and increasing in superficial cells), lowering vaginal pH, and reducing the severity of vaginal dryness and dyspareunia among healthy post-menopausal women.

1.2 Background

NDA 21788 was first submitted on June 6 of 2004 with drug name Cenestin® (Synthetic Conjugated Estrogens, A) Vaginal Cream. The submission was based on a five-arm, randomized, double-blind, parallel multicenter study to evaluate the efficacy at 12 weeks of treatment with daily or twice-weekly doses of Cenestin versus a matching placebo vaginal cream or daily doses of Premarin vaginal cream. The study showed statistically significant results for two objective laboratory endpoints: maturation index (decrease from baseline in parabasal cells at week 12, increase from baseline in superficial cells at week 12), and decrease from baseline in vaginal pH. However, no statistically significant improvement was demonstrated for the change in the most bothersome symptoms.

This resubmission with a new name of the drug Bijuva™, dated March 12 of 2008, included data from another four-arm, randomized, double-blind, placebo-controlled multicenter study. In this study, the objective was to compare the efficacy of two once a day for the first 7 days and then twice-weekly doses of Bijuva™ vaginal cream with their respective matching placebo in subjects with vulvovaginal atrophy.

Subjects 30-80 years of age who were naturally or surgically postmenopausal, with or without hysterectomy and/or oophorectomy, who were experiencing moderate to severe symptoms of vulvovaginal atrophy (as scored on a subject self-assessment questionnaire) and who consented to participate were evaluated for eligibility during the screening period. Continued participation in the study was dependent on the subject meeting all inclusion and none of the exclusion criteria at the Randomization Visit. The procedures done at the initial visit of the Screening Period depended on whether the potential subject was using HT therapy when first evaluated.

A total of 622 subjects were randomized and treated (161 and 156 randomized to 2g Bijuva™ vaginal cream and its matching placebo, respectively; 150 and 155 randomized to 1g Bijuva™ vaginal cream and its matching placebo, respectively) for 12 weeks. The maturation index, vaginal pH and change in severity of the most bothersome self-assess symptom were evaluated over the 12 week treatment period.

The primary efficacy analysis consisted of statistical testing for the differences between the study drug and placebo in mean change from baseline to end-of-treatment for each of the three co-primary efficacy endpoints:

- Maturation Index (with additional analysis of superficial cells and parabasal cells)
- Vaginal pH
- Severity of the most bothersome symptoms (MBS).

1.3 Statistical Issues and Findings

This reviewer found the following two issues:

1. Many study subjects had more than one moderate or severe symptom at baseline. Each symptom was recorded during the study period. However, only the most bothersome symptom identified at baseline was used in analysis of individual symptoms. In this reviewer's opinion, when assessing individual symptoms at baseline, we should use data from all patients who had the moderate or severe symptom in the statistical analysis regardless of their most bothersome symptom identified at baseline. The results from such analyses would be more meaningful than those from MBS-by-symptom analysis.

2. All results were based on MITT cohort. The reasons for using MITT are acceptable (See the definition of MITT on page 7). However, the reviewer does not agree with the definition of ITT cohort on page 38 in the sponsor's report, that is,

ITT cohort: All subjects who had been randomized to treatment, received at least one dose of study medication and for whom there were a baseline assessment and at least one post-randomization assessment of vaginal atrophy consisting of all three co-primary efficacy endpoints (maturation index, vaginal pH, and severity of MBS).

ITT cohort should include all randomized subjects who received at least one dose of the study medication.

Before the sponsor constructed MITT cohort, fifty four subjects (8.7%) had been eliminated from 622 subjects in ITT cohort under the reviewer's definition (12, 14, 12 and 16 subjects in 1g Bijuva™, 1g Placebo, 2g Bijuva™ and 2g Placebo, respectively). In this submission, however, results using MITT cohort were highly significant for two symptoms, vaginal dryness and dyspareunia, and likely to hold even if MITT was a subset of the correct ITT cohort.

In keeping with the intent-to-treat principle, the reviewer recommends using correct ITT cohort before modifying it into MITT cohort in future studies. For those patients who had no post-randomization assessment, the sponsor should either follow up those patients to get the responses from them, or using baseline observation forward method to impute the missing data.

