CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	November 25, 2008
From	George S. Benson, MD
Subject	Deputy Division Director Review
NDA# **Supplement#**	21-788 000
Applicant	Duramed Pharmaceuticals, Inc.
Date of Submission	September 29, 2008
PDUFA Goal Date	November 29, 2008
Proprietary Name/ **Established name**	Tradename pending/ Synthetic conjugated estrogens, A
Dosage forms/Strength	Vaginal cream (0.625 mg synthetic conjugated estrogens, A per gram of cream)
Proposed Indication	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause
Recommendation	Approval (without tradename)

Medical	Phill Price Shelley Slaughter
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Pharmacology/toxicology	Krishan Rajeha Lynnda Reid
Clinical pharmacology	LaiMing Lee Myong-Jin Kim
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OSE/DMEPA	Richard Abate Kellie Taylor Denise Toyer
Project Management Staff	George Lyght Margie Kober

Background:

NDA 21-788 (synthetic conjugated estrogens, A) for the indication "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause" was originally submitted on June 25, 2004, and received a "not approvable" regulatory decision on April 25, 2005. The reasons for this "not approvable" action dealt primarily with the lack of demonstration of efficacy. A complete response to the "not approvable" letter was submitted on March 13, 2008.

The March 13, 2008, submission received a complete response action on September 12, 2008. The action letter stated:

"We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

1. Labeling remains unresolved. Because we have failed to come to agreement on the labeling, we will continue discussions based on the version you sent to us this morning. In addition, revised carton and container labeling should be submitted when we have agreed on a mutually acceptable proprietary name.
2. The details pertaining to your postmarketing commitment have not been finalized. We acknowledge your intention to conduct a study to evaluate lower exposure of synthetic conjugated estrogens, A vaginal cream that might prove effective for the treatment of vulvovaginal atrophy associated with menopause. We will continue discussion of this commitment based on the letter you sent to us this morning. In addition, propose a timeframe for protocol submission, study start, and final report submission.

In summary, efficacy was demonstrated in Study DR-CEN-302. There are no new safety concerns with the use of synthetic conjugated estrogens, A for the indication treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Three issues remain to be resolved:

- Labeling
- Tradename
- Post-marketing commitment study to determine effect of lower dose of synthetic conjugated estrogens, A

A complete response was submitted by the sponsor on September 29, 2008 (FDA stamp date).

The Summary Review for Regulatory Action (September 12, 2008) which contains a review of the efficacy and safety data is attached to this review.

Review of Complete Response (September 29, 2008):

The sponsor addressed the two deficiencies described above in the complete response action letter in their complete response submission.

1. Labeling remains unresolved. Because we have failed to come to agreement on the labeling, we will continue discussions based on the version you sent to us this morning. In addition, revised carton and container labeling should be submitted when we have agreed on a mutually acceptable proprietary name.

The sponsor resubmitted their September 12, 2008, version of the draft labeling. Specifically, "this draft labeling maintains in Section 12.2 the description of the pharmacokinetic parameters seen after intravaginal administration of Bijuva Vaginal Cream, 0.625 mg/g and oral administration of Cenestin 0.3 mg tablets. Duramed strongly believes that this information is important to prescribing healthcare professionals when making a clinical decision to prescribe Bijuva. In addition, and to enhance transparency in the Bijuva labeling, we have changed "Cenestin" to "synthetic conjugated estrogen, A. Also note that we have added the statement, "

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to Section 2.1 This addition is in response to your second reason noted for the September 12, 2008, Complete Response letter and is discussed further below."

The sponsor also submitted revised carton and container labeling bearing the proprietary name "Bijuva" Vaginal Cream. "We now understand that the Division of Medication Error Prevention is concerned about two proprietary products containing the same active ingredient having different proprietary names and the possibility that a woman could inadvertently be prescribed both products at once, or could receive the wrong product. We respectfully acknowledge this concern and feel that it can be adequately managed such that medication errors can be avoided." The sponsor's specific arguments are presented on page 2 of the amendment which was submitted as the complete response.

2. The details pertaining to your postmarketing commitment have not been finalized. We acknowledge your intention to conduct a study to evaluate lower exposure of synthetic conjugated estrogens, A vaginal cream that might prove effective for the treatment of vulvovaginal atrophy associated with menopause. We will continue discussion of this commitment based on the letter you sent to us this morning. In addition, propose a timeframe for protocol submission, study start, and final report submission.

In the complete response submission (September 26, 2008), the sponsor responded:

"Duramed commits to design and conduct a Phase IV clinical trial to find the lowest effective dose of Bijuva Vaginal Cream, 0.625 mg/g, for the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. Duramed commits to the following timeline for this study:

Protocol Submission:	Within 6 months of the date of the receipt of an Approval letter
Study Start:	Within 6 months of protocol agreement with the Division
Final Report Submission:	Within 6 months of study completion

In addition, the statement, " [redacted] has been added to the Bijuva labeling. b(4)

No safety update was submitted because "there are no ongoing nonclinical and clinical studies/trials of synthetic conjugated estrogens, A under consideration that Duramed is aware of. Therefore, this declaration stands as the formal Safety Update."

In summary, the sponsor agrees to the postmarketing commitment to evaluate lower exposure of synthetic conjugated estrogens, A vaginal cream that might prove effective for the treatment of vulvovaginal atrophy associated with menopause. The sponsor's proposed timelines are acceptable.

A fax was sent to the sponsor on October 20, 2008, which again notified the sponsor that the proprietary name Bijuva was not acceptable to DMEPA and DRUP because of potential confusion with the marketed drug Enjuvia. In a submission (letter date October 27, 2008) the sponsor responded that "Duramed feels the product characteristics of Bijuva Vaginal Cream have minimal overlap with Enjuvia tablets and that the orthographic similarities can be minimized to avoid potential confusion between the products." The sponsor again listed the reasons why they believe that the tradename Bijuva should be acceptable (see pages 2 and 3 of October 27, 2008 submission). An e-mail received from the sponsor on October 27, 2008, stating that "We are required to finalize the artwork by November 4 for launch supplies and it would be helpful if you could give this issue immediate consideration. If we do not have a response by November 4 we will have to move forward with printing labeling at risk." Duramed was again notified that the tradename Bijuva was not acceptable and the sponsor requested that this decision be formalized by a letter.

On November 17, 2008, a letter was sent to the sponsor which stated:

"We have reviewed the referenced material. Following consultation with the Division of Medication Error Prevention and Analysis (DMEPA), we continue to believe that the proprietary name Bijuva is unacceptable because of the potential for confusion with the marketed drug Enjuvia. The following were considered in reaching this decision.

1. Enjuvia and Bijuva share overlapping product characteristics such as active ingredient (synthetic conjugated estrogen), numerical strength (0.625 mg vs. 0.625 mg/g), indications for use (vasomotor symptoms due to menopause or symptoms of vulvar and vaginal atrophy due to menopause), frequency of administration, and patient and prescriber population.
2. Depending on the handwriting, it is possible that a prescription written for "Enjuvia 0.625 mg, use as directed" may be misinterpreted as "Bijuva 0.625 mg/g, use as directed."

Therefore, we conclude that there is a potential for confusion between Bijuva and Enjuvia due to the overlapping product characteristics and orthographic similarities."

A letter from the sponsor dated November 18, 2008 stated "While we respectfully disagree with the decision by DRUP and DMEPA that the proposed proprietary names Bijuva is unacceptable, we are dropping it as a proposed proprietary name to keep the regulatory review moving forward. In its place, we are proposing to use the proprietary name ——— Proposed alternate names, in rank order, are ——— and ———."

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A teleconference concerning the tradename was held with the sponsor on November 18, 2008. The sponsor was advised that a new tradename could not be reviewed by DMEPA during this review cycle because of time constraints.

The Division of Medication Errors and Technical Support [now the Division of Medication Error Prevention and Analysis (DMEPA)] found the tradename "Bijuva" unacceptable in consultations dated August 9, 2004, and March 3, 2005, because of potential confusion with the marketed drug Enjuvia. The March 3, 2005, consultation stated that "this is considered a final decision." In a consultation dated August 19, 2008, regarding carton and container labels, DMEPA again stated that "DMEPA requests an alternative name for this product be submitted for our review." DMEPA reiterated at an internal meeting held on November 17, 2008, that the sponsor's arguments submitted on September 29 and October 27, 2008, were not persuasive and that DMEPA still believes that the tradename "Bijuva" is unacceptable.

Labeling negotiations were concluded and agreed upon on November 25, 2008.

The statistical and pharmacology/toxicology reviewers concurred with the labeling and found it to be acceptable.

In summary, responses to the three deficiencies noted in the September 12, 2008, complete response letter have been adequately addressed:

- Labeling – labeling negotiations were concluded and agreed upon on November 25, 2008. Statistics and pharmacology/toxicology have concurred with the label. As of the time of writing this review, the medical, chemistry, and pharmacology/toxicology reviews have not been completed.
- Tradename – The sponsor has withdrawn the tradename Bijuva. The sponsor's proposed proprietary name " ——— ' will be reviewed by DMEPA. NDA 21-788 (for synthetic conjugated estrogens, A) will be approved without an agreed upon tradename.
- Post-marketing commitment study to determine effect of lower dose of synthetic conjugated estrogens, A – The sponsor agrees to the postmarketing commitment to evaluate lower exposure of synthetic conjugated estrogens, A vaginal cream that might prove effective for the treatment of vulvovaginal atrophy associated with menopause. The sponsor's proposed timelines are acceptable. This commitment will be included in the approval letter.

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Conclusion and recommendation:

I believe that NDA 21-788 should be approved pending completed concurring reviews regarding labeling from the medical, clinical pharmacology, and chemistry reviewers (to include review of the container and carton labeling). Synthetic conjugated estrogens, A vaginal cream will be approved without an agreed upon tradename.

Addendum (November 28, 2008):

The medical, chemistry, and clinical pharmacology reviews have been completed and archived. All of these disciplines have found the label to be acceptable. Chemistry has determined that the updated carton and container labels are acceptable. Final wording for the action letter for the Phase IV trial has been agreed upon by the sponsor.

There are no outstanding issues (other than tradename) with NDA 21-788. An approval letter will be sent to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

George Benson
11/28/2008 09:58:24 AM
MEDICAL OFFICER

Summary Review for Regulatory Action

Date	**September 12, 2008**
From	**George S. Benson, MD**
Subject	**Deputy Division Director Review**
NDA# **Supplement#**	**21-788** **000**
Applicant	**Duramed Pharmaceuticals, Inc.**
Date of Submission	**March 13, 2008**
PDUFA Goal Date	**September 13, 2008**
Proprietary Name/ **Established name**	**Tradename pending/** **Synthetic conjugated estrogens, A**
Dosage forms/Strength	**Vaginal cream (0.625 mg synthetic conjugated estrogens, A per gram of cream)**
Proposed Indication	**Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause**
Recommendation	**Complete Response**

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
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11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Synthetic conjugated estrogens, A is presently marketed in the U.S. in a tablet formulation (Cenestin®). Synthetic conjugated estrogens, A contains the following nine estrogenic substances in combination: sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, 17β-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17β-estradiol sulfate. Cenestin® 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg oral tablets are approved for marketing in the United States for the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.

Cenestin® 0.3 mg oral tablets were approved on June 21, 2002, for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with the menopause. Approval of Cenestin® 0.3 mg tablets was based on the results from a single randomized, double-blind, placebo-controlled clinical trial. In this trial, Cenestin® was shown to be statistically superior to placebo in terms of "improving" the vaginal maturation index (the percentage of superficial epithelial cells increased) and reducing the vaginal pH. At the time of the approval of the 0.3 mg Cenestin® tablet for VVA, no assessment of vaginal symptoms was required.

Synthetic conjugated estrogens, A vaginal cream is a new dosage form of synthetic conjugated estrogens, A and contains the same 9 estrogenic substances found in Cenestin® tablets. Each gram of the vaginal cream contains 0.625 mg of synthetic conjugated estrogens, A.

NDA 21-788 (synthetic conjugated estrogens, A) for the indication "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause" was originally submitted on June 25, 2004, and received a "not approvable" regulatory decision on April 25, 2005. The reasons for this "not approvable" action dealt primarily with the lack of demonstration of efficacy and are discussed in the **Background** section below. A complete response to the "not approvable" letter was submitted on March 13, 2008, and is the subject of this NDA review.

2. Background

A successful efficacy outcome for the indication of treatment of VVA, based on the Agency's 2003 draft Guidance, currently requires that the proposed therapy demonstrate statistical superiority over placebo for the following three co-primary endpoints:

1. Mean change from baseline in vaginal maturation index at Week 12
   - Should show a statistically significant increase in vaginal superficial cells
   - Should show a statistically significant decrease in vaginal parabasal cells
2. Mean change from baseline in vaginal pH at Week 12
   - Should show a statistically significant lowering of vaginal pH
3. Mean change from baseline to Week 12 in the moderate to severe symptom of VVA identified by the subject as being the most bothersome to her at baseline.