2. INTRODUCTION

2.1 Overview

The submission contains a single study DR-CEN-302. This study was a four-arm, randomized double-blind, placebo-controlled multicenter study to compare two once daily for the first 7 days then twice-weekly doses of Bijuva™ vaginal cream with their respective placebo in subjects with vulvovaginal atrophy.

The study was conducted at 88 sites in the United States. Among the 88 sites that screened subjects, 81 sites enrolled subjects who were randomized to treatment and 80 sites provided data for the efficacy analyses. A total of 69 sites had insufficient numbers of subjects per treatment group (< 3 subjects in at least one treatment group) were therefore pooled together into a "super site" in efficacy assessment by the Sponsor.

The protocol specified three co-primary endpoints were:

- Change from baseline in Maturation Index (%superficial and parabasal cells) at Week 12
- Change from baseline in vaginal pH at Week 12
- Change from baseline in severity of most bothersome symptom at Week 12

Per current FDA guidance, the efficacy analysis with respect to the above co-primary endpoints was limited to patients who had a superficial cell percentage of $\leq 5\%$, vaginal pH > 5 and at least one subject-assessed moderate or severe symptom identified at the Randomization Visit as the MBS.

There were a total of 556 subjects in this modified intention-to-treat (MITT) cohort (146 and 135 in 2g Bijuva™ vaginal cream and its matching placebo groups, respectively; 135 and 140 in 1g Bijuva™ vaginal cream and its matching placebo groups, respectively).

The pre-specified statistical analysis method was a two-way analysis of covariance (ANCOVA) with treatment, site and treatment-by-site interaction as fixed effects, and baseline value as the covariate. It was stated in the protocol that if the interaction term was not significant, it would be dropped from the model. For missing data, a last-observation-carried-forward (LOCF) approach was used.

Each active treatment was compared with its corresponding placebo group:

2 g Bijuva™ Vaginal Cream versus 2 g placebo
1 g Bijuva™ Vaginal Cream versus 1 g placebo

A step-down testing procedure was used for drug efficacy assessment. That is, only if higher dose group compared to its respective placebo group met statistical significance for three co-primary endpoints, the lower dose was then formally evaluated compared to its respective placebo group for those endpoints.

2.2 Data Sources

The study report and additional information for this submission are available in electronic format. The SAS data sets are complete and well documented. These items are located in the Electronic Document Room at **\\FDSWA150\NONECTD\N21788\N_000\2008-03-12_** under submission date 3-12-2008.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

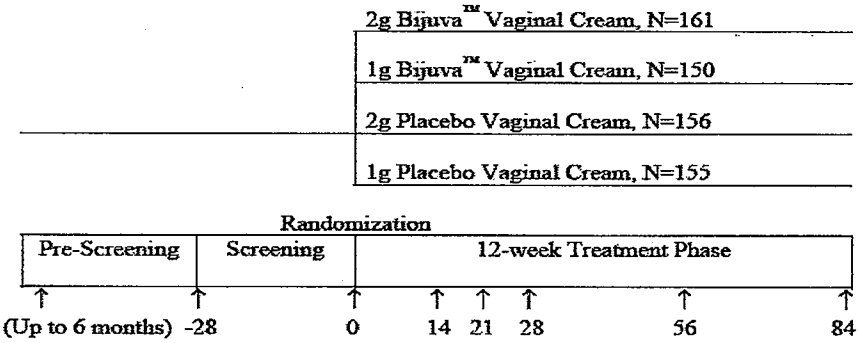
Study DR-CEN-302 "Randomized, Multicenter, Double-blind, Placebo-Controlled Trial to Compare the Effects of 12 Week of Treatment with SCE-A Vaginal Cream on Vulvovaginal Atrophy in Healthy Postmenopausal Women" was conducted in 88 centers within U.S. SCE-A is

a synthetic conjugated estrogens, A (1.25 mg for 2g Bijuva™, 0.625 for 1g Bijuva™). The active ingredient was referred to DR-2041 in protocol DR-CEN-302. Placebo vaginal cream was visually identical to each of the test products containing no active pharmaceutical ingredient

Study subjects were to be naturally or surgically postmenopausal females age 30 through 80 at initiation of study drug, capable of giving and willing to give informed consent, who agreed to routinely use study hormone therapy, had no concurrent use of estrogens or progestins, and had at least one symptom rated as moderate or severe on self-assessment of their vaginal atrophy as determined by the Vaginal Atrophy/Sexual Function Questionnaire.