In the original submission of NDA 21-788 dated June 25, 2004, a single phase 3 trial (DP3-2002-002) was submitted to support efficacy. The deficiencies in the "not approvable" letter dated April 25, 2005, were the following:

1. "Effectiveness has not been established because in the single phase 3 study, Study DP3-2002-002, neither the twice weekly nor the daily dosing regimens of synthetic conjugated estrogens, A vaginal cream achieved statistical significance compared to placebo at week 12 for the co-primary endpoint "subject self-assessment of most bothersome vulvar and vaginal atrophy symptom at baseline."
2. Labeling remains unresolved."

The not approvable letter detailed that the following are needed to address these deficiencies:

1. Submission of the results of an adequate and well-controlled clinical trial that establishes the effectiveness of synthetic conjugated estrogens, A vaginal cream in the treatment of vulvar and vaginal atrophy by demonstrating a statistically significant improvement compared to placebo in all 3 of the co-primary endpoints described in the draft Guidance for Industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation (January 2003)" at week 12 relative to baseline.
2. Submission of proposed revised draft labeling that incorporates the results of the clinical trial that addresses the first deficiency.

NDA 21-788 was resubmitted on March 13, 2008. The submission included a new phase 3 efficacy and safety study DR-CEN-302 as well as data from a pharmacokinetic study (#10716214) which compared the pharmacokinetics (PK) of three estrogens (equilin, estrone, and estradiol) contained in synthetic conjugated estrogens, A with the same three estrogens contained in the approved product Cenestin 0.3 mg tablets.

3. CMC

There were no outstanding CMC deficiencies other than labeling identified during the first review cycle. The Primary Chemistry Reviewer concluded the following:

"From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is Approvable pending the submission of acceptable container/carton labeling, including the Patient Information and Physician's Package Insert."

A new CMC issue emerged during the current review cycle. The analytical method for measuring "Free Steroids" was changed from the USP procedure based on gas chromatography to a high pressure liquid chromatography method. The new method was noted to yield results ~ times lower than the previous method. The sponsor was asked to provide additional data to support the validation report findings. The sponsor responded with information that demonstrated that "Free Steroids" are not lost during the extraction step in the new method. The "Free Steroids" specification limit was lowered by a factor of — from 3% to — . This issue

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is now considered to be resolved and the chemistry reviewer concluded that "the method and its validation results are acceptable."

The chemistry reviewer concluded that "This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Therefore, from a CMC perspective, this NDA is recommended for "Approval." The CMC reviewer noted that labeling was pending.

The Division of Medication Errors and Technical Support DMETS found the proposed tradename Bijuva unacceptable due to the potential for confusion with the marketed drug Enjuvia and the Division concurred. A letter was sent to the sponsor on July 8, 2008, which stated "We do not recommend the use of the proprietary named Bijuva. The potential for confusion with other proprietary names is a safety issue. We recommend that another name along with container labels, carton labeling, and package insert labeling be submitted for review."

On September 9, 2008, the sponsor returned the label which had been edited and sent to the sponsor approximately three weeks previously. The sponsor acknowledged receipt of the Division's July 8, 2008, letter requesting that the sponsor propose a different tradename. The Sponsor, in the September 9, 2008, letter, stated that "Duramed will respond to the Agency at a later date and respectfully requests the Agency's report regarding the safety concerns with the name Bijuva Vaginal Cream."

I concur with the conclusion reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing support an expiry of 18 months. Labeling remains an unresolved issue.

4. Nonclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology information was submitted; the pharmacology/toxicology review was conducted during the original review cycle. Although the inactive ingredients differ for Cenestin® tablets and synthetic conjugated estrogens, A vaginal cream, "all are either compendial" or listed in the "FDA Inactive Ingredients list." The primary Pharmacology/Toxicology Reviewer made the following recommendation regarding approvability during the original review cycle:

"Pharmacology recommends approval of NDA 21-788 for synthetic conjugated estrogens, A vaginal cream 0.625 mg/g for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause....Furthermore the non-clinical pharmacology and toxicology of synthetic conjugated estrogens is expected to be similar to other short-acting oral estrogen information, which has been incorporated in the Estrogen Class Labeling."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

In the review of the original NDA 21-788 submission (June 25, 2004), the Clinical Pharmacology Reviewer stated the following:

"The submission of NDA 21-788 for synthetic conjugated estrogens, A is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective."

In the resubmission of NDA 21-788 (March 13, 2008), in addition to the phase 3 trial DR-CEN-302, the sponsor submitted pharmacokinetic study #10716214. This study compared estrogen exposure of synthetic conjugated estrogens A vaginal cream, 1g and 2g dosages, to a daily oral dose of the approved product 0.3 mg Cenestin.

Study 10716214 was a randomized, multiple-dose, three-treatment parallel design study. The study is entitled "A Study to Compare the Pharmacokinetics of Synthetic Conjugated Estrogens A, (synthetic conjugated estrogens, A) 0.625 mg/g Vaginal Cream to Cenestin® (synthetic conjugated estrogens, A) 0.3 mg tablets in Postmenopausal Females." The primary objective of this study was to compare the pharmacokinetic profile of two different doses (0.625 mg and 1.25 mg) of synthetic conjugated estrogens A, vaginal cream when given at intervals over a 27-day period to Cenestin 0.3 mg tablet taken once a day for 27 days in postmenopausal women.

The study was conducted in 60 (59 completing) healthy post menopausal female subjects who were randomized to one of three dosing regimens: 1 gram (0.625 mg) of synthetic conjugated estrogens, A vaginal cream applied intra-vaginally on Days 1, 2, 3, 4, 5, 6, 7, 10, 13, 17, 24, and 27; or 2 gram (1.25mg) of synthetic conjugated estrogens, A vaginal cream applied intra-vaginally on Days 1, 2, 3, 4, 5, 6, 7, 10, 13, 17, 24 and 27; or one Cenestin® 0.3 mg tablet administered once a day for 27 consecutive days.

Blood samples were collected from 48 hours prior to initial study dosing (Day -2) for baseline levels and at multiple occasions during the study until 48 hours after the final study dosing (Day 29).

The mean pharmacokinetic parameters (AUC and C_{max}) at day 27 comparing synthetic conjugated estrogens A vaginal cream and a Cenestin oral tablet are shown in Table 1. (Synthetic conjugated estrogen, A is referred to in several of the tables below as Bijuva. This proposed tradename has not been accepted by either DMETS or the Division.)

Table 1: Mean Pharmacokinetic parameters at Day 27 comparing Bijuva vaginal cream and a Cenestin oral tablet:

Product	Unconjugated Estrogen	AUCweekly (pg.hr/mL)	*P-values*
(A) Bijuva®, 1 gm (0.625 mg) Vaginal Cream	Equilin	66.84	0.4948 (A vs. B) <0.0001 (A vs. C)
	Estrone*	1246.35	0.3749 (A vs. B) <0.0001 (A vs. C)
	Estradiol*	350.23	0.9438 (A vs. B) 0.0055 (A vs. C)
(B) Bijuva®, 2 gm (1.25 gm) Vaginal Cream	Equilin	171.67	<0.0001 (B vs. C)
	Estrone*	1635.65	<0.0001 (B vs. C)
	Estradiol*	357.53	0.0060 (B vs. C)
(C) Cenestin®, 0.3 mg Oral Tablet	Equilin	1860.38	
	Estrone*	4335.47	
	Estradiol*	648.13	

*Baseline Corrected

Product	Unconjugated Estrogen	Cmax (pg/mL)	*P-values*
(A) Bijuva®, 1 gm (0.625 mg) Vaginal Cream	Equilin	5.49	0.1918 (A vs. B) 0.0020 (A vs. C)
	Estrone*	23.99	0.2082 (A vs. B) 0.0003 (A vs. C)
	Estradiol*	7.90	0.9201 (A vs. B) 0.4465 (A vs. C)
(B) Bijuva®, 2 gm (1.25 gm) Vaginal Cream	Equilin	11.45	0.0574 (B vs. C)
	Estrone*	31.44	0.6712 (B vs. C)
	Estradiol*	7.74	0.5027 (B vs. C)
(C) Cenestin®, 0.3 mg Oral Tablet	Equilin	20.09	
	Estrone*	46.83	
	Estradiol*	6.65	

*Baseline Corrected

For AUC of the three estrogens measured (equilin, estrone, and estradiol), the weekly values for the synthetic conjugated estrogen, A vaginal cream 0.625 mg dose are less (and statistically significantly less) than for oral Cenestin 0.3 mg. For C_{max} the 0.625 dose is statistically

significantly less in regards to estrone and equilin. The C_{max} for estradiol seen with synthetic conjugated estrogens, A vaginal cream is similar to oral Cenestin 0.3 mg.

The clinical pharmacology reviewer found "this NDA acceptable from a clinical pharmacology perspective. The pending issue is agreement from the sponsor on the Agency's proposed recommendations on the label."

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Labeling, however, remains an unresolved issue.

6. Clinical Microbiology

The microbiologic data were reviewed during the original review cycle and were deemed to be acceptable.

7. Efficacy/Statistics

In response to the "not approvable" letter of April 25, 2005, the sponsor submitted the results of a single twelve week efficacy and safety study of synthetic conjugated estrogens, A. Study DR-CEN-302 was a randomized, multicenter, double-blind, placebo controlled trial to compare the safety and efficacy of synthetic conjugated estrogens, A vaginal cream to placebo vaginal cream for 12 weeks of treatment. Six hundred twenty-two (622) patients were randomized and treated at 88 sites in the United States. After the screening period, subjects were randomized in a 1:1:1:1 blinded fashion to 2 g (1.25 mg synthetic conjugated estrogens, A) vaginal cream or its matching placebo, or 1g (0.625 mg synthetic conjugated estrogens, A) vaginal cream or its matching placebo for twelve weeks of double-blind treatment.

Enrolled subjects were 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).

Inclusion criteria included:

1. Naturally or surgically postmenopausal women, with or without an intact uterus, age 30 to 80 years, inclusive. Postmenopausal was defined as:

    a. At least 12 months natural spontaneous amenorrhea, or
    b. At least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, or
    c. Six months spontaneous amenorrhea with serum FSH concentrations >40 mIU/mL, or
    d. For hysterectomized subjects without bilateral oophorectomy: serum FSH concentrations >40 mIU/mL AND estradiol concentrations of <20 pg/ml.
2. On self-assessment of vaginal atrophy (Vaginal Atrophy/Sexual Function

Questionnaire) at the Randomization Visit, the subject rated at least one symptom as moderate or severe and had to identify, among those symptoms rated moderate or severe, the one considered by the subject to be the most bothersome.

3. No greater than 5% superficial cells on vaginal smear (subjects qualified for randomization based on the Screening Visit evaluation. Continued participation in the study was dependent on the Randomization Visit cytology evaluation also meeting this criterion).
4. Vaginal pH >5.0 at the Randomization Visit.
5. Have had a normal (atrophic, proliferative, or secretory) endometrial biopsy without evidence of endometrial hyperplasia or cancer (for subjects with an intact uterus).
6. Subjects >40 years of age had a negative mammogram performed at the Screening Visit (Visit 0) (or must have provided the investigator with documentation of a normal mammogram performed within 9 months of Visit 0) and had a normal clinical breast examination at Visit 0.

The remainder of the inclusion/exclusion criteria are detailed in the Medical Officer review and are consistent with previous trials of estrogen products for the treatment of VVA.

Primary endpoints:

The three co-primary endpoints for study DR-CEN-302 were:

- The mean change in the maturation index between Baseline and End of Treatment (Day 84). In addition, the mean changes in the percentage of parabasal and superficial cells from Baseline to End of Treatment were evaluated.

- The mean change in vaginal pH between Baseline and End of Treatment,

- The mean change in severity between the Baseline and End of Treatment for the moderate to severe symptom that has been identified at Baseline by the subject as being the most bothersome. The most bothersome symptom (MBS) was derived from the subject self-assessment of vaginal atrophy, that consisted of 5 questions concerning the severity of individual symptoms graded on a scale of 0 to 3 (corresponding to, None, Mild, Moderate, or Severe, respectively) or 7 for N/A (not applicable). The subject then classified the MBS as the single symptom rated as either moderate or severe at baseline that she considered the most bothersome from among all symptoms rated moderate or severe. The symptoms considered for determination of the MBS were:

    - Vaginal Dryness
    - Vaginal Irritation/Itching
    - Vaginal Soreness
    - Pain during intercourse (could be score as 7 ["N/A]
    - Bleeding after intercourse (could be score as 7 ["N/A].

A summary of subject disposition is shown in Table 2.

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

The largest number of withdrawals was "subject request to be withdrawn" and most of these were "due to lack of efficacy." All of the withdrawals "due to lack of efficacy" were in the placebo groups.

The baseline characteristics of the patients with regard to the three primary endpoint variables were comparable across treatment groups (Table 3). The percentages of patients identifying the various "most bothersome symptoms" across the four treatment groups were reasonably comparable.