All enrolled subjects were to receive 12 weeks of therapy during the course of the study. After the screening period, subjects were randomized in a 1:1:1:1 blinded fashion to 2g Bijuva™ Vaginal cream or its matching placebo, or 1g Bijuva™ Vaginal cream or its matching placebo for twelve weeks of double-blind treatment. Figure 1 gives the study design and schedule of assessments.

Figure 1: Study design and schedule of assessments



(↑ Indicates clinic visit; number indicates study days from the date of Randomization Visit)

Source: Sponsor's report

A brief summary of clinical study DR-CEN-302 for Bijuva™ is listed in Table 1.

Table 1: Brief summary of the Clinical Study for Bijuva™

Study Number (No. of Sites/Country) Dates of Study Conduct	Subject Population	Treatment	Number Randomized (MITT[1])	Design[2] (Treatment Duration)
Bijuva™ Dr-CEN-302 Clinical Study 8-28-2006 to 9-25-2007	Naturally or surgically postmenopausal females age 30 through 80 had at least one symptom rates as moderate or severe on self-assessed Vaginal atrophy Questionnaire.	Bijuva 2g Bijuva 1g Placebo 2g Placebo 2g	161 (146) 150 (135) 156 (135) 155 (140)	DB,R PC, PG, MC (12 Wks)

Source: Statistical Reviewer's listing.
[1]MITT = modified Intent-to-Treat
[2]DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

The MITT cohort defined as follows:

A subset of the ITT cohort which met the study protocol requirements at baseline for all three primary efficacy inclusion criteria, i.e., a superficial cell percentage of ≤ 5%, vaginal pH > 5 and at least one subject-assessed moderate or severe symptom identified at the Randomization Visit as the MBS.

A total of 556 subjects were in MITT cohort. Statistical analyses were based on MITT cohort.

3.1.2 Disposition of Subjects

A total of 1,538 subjects were screened for participation in this study. Of those, 622 were randomized and treated. As the primary analysis cohort for all inferences regarding the efficacy of each Bijuva™ dose compared to its matching placebo, the MITT cohort constituted 97.9% (556 of 568 subjects) of the total number of ITT subjects and 89.4% (556 of 622 subjects) of the total number of subjects treated. Six Bijuva™ subjects with 3 from each active arm and 6 placebo subjects in the ITT cohort were further excluded from the MITT cohort because they failed to meet the baseline qualification criteria. Among the 12 excluded subjects, 6 did not meet the MBS entry criteria, 5 were due to a baseline pH of ≤ 5. Given the sample size calculated for this study, the numbers of analyzable subjects in the MITT was considered adequate and consistent with the protocol-specified minimum sample size requirement.

Table 2 is the summary of subject disposition.

Table 2: Summary of Subject Disposition

	2g Bijuva	1g Bijuva	2g Placebo	1g Placebo	Total
All Treated (Safety)	161	150	156	155	622
Completed Study	150 (93.2%)	138 (92.0%)	135 (86.5%)	137 (88.4%)	560 (90.0%)
Did Not Complete Study	11 (6.8%)	12 (8.0%)	21 (13.5%)	18 (11.6%)	62 (10.0%)
Discontinued due to:					
Did Not Meet Protocol Requirements	2 (1.2%)	0 (0.0%)	2 (1.3%)	2 (1.3%)	6 (1.0%)
Non Compliance with the Protocol	0 (0.0%)	3 (2.0%)	0 (0.0%)	2 (1.3%)	5 (0.8%)
Investigator Discretion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Request to be Withdrawn	1 (0.6%)	2 (1.3%)	14 (9.0%)	9 (5.8%)	26 (4.2%)
Due to lack of efficacy	0 (0%)	0 (0%)	7 (4.5%)	6 (3.9%)	13 (2.1%)
Adverse Event	5 (3.1%)	3 (2.0%)	2 (1.3%)	2 (1.3%)	12 (1.9%)
Subject Pregnant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-Up	3 (1.9%)	2 (1.3%)	2 (1.3%)	3 (1.9%)	10 (1.6%)
Other	0 (0.0%)	2 (1.3%)	1 (0.6%)	0 (0.0%)	3 (0.5%)

Note: Numbers in parentheses are percentages of all treated (safety) subjects for each and total treatment groups

Source: Table 2, on page 46 of the sponsor's report.

3.1.3 Results

3.1.3.1 Descriptive Statistics

Tables 3 and 4 are the descriptive statistics (mean, standard deviation, minimum, the first quartile, median, the third quartile and maximum) of change from baseline at Week 12 scores for each treatment by co-primary endpoints, and by components of MBS respectively.

Table 3: Summary Statistics of Co-primary Endpoints (MITT Cohort, LOCF)

Endpoint	Treatment	N	Mean	Std Dev	Min	Q1	Med	Q3	Max
Maturation Index	1g Bijuva	135	29.99	19.784		13.5	28.5	43.5	
	1g Placebo	140	3.24	12.812		-2.5	2.5	9.875	
	2g Bijuva	146	33.37	20.365		15.25	34.5	49	
	2g Placebo	135	8.15	15.531		0	6.5	18	
% Parabasal Cells	1g Bijuva	135	-36.59	33.093		-65	-27	-4	
	1g Placebo	140	-5.30	25.236		-17	-3	5.75	
	2g Bijuva	146	-41.58	31.489		-67	-42.5	-12	
	2g Placebo	135	-13.02	29.556		-35	-9	0	
% Superficial Cells	1g Bijuva	135	23.39	15.495		11	22	35	
	1g Placebo	140	1.19	3.706		0	0	2	
	2g Bijuva	146	25.15	18.367		11.75	22	36.25	
	2g Placebo	135	3.28	6.876		0	1	4	
Vaginal pH	1g Bijuva	135	-1.39	0.996		-2.3	-1.5	-0.7	
	1g Placebo	140	-0.18	0.790		-0.5	0	0.075	
	2g Bijuva	146	-1.36	0.865		-2	-1.4	-0.8	
	2g Placebo	135	-0.27	0.828		-0.8	-0.1	0.3	
MBS	1g Bijuva	135	-1.70	0.866		-2	-2	-1	
	1g Placebo	140	-1.06	0.891		-2	-1	0	
	2g Bijuva	146	-1.75	0.929		-2	-2	-1	
	2g Placebo	135	-1.07	0.919		-2	-1	0	

b(4)

Source: Statistical Reviewer's listing.

It can be seen from Table 4 that because each subject only had one most bothersome symptom at baseline, in MBS-by-symptom analysis, there was no sufficient samples to analyze symptoms Vaginal Irritation/Itching, Vaginal Soreness and Bleeding after Intercourse. Table 5 lists frequencies of subjects with moderate or severe symptoms at baseline. It can be seen that when doing MBS-by-symptom analysis, large data information was not used for analyzing individual symptoms.

Table 4: Summary Statistics of Components of MBS (MITT Cohort, LOCF)

Symptom	Treatment	N	Mean	Std Dev	Min	Q1	Med	Q3	Max
Bleeding	1g Bijuva	1	-2.00	0.000		-2	-2	-2	
Pain During Intercourse	1g Bijuva	45	-1.71	0.991		-2	-2	-1	
	1g Placebo	41	-0.83	0.834		-1	-1	0	
	2g Bijuva	57	-1.68	0.967		-2	-2	-1	
	2g Placebo	47	-0.79	0.907		-2	-1	0	
Vaginal Dryness	1g Bijuva	60	-1.63	0.802		-2	-2	-1	
	1g Placebo	72	-1.11	0.928		-2	-1	-0.3	
	2g Bijuva	76	-1.83	0.870		-2	-2	-1	
	2g Placebo	70	-1.27	0.867		-2	-1	-1	
Vaginal Irritation /Itching	1g Bijuva	23	-1.74	0.810		-2	-2	-1	
	1g Placebo	22	-1.23	0.752		-2	-1	-1	
	2g Bijuva	10	-1.50	1.179		-2.3	-1.5	-1	
	2g Placebo	15	-1.07	0.884		-2	-1	0	
Vaginal Soreness	1g Bijuva	6	-2.00	0.894		-3	-2	-1	
	1g Placebo	5	-1.60	1.140		-2.5	-2	-0.5	
	2g Bijuva	3	-2.00	1.000		-3	-2	-1	
	2g Placebo	3	-1.00	1.732		-3	0	0	