Table 3: Baseline distribution of the MBS, Vaginal pH, and Vaginal Cytology in the MITT

	2g Bijuva (N=146)	1g Bijuva (N=135)	2g Placebo (N=135)	1g Placebo (N=140)	Total (N=556)
Most Bothersome Symptoms					
Vaginal Dryness	76 (52.1%)	60 (44.4%)	70 (51.9%)	72 (51.4%)	278 (50.0%)
Vaginal Irritation/Itching	10 (6.8%)	23 (17.0%)	15 (11.1%)	22 (15.7%)	70 (12.6%)
Vaginal Soreness	3 (2.1%)	6 (4.4%)	3 (2.2%)	5 (3.6%)	17 (3.1%)
Dyspareunia	57 (39.0%)	45 (33.3%)	47 (34.8%)	41 (29.3%)	190 (34.2%)
Bleeding After Intercourse	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vaginal pH					
N	146	135	135	140	556
Mean (Std)	6.3 (0.65)	6.3 (0.67)	6.3 (0.62)	6.3 (0.63)	6.3 (0.64)
Median	6.5	6.5	6.1	6.1	6.5
(Min, Max)	(5.1, 7.5)	(5.1, 8.0)	(5.1, 7.5)	(5.3, 7.0)	(5.1, 8.0)
***Superficial Cells* (%)**					
N	146	135	135	140	556
Mean (Std)	1.0 (1.52)	1.1 (1.62)	1.1 (1.56)	1.3 (1.71)	1.1 (1.61)
Median	0.0	0.0	0.0	0.0	0.0
(Min, Max)	(0.0, 5.0)	(0.0, 5.0)	(0.0, 5.0)	(0.0, 5.0)	(0.0, 5.0)
***Parabasal Cells* (%)**					
N	146	135	135	140	556
Mean (Std)	42.6 (30.98)	38.5 (32.54)	40.4 (33.83)	37.6 (31.86)	39.8 (32.26)
Median	43.5	32.0	31.0	30.5	32.0
(Min, Max)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 98.0)	(0.0, 100.0)
Maturation Index					
N	146	135	135	140	556
Mean (Std)	29.2 (15.68)	31.3 (16.53)	30.3 (17.19)	31.8 (16.16)	30.7 (16.37)
Median	29.5	34.5	35.5	35.3	34.0
(Min, Max)	(0.0, 52.5)	(0.0, 52.5)	(0.0, 52.5)	(1.0, 52.5)	(0.0, 52.5)

Primary endpoints:

A. Maturation Index – Change in Superficial and Parabasal Cells

A highly statistically significant increase over placebo was demonstrated in the Maturation Index at 12 weeks in both the 2 gram and 1 gram dose groups.

The change in superficial cells and parabasal cells was also highly statistically significant for both dose groups. These results are shown Tables 4 and 5.

Table 4: Superficial Cells: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva	146	0.97	26.79	1.237	21.79	<.0001
2g Placebo	135	1.08	5.00	1.271		
1g Bijuva	135	1.13	25.16	1.270	22.05	<.0001
1g Placebo	140	1.31	3.11	1.256		

Change = Change in Superficial Cells (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

Table 5: Parabasal Cells: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva	146	42.56	-39.82	1.796	-26.97	<.0001
2g Placebo	135	40.41	-12.85	1.844		
1g Bijuva	135	38.51	-37.75	1.842	-30.55	<.0001
1g Placebo	140	37.64	-7.20	1.818		

Change = Change in Parabasal Cells (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

The difference between the effects of the 1 g and 2 g doses of synthetic conjugated estrogens, A vaginal cream on the percentages of superficial and parabasal cells appears to be small.

B. Vaginal pH

The mean change from baseline to Week 12 in the vaginal pH was the second of the three co-primary efficacy endpoints for protocol DR-CEN-302. The results are shown in Table 6.

Table 6: Vaginal pH: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Raw Data)***
2g Bijuva	146	6.35	-1.44	0.071	-1.06	<.0001
2g Placebo	135	6.30	-0.38	0.073		
1g Bijuva	135	6.32	-1.48	0.073	-1.17	<.0001
1g Placebo	140	6.27	-0.31	0.072		

** Change = Change in Vaginal pH (Day 0 to Day 84 [or End-of-Treatment]).*
*** Difference = Difference between active treatment group and matching placebo.*
**** P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis. Normality test: p-value=0.0515.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

The placebo subtracted changes in vaginal pH from baseline to endpoint for both the 2 g and 1 g doses are statistically significant. The difference between the two doses is small.

C. Most Bothersome Symptom (MBS)

The most bothersome symptom (MBS) is determined from the subject self-assessment of symptoms of vaginal atrophy, which consists of five questions concerning the severity of individual symptoms graded on a scale of 0 -3 (corresponding to None, Mild, Moderate, or Severe, respectively) or 7 for N/A (non-applicable). The subject then classified the MBS as the single symptom rated as either moderate or severe at baseline that she considers the most bothersome from among all symptoms rated moderate or severe. (These symptoms are Vaginal Dryness, Vaginal Irritation/Itching, Vaginal Soreness, Pain during Intercourse, and Bleeding after Intercourse.)

Two of the symptoms rated as "most bothersome" (vaginal dryness and pain during intercourse) showed statistically significant improvement from baseline to week 12. These results are shown in Tables 7 and 8.

Table 7: Individual MBS Symptom-Vaginal Dryness: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	76	2.61	-1.84	0.114	-0.55	<.0001
2g Placebo	70	2.54	-1.29	0.114		
1g Bijuva	60	2.58	-1.65	0.123	-0.48	0.0012
1g Placebo	72	2.47	-1.17	0.113		

** Change = Change in the Severity of Individual MBS Symptom - Vaginal Dryness (Day 0 to Day 84 [or End-of-Treatment]).*

Table 8: Individual MBS Symptom-Pain during Intercourse: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	57	2.68	-1.78	0.186	-0.89	<.0001
2g Placebo	47	2.72	-0.89	0.196		
1g Bijuva	45	2.71	-1.76	0.184	-0.82	<.0001
1g Placebo	41	2.76	-0.94	0.199		

** Change = Change in the Severity of Individual MBS Symptom - Pain during Intercourse (Day 0 to Day 84 [or End-of-Treatment]).*
*** Difference = Difference between active treatment group and matching placebo.*
**** P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

The differences between the 1 g and 2 g doses of synthetic conjugated estrogens, A vaginal cream in improving the symptoms of vaginal dryness and pain during intercourse appear to be small.

The changes in the MBS's of vaginal irritation/itching and vaginal soreness did not reach statistical significance when comparing the drug groups to placebo groups at either dose at week 12. The number of patients selecting these MBS's was small.

The statistical reviewer concluded that the study results were "statistically significantly superior to placebo with respect to the following endpoints: vaginal maturation index (decreasing parabasal cells and increasing superficial cells), lowering vaginal pH, and reducing the severity of vaginal dryness and dyspareunia among healthy post-menopausal women." Statistical analyses were based on the MITT cohort defined as "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 maximal bothersome symptom. A total of 556 subjects were included in the MITT. Because the p-values for the two most bothersome symptoms (vaginal dryness and dyspareunia) versus placebo were low (<0.0016), the statistical reviewer believes that any adjustment for multiplicity would not change the conclusions of the statistical analysis.