b(4)

Source: Statistical Reviewer's listing.

Table 5: Frequency of Study Subjects Who had Moderate or Severe Symptoms at Baseline (MITT Cohort)

Individual Symptom	2g Bijuva	2g Placebo	TOTAL	1g Bijuva	1g Placebo	TOTAL
Bleeding after Intercourse	13	13	26	10	11	21
Dyspareunia	97	85	182	80	80	160
Vaginal Dryness	134	126	260	123	125	248
Vaginal irritation/itching	59	65	124	60	60	120
Vaginal Soreness	61	54	115	60	54	114

Source: Statistical Reviewer's listing.

3.1.3.2 Efficacy

Primary analysis:

Per the statistical analysis plan (SAP), an ANCOVA model was employed to assess the significance of differences between the active treatment and placebo groups. The model included terms for baseline, treatment, site and treatment-by- site interaction. Total 80 sites provided data for the efficacy analyses. Because 69 sites had less than 3 subjects in at least one of the treatment arms, the 69 sites were combined as one super site by the sponsor with 350 subjects. The reviewer checked the mean and standard deviation of endpoints for the super site, and found they were within the range of the mean and standard deviation of the endpoints in other sites. Therefore, the reviewer's analyses used 11 regular sites and one super site. It was found that the treatment-by-site interaction was not significant in the model of three co-primary Endpoints

including % of parabasal cells and % of superficial cells at 0.05 level. Thus, this term was removed from the model in the reviewer's primary analyses.

Shapiro-Wilk test (W-test) was used to check the normality assumption of the model. If the test result was significant at 0.05 level, ranked data would be replaced the raw data in the analysis.

A pre-specified step-down testing procedure was used to assess the drug efficacy. That is, only if the high dose group comparison to its respective placebo group met statistical significance for all three co-primary endpoints, was the lower dose then formally evaluated compared to its respective placebo group for those endpoints. Otherwise, inferences regarding the efficacy of the active treatment groups would be limited to the higher dose treatment.

Table 6 shows the results from the reviewer's primary analyses. Three co-primary endpoints (including % of parabasal cells, and % of superficial cells) were highly significant with p-value < 0.0001 in comparison between Bijuva™ and matching placebo for both doses.

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Table 6: Analysis of Primary Endpoints: Change from Baseline (Day 0) to End of Treatment (MITT Cohort, LOCF)

Endpoint	Treatments	N	Baseline	LS Mean Change	Standard Error	Difference Trt-Pl	W-test P-Value	P-Values*
Vaginal Matration Index	2g Bijuva	146	29.20	33.71	1.398	24.26	0.0129	<0.0001
	2g placebo	135	30.34	9.44	1.427			
	1g Bijuva	135	31.31	31.09	1.330	26.38	0.0032	<0.0001
	1g placebo	140	31.84	4.71	1.315			
% of Superficial Cells	2g Bijuva	146	0.97	26.09	1.555	21.71	0.0000	<0.0001
	2g placebo	135	1.08	4.38	1.589			
	1g Bijuva	135	1.33	25.86	1.248	22.07	0.0000	<0.0001
	1g placebo	140	1.31	3.80	1.236			
% of Parabasal Cells	2g Bijuva	146	2.68	-41.39	2.044	-26.89	0.0000	<0.0001
	2g placebo	135	2.72	-14.50	2.085			
	1g Bijuva	135	38.51	-36.32	2.086	-30.67	0.0000	<0.0001
	1g placebo	140	37.64	-5.65	2.062			
Vaginal pH	2g Bijuva	146	6.35	-1.45	0.070	-1.05	0.0716	< 0.0001
	2g placebo	135	6.30	-0.40	0.071			
	1g Bijuva	135	6.32	-1.47	0.082	-1.17	0.3026	<0.0001
	1g placebo	140	6.27	-0.30	0.081			
MBS	2g Bijuva	146	2.61	-1.77	0.098	-0.66	0.0004	<0.0001
	2g placebo	135	2.59	-1.11	0.100			
	1g Bijuva	135	2.62	-1.71	0.097	-0.60	0.0005	<0.0001
	1g placebo	140	2.55	-1.11	0.095			