Efficacy Summary:

Both the 1 gram and 2 gram doses of synthetic conjugated estrogens, A vaginal cream produced statistically significant improvement in symptoms for all three primary endpoints. The efficacy differences between the two doses (1 g and 2 g) are small. The sponsor does not seek approval for the 2 mg dose and I agree that the 1 mg dose is the only dose which should be approved.

8. Safety

In the phase 3 study protocol (DR-CEN-302) a total of 622 subjects were randomized and treated with one of four vaginal creams: 2g synthetic conjugated estrogens, A (N =161), 2g placebo (N = 156), 1g synthetic conjugated estrogens, A (N = 150) or 1g placebo (N = 155). The treatment period was 84 days. Safety and tolerability were assessed by comparisons between treatment groups of treatment-emergent adverse events (TEAEs), standard laboratory test results, vital signs, transvaginal ultrasound (TVU) and endometrial biopsy results (Day -28 and Day 84) or end of treatment for non-hysterectomized subjects.

Deaths:

There were no study deaths.

Serious adverse events (SAE):

A total of 8 subjects experienced a SAE during the study. SAE's occurred in four placebo subjects, two active drug treated subjects, and two subjects who were not randomized (Table 9). One deep venous thrombosis/pulmonary embolus was observed in a placebo-treated subject.

Table 9: Serious Adverse Events

Treatment	Subject	SAE Descripton	Causality	Ongoing?
	0027/27019*	DIVERTICULITIS	None	Resolved
		MILD PANCREATITIS	None	Resolved
	0097/97008*	CARDIAC CHEST PAIN	None	Resolved
		HYPERTENSION	None	Resolved
2g Bijuva	0084/84004	CHRONIC SINUSITIS	None	Resolved
1g Bijuva	0044/44006	VENTRICULAR TACHYCARDIA	None	Resolved
2g Placebo	0027/27041	DEEP VEIN THROMBOSIS	Possibly	Resolved
		PULMONARY EMBOLISM	Possibly	Yes
	0055/55003	CARDIAC CHEST PAIN	Possibly	Resolved
	0059/59013	HYPONATRAEMIA	None	Resolved
1g Placebo	0045/45018	HODGKIN'S DISEASE	None	Yes

**Not randomized, not treated.*

I agree with the primary medical officer's conclusion that the two SAE's in patients on active drug are unlikely to be related to study medication.

Study discontinuations:

Patients who discontinued due to an adverse event (AE) judged to be treatment related are shown in Table 10.

Table 10: Adverse Events Leading to Study Discontinuation

Treatment	Site	Subject	AE Description	Severity
2g Bijuva	0012	12002	ABD BLOATING	Moderate
			ABD TENDERNESS	Mild
			ABD. CRAMPING	Mild
			PRESSURE IN LOWER ABD.	Moderate
	0033	33006	BACTERIAL VAGINOSIS	Mild
	0049	49033	BILATERAL BREAST SORENESS	Moderate
			BILATERAL LEG CRAMPS	Moderate
	0077	77005	VAGINAL IRRITATION	Moderate
	0081	81011	VAGINAL ITCHING	Moderate
1g Bijuva	0006	6004	ANTERIOR CHEST PAIN (NON CARDIAC)	Moderate
			HEADACHE	Moderate
			SHORTNESS OF BREATH	Moderate
			VAGINAL BURNING	Moderate
	0043	43009	FACIAL REDNESS	Mild
			FACIAL SWELLING	Mild
	0052	52016	YEAST INFECTION, VAGINAL ITCHING + BURNING	Moderate
2g Placebo	0052	52015	VAGINAL YEAST INFECTION	Moderate
	0078	78020	HEADACHE	Severe
1g Placebo	0033	33011	INCREASED HOT FLASHES	Mild
			INCREASED INSOMNIA	Mild
	0066	66015	POSTERIOR FORCHETTE FISSURE	Moderate

Two subjects discontinued due to AE but were not treated with study medication , therefore, not displayed.

Eight patients in the active drug groups and four in the placebo groups discontinued because of an AE judged to be treatment related.

Table 11 shows the incidence of TEAE's which occurred in 3% or more of the patients in each treatment group.

Table 11: Adverse Events: Incidence of Treatment-Emergent Adverse Events occurring in 3% or more of Patients

MedDRA System Organ Class	2g Bijuva (N=161)		1g Bijuva (N=150)		2g Placebo (N=156)		1g Placebo (N=155)		Total (N=622)	
and Preferred Term	N	%	N	%	N	%	N	%	N	%
GASTROINTESTINAL DISORDERS										
ABDOMINAL PAIN	7	4.35	1	0.67	0	0.00	1	0.65	9	1.45
INFECTIONS AND INFESTATIONS										
UPPER RESPIRATORY TRACT INFECTION	6	3.73	7	4.67	6	3.85	7	4.52	26	4.18
URINARY TRACT INFECTION	5	3.11	3	2.00	6	3.85	2	1.29	16	2.57
VULVOVAGINAL MYCOTIC INFECTION	3	1.86	7	4.67	2	1.28	5	3.23	17	2.73
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS										
BACK PAIN	6	3.73	0	0.00	2	1.28	0	0.00	8	1.29
REPRODUCTIVE SYSTEM AND BREAST DISORDERS										
GENITAL PRURITUS FEMALE	5	3.11	4	2.67	1	0.64	0	0.00	10	1.61
NERVOUS SYSTEM DISORDERS										
HEADACHE	2	1.24	6	4.00	6	3.85	0	0.00	14	2.25
VASCULAR DISORDERS										
HOT FLUSH	2	1.24	5	3.33	5	3.21	2	1.29	14	2.25
HYPERTENSION	0	0.00	1	0.67	5	3.21	1	0.65	7	1.13

The incidence of TEAEs appears comparable across treatment groups. A higher incidence of abdominal pain was reported for the active groups (8/33 [2.6%]) than for placebo (1/311 [0.3%]). Nine (9) synthetic conjugated estrogens, A subjects (2.9%) and one placebo subject (0.3%) reported genital pruritus as an adverse event. The most commonly reported AE was upper respiratory tract infection (4.2%) for both placebo and synthetic conjugated estrogens, A. All other incidence rates of TEAEs were < 3% or similarly distributed across treatment groups

A total of 272 patients had an endometrial biopsy (EMB) done at the screening visit and also had an EMB performed at the end of treatment. Two hundred twenty-seven (227) patients had valid biopsy results obtained at both screening visit and the end of treatment. No findings among the successful entrance and exit biopsies were considered to be clinically significant.

Review of serum chemistry, serum lipid profile, hematology, and urinalysis demonstrate no changes that are thought to be clinically significant.

Safety summary:

No new safety concerns with this estrogen vaginal cream were identified.

Dose selection:

The efficacy and safety findings in DR-CEN-302 do not show significant differences between the 2 g (1.25 mg synthetic conjugated estrogens, A) and 1 g (0.625 mg synthetic conjugated estrogens) doses of synthetic conjugated estrogens, A vaginal cream. The sponsor has also identified no significant differences in the two dosages and is seeking to market only the 1g

(0.625mg) dosage. The dosing regimen is 1 g (1 applicator) intravaginally daily for one week followed by 1 g (1 applicator) intravaginally twice per week.

9. Advisory Committee Meeting

No advisory committee was convened for this drug. Synthetic conjugate estrogens, A is an approved drug (oral administration). No new safety concerns were identified.

10. Pediatrics

Synthetic conjugate estrogens, A are not indicated for use in the pediatric population. The indication (VVA) does not occur in children. According to a September 11, 2008, e-mail, "as a follow-up to NDA 21-788, synthetic conjugated estrogens, the PeRC members agreed with the Division to grant a full waiver of pediatric studies in the 0-16 age group."

11. Other Relevant Regulatory Issues:

a. Division of Scientific Investigations:

Three clinical sites were inspected for the previous phase 3 trial DP3-2002-002 submitted during the original review cycle. No significant deficiencies were identified. No additional inspections were requested for the sites participating in the new phase 3 trial DR-CEN-302 submitted during the current review cycle.

b. **Division of Medication Error Prevention (DMEP):**

The Division of Medication Errors and Technical Support DMETS found the proposed tradename Bijuva unacceptable due to the potential for confusion with the marketed drug Enjuvia and the Division concurred. A letter was sent to the sponsor on July 8, 2008, which stated "We do not recommend the use of the proprietary name Bijuva. The potential for confusion with other proprietary names is a safety issue. We recommend that another name along with container labels, carton labeling, and package insert labeling be submitted for review."

c. **Financial Disclosure:**

The primary medical officer noted that financial disclosure information was submitted and appears acceptable.

12. Labeling:

The Division's edited label was returned to the Sponsor on August 18, 2008. The sponsor returned the label on September 9, 2008, and discussions were held with the sponsor on September 11, 2008. The sponsor returned their latest version of the label today (September 12, 2008). The sponsor "respectfully disagrees with the Agency's comment that the exposure comparison to the lowest oral dose and the 1 gram dose of Synthetic Conjugated Estrogens, A

Vaginal Cream be removed from the label." This issue remains unresolved and will require further discussion both internally and with the sponsor.

13. Decision/Action/Risk Benefit Assessment:

Synthetic conjugated estrogens, A vaginal cream was demonstrated (in trial DR-CEN-302) to be effective in the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, symptoms of vulvar and vaginal atrophy due to menopause. Both the 1 gram and 2 gram doses of synthetic conjugated estrogens, A vaginal cream produced statistically significant improvement for all three primary endpoints. The efficacy differences between the two doses [1 g vaginal cream (0.625 mg synthetic conjugated estrogens, A) and 2 g vaginal cream (1.250 mg synthetic conjugated estrogens, A)] are small. The sponsor does not seek approval for the 2 mg dose and I agree that the 1 mg dose is the only dose which should be approved. No new safety concerns were identified with this estrogen vaginal cream.

I agree with the medical team leader, the primary medical reviewer, the pharmacology/toxicology reviewer, the clinical pharmacology reviewer, the chemistry reviewer, and the statistics reviewer that NDA 21-788 (synthetic conjugated estrogens, A for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause) should be approved pending agreement on labeling and clarification of the Phase 4 commitment regarding a study to evaluate the lowest effective dose of synthetic conjugated estrogens, A vaginal cream.

No agreement has been reached with the sponsor on the tradename of synthetic conjugated estrogens, A vaginal cream. On September 9, 2008, the sponsor returned the label which had been edited and sent to the sponsor on August 18, 2008. The sponsor acknowledged receipt of the Division's July 8, 2008, letter requesting that the sponsor propose a different tradename. The Sponsor, in the September 9, 2008, letter, stated that "Duramed will respond to the Agency at a later date and respectfully requests the Agency's report regarding the safety concerns with the name Bijuva Vaginal Cream."

The Division requested that the sponsor agree to a post-marketing commitment to study synthetic conjugated estrogens, A vaginal cream to determine the lowest effective dose. The sponsor, in a letter received today (September 12, 2008), stated that they "would also like to inform the Agency of our intent to conduct a Phase IV study with Synthetic Conjugated Estrogens, A Vaginal Cream" and proposed wording concerning the Phase 4 commitment for the action letter."

The sponsor returned their latest version of the label today (September 12, 2008). The sponsor "respectfully disagrees with the Agency's comment that the exposure comparison to the lowest oral dose and the 1 gram dose of Synthetic Conjugated Estrogens, A Vaginal Cream be removed from the label." This issue remains unresolved and will require further discussion both internally and with the sponsor. A Complete Response action letter will be sent to the sponsor today.

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/s/

George Benson
9/12/2008 04:28:03 PM
MEDICAL OFFICER

Medical Officer's/ CDTL Review of NDA 21-788 Labeling

Date:	**November 26, 2008**
From:	**Shelley R. Slaughter**
NDA:	**21-788**
Applicant:	**Duramed Pharmaceuticals, Inc.**
Original Submission Date:	**June 25, 2004**
Original Regulatory Decision and Date:	**April 25, 2005 "Not approvable"**
Complete Response Receipt Date:	**March 13, 2008**
Complete Response Action Date:	**September 12, 2008**
Class I Resubmission Date:	**September 29, 2008**
Requested Proprietary Name:	**Bijuva™ Vaginal Cream**
Established (USAN) name:	**synthetic conjugated estrogens, A vaginal cream**
Dosage forms/ Strength:	
Indications:	**1. Treatment of Moderate to Severe Vaginal Dryness, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause.** **2. Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal atrophy, due to Menopause.**
Recommendation:	**Approval based upon the agreed upon labeling. In addition the Division of Reproductive and Urologic Products (henceforth referred to as the Division) has requested and Duramed has agreed to conduct Phase 4 randomized and placebo-controlled clinical trial to study the lowest effective dose for each or the above noted indications.**

Background:

NDA 21-788 was submitted by Duramed Pharmaceuticals on June 25, 2004 for an indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, due to menopause. The application received a "not-approvable" regulatory decision because of failure to demonstrate efficacy.