* If Wilk-Shapiro W-test for residuals in ANCOVA model was significant at 0.05, the p-value (last column) of the significance between active treatment group and matching placebo was from ranked data analysis.

Source: Statistical reviewer's listing.

Notice that LOCF was applied to 13, 105 and 10 subjects in analysis of MBS, Vaginal Maturation Index (including parabasal calls and superficial cells), and Vaginal pH respectively.

Most Bothersome Symptoms:

The severity of individual symptoms graded on a scale of 0 to 3 (corresponding to, respectively, None, Mild, Moderate, or Severe) or 7 for N/A (not applicable) which only applied to symptoms Dyspareunia or Bleeding after Intercourse. Table 7 gives a summary of number of subjects marked N/A in their response to those two symptoms in each treatment arm by visits.

Table 7: Number of Subjects Responding N/A (MITT Cohort, LOCF)

	Treatment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Dyspareunia	1g Bijuva	37	51	48	51	43	36
	1g Placebo	31	54	53	50	38	36
	2g Bijuva	29	50	51	52	46	38
	2g Placebo	24	45	48	39	34	33
	Total	121	200	200	192	161	143
Bleeding After Intercourse	1g Bijuva	35	53	48	51	45	37
	1g Placebo	33	51	51	50	37	36
	2g Bijuva	33	50	50	49	46	38
	2g Placebo	26	44	49	40	34	35
	Total	127	198	198	190	162	146

Source: Statistical Reviewer's listing.

Table 8 lists the sample sizes available for analyzing each individual symptom (component of MSB). There was only one subject reported Bleeding after Intercourse as her most bothersome symptom at baseline. There were total of 17 subjects reported Vaginal Soreness as their MBS at baseline. These subjects distributed as 3, 3, 6, and 5 for 2g Bijuva™, 2g Placebo, 1 g Bijuva™ and 1 g Placebo respectively. The sample sizes available for analyzing individual symptoms Bleeding after Intercourse and Vaginal Soreness were too small to make any inference. Therefore, those two symptoms were eliminated from this reviewer's analysis.

Table 8: Summary of Available Sample Size in MBS-by-Symptom Analysis (MITT Cohort)

Individual Symptom	2g Bijuva	2g Pl	Total	1g Bijuva	1g Pl	Total
Bleeding after Intercourse	0	0	0	1	0	1
Dyspareunia	57	47	104	45	41	86
Vaginal Dryness	76	70	146	60	72	132
Vaginal Irritation/Itching	10	15	25	23	22	45
Vaginal Soreness	3	3	6	6	5	11

Source: Statistical Reviewer's listing.

This reviewer used the same model (treatment-by-site interaction was removed from the initial model due to insignificance) and the same step-down testing procedure for the MBS-by-symptom analysis as the primary analysis.

Table 9 shows that both doses of Bijuva were statistically significantly superior to placebo in the improvement of Vaginal Dryness and Dyspareunia.

Table 9 : Analysis of Individual Symptoms Classified by Subject as the MBS: Change from Baseline (Day 0) to End of Treatment (MITT Cohort, LOCF)

Endpoint	Treatments	N	Baseline	LS Mean Change	Standard Error	Difference	W-test P-Value	P-Value*
Dyspareunia	2g Bijuva	57	2.68	-1.87	0.202	-0.95	0.0042	<0.0001
	2g placebo	47	2.72	-0.92	0.214			
	1g Bijuva	45	2.71	-1.75	0.208	-0.93	0.0963	0.0002
	1g placebo	41	2.76	-0.82	0.233			
Vaginal Dryness	2g Bijuva	76	2.61	-1.83	0.131	-0.54	0.0053	0.0002
	2g placebo	70	2.54	-1.29	0.129			
	1g Bijuva	60	2.58	-1.65	0.144	-0.49	0.0387	0.0016
	1g placebo	72	2.47	-1.17	0.130			
Vaginal Irritation/Itching	2g Bijuva	10	2.30	-1.22	0.322	-0.51	0.0111	0.2761
	2g placebo	15	2.40	-0.72	0.354			
	1g Bijuva	23	2.52	-1.54	0.272	-0.34	0.0138	0.2813
	1g placebo	22	2.32	-1.21	0.239			

* If Wilk-Shapiro W-test for residuals in ANCOVA model was significant at 0.05, the p-value (last column) of the significance between active treatment group and matching placebo was from ranked data analysis.

Source: Statistical reviewer's listing.

3.3 Evaluation of Safety

See Medical Officer's review.

4. FINDINGS IN SUBGROUP POPULATIONS

4.1 Gender, Race and Age

All subjects studied in this application were female. Analyses by race and age were not performed.

4.2 Other Special/Subgroup Population

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For the composite endpoint of change from baseline to Week 12 for the most bothersome symptom, the results showed statistically significant differences between each active treatment and its matching placebo. However, when the components of this composite endpoint were examined, only Vaginal Dryness and Dyspareunia demonstrating statistically significant improvements among those randomized to active treatment as compared to those randomized to matching placebo. Because the p-values for these two symptoms were ≤ 0.0016, multiplicity adjustments do not change the conclusions.

Majority of study subjects chose either Vaginal Dryness or Dyspareunia as their most bothersome symptom at baseline.

Notice that most study subjects had more than one moderate or severe symptom when entering the study. However, only responses to the MBS were used in analysis of individual symptoms. Table 5 in Section 3.1.3.1 gives the number of study subjects who identified moderate or severe symptom at baseline by each individual symptom. Comparing the numbers in Table 5 to what in Table 8, one may see how much data information was not used in MBS-by-symptom analysis.

Another issue is regarding the population used in statistical analysis for this NDA.

All results were based on MITT cohort. The reasons for using MITT are acceptable (See the definition of MITT on page 7). However, the reviewer does not agree with the definition of ITT cohort on page 38 in the sponsor's report, that is,

ITT cohort: All subjects who had been randomized to treatment, received at least one dose of study medication and for whom there were a baseline assessment and at least one post-randomization assessment of vaginal atrophy consisting of all three co-primary efficacy endpoints (maturation index, vaginal pH, and severity of MBS).

Before the sponsor constructed MITT cohort, fifty four subjects (8.7%) had been eliminated from 622 subjects in ITT cohort under the reviewer's definition (12, 14, 12 and 16 subjects in 1g Bijuva™, 1g Placebo, 2g Bijuva™ and 2g Placebo, respectively). In this submission, however, results using MITT cohort were highly significant for two symptoms, vaginal dryness and dyspareunia, and likely to hold even if MITT was a subset of the correct ITT cohort.

In keeping with the intent-to-treat principle, the reviewer recommends using correct ITT cohort before modifying it into MITT cohort in future studies. For those patients who had no post-randomization assessment, the sponsor should either follow up those patients to get the responses from them, or using baseline observation forward method to impute the missing data.

5.2 Conclusions and Recommendations

Results from the reviewer's analyses support the efficacy of both 1g and 2 g Bijuva™ Vaginal Cream (containing 0.625 mg and 1.25 mg SCE-A respectively) applied once daily for the first 7 days and then two times/week in their ability to decrease parabasal cells, increase in superficial cells), lower vaginal pH, and reduce the severity of vaginal dryness and dyspareunia among

healthy post-menopausal women with moderate-to-severe vaginal atrophy. Differences between treatment and placebo were not statistically significant for the other three symptoms: Vaginal Irritation, Vaginal Soreness and Bleeding after Intercourse.

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