Duramed submitted a complete response to the "not-approvable" action on March 13, 2008. A complete response action was taken on September 12, 2008 because of failure to come to agreement on labeling and language on a Phase 4 agreement to assess the lowest effective doses for the indications of "Treatment of Moderate to Severe Vaginal Dryness, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause" and "Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal atrophy, due to Menopause." Please refer to the Cross-Discipline Team Leader (CDTL) review, dated and archived on September 12, 2008, for a more detailed discussion of issues involved with the March 13, 2008 complete response submission.

September 29, 2008 Submission - Labeling Issues:

In their September 29, 2008 submission, Duramed included in the text of Section 12.3 comparative pharmacokinetic data on Cenestin® 0.3 mg oral tablets. This information was deleted by the Division during the previous regulatory review cycle and Duramed had originally

agreed to its deletion. The clinical review team and Office of Clinical Pharmacology strongly disagree with the inclusion of the comparative pharmacokinetic data on Cenestin® 0.3 mg oral tablets. The following is our rationale for not including the oral tablet comparative information:

- The treatment of the **symptoms** of vulvar and vaginal atrophy is, as can be realized from the indication, a symptom-driven indication. Dosing decisions are made on the basis of relief of symptoms and not on achievement of a given serum hormone level as in replacement therapy.
- Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.
- There is no clinical trial data demonstrating that a lower serum level of estradiol or estrone as seen with this vaginal cream translates into a less concerning safety profile.
- For these symptomatic indications, information on the pharmacokinetics of one dosage form (i.e. tablets) can not be relied upon to guide the usage of a different dosage form (i.e. vaginal cream).

The Division removed the comparative PK information.

b(4)

Duramed added to section 2.1 the following language "[redacted]. This language had not been considered in the original review cycle and was removed from the Prescribing Information.

In addition to the above discussed items, the Division recommended that respective sections of the Prescribing Information or Patient Information sections be modified as follows:

- [redacted]

b(4)

- [redacted]

b(4)

Labeling negotiations were concluded on November 26, 2008. All changes as presented in the attached labeling and the carton/container label have been agreed upon.

September 29, 2008 Submission – Proprietary Name Issues:

Duramed was informed during the previous review cycle that the proprietary name Bijuva was not acceptable. The Prescribing Information, carton and container labeling submitted by Duramed on September 29, 2008 all referenced the proprietary name Bijuva. Per the Sponsor, "we respectfully acknowledge this concern and feel that it can be adequately managed such that medication errors can be prevented. On October 20, 2008 during the current review cycle, the Sponsor was once again notified that the proprietary name Bijuva was not acceptable to this Division and to the Division of Medication Prevention and Analysis (DMEPA). The Sponsor requested a formal response in the form of a regulatory letter with signatory authority represented. On November 17, 2008 a letter was sent with advice as follows:

> "We have reviewed the referenced material. Following consultation with the Division of Medication Error Prevention and Analysis (DMEPA), we continue to believe that the proprietary name Bijuva is unacceptable because of the potential for confusion with the marketed drug Enjuvia. The following were considered in reaching this decision.
>
> 1. Enjuvia and Bijuva share overlapping product characteristics such as active ingredient (synthetic conjugated estrogen), numerical strength (0.625 mg vs. 0.625 mg/gram), indications for use (vasomotor symptoms due to menopause or symptoms of vulvar and vaginal atrophy due to menopause), frequency of administration, and patient and prescriber population.
>
> 2. Depending on the handwriting, it is possible that a prescription written for "Enjuvia 0.625 mg, use as directed" may be misinterpreted as "Bijuva 0.625 mg/g, use as directed."
>
> Therefore, we conclude that there is a potential for confusion between Bijuva and Enjuvia due to the overlapping product characteristics and orthographic similarities."

Duramed responded on November 18, 2008 with the following: "While we respectfully disagree with the decision by DRUP and DMEPA that the proprietary name Bijuva is unacceptable, we are dropping it as a proposed proprietary name to keep the regulatory review moving forward. In its place, we are proposing to use the proprietary name —— Proposed alternate names, in rank order, are —— and —— Duramed was notified that they would need to submit a separate submission with proposed proprietary names to DMEPA and this would start the official review clock for the name which is separate from the NDA clock. The submission to DMEPA was

b(4)

received on November 20, 2008. The alternative proprietary name review is now underway by DMEPA.

September 29, 2008 Submission – Phase 4 Agreements:

In their September 29, 2008 submission, Duramed stated:

> "Duramed commits to design and conduct a Phase IV clinical trial to find the lowest effective dose of Bijuva Vaginal Cream, 0.625 mg/g for the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. Duramed commits to the following timeline for this study:
>
> | | |
> |---|---|
> | Protocol Submission: | Within 6 months of the date of the receipt of an Approval letter. |
> | Study Start: | Within 6 months of protocol agreement with the Division. |
> | Final Report Submission: | Within 6 months of study completion." |

On November 26, 2008, the Division reached agreement with Duramed to modify the language on the Phase 4 agreement as follows:

> "Duramed commits to design and conduct a Phase 4 randomized and placebo-controlled clinical trial to find the lowest effective dose of synthetic conjugated estrogens, A vaginal cream for the indication of (1) Treatment of Moderate to Severe Vaginal Dryness, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause and (2) Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal atrophy, due to Menopause."

Conclusions and Recommendations:

As of the date of this review, we have reached agreement with Duramed on the Prescribing Information, Patient Information, the carton and container labeling and the Phase 4 commitment to study the lowest effective dose. The review from ONDQA has been reviewed and they recommend "Approval" from a chemistry, manufacturing and control viewpoint. The Clinical Pharmacology is not yet archived. The Clinical Team (this review will serve as both Medical Officer and CDTL review) recommends "Approval" as Synthetic Conjugated Estrogens, A Vaginal Cream. The proprietary name issues will be reviewed and resolved with DMEPA.

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/s/

Shelley Slaughter
11/26/2008 05:27:42 PM
MEDICAL OFFICER
Combined MO/CDTL review of labeling

Application Type	NDA
Submission Number	21-788
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Letter Date	March 12, 2008
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PDUFA Goal Date	September 13, 2008
Reviewer Name	Phill H. Price, M.D.
Review Completion Date	September 10, 2008
Established Name	Synthetic conjugate estrogens, A
(Proposed) Trade Name	Bijuva® Vaginal Cream
Therapeutic Class	Estrogen
Applicant	Duramed Pharmaceuticals, Inc. (Subsidiary of Barr Pharmaceuticals, Inc.)
Priority Designation	S
Formulation	Vaginal cream (0.625 mg synthetic conjugated estrogens, A per gram
Dosing Regimen	One gram daily for one week, followed by one gram twice weekly
Indication	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause
Intended Population	Postmenopausal women

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1 EXECUTIVE SUMMARY

Approval of synthetic conjugated estrogens, A vaginal cream 1g (0.625mg synthetic conjugated estrogens, A) is recommended for the treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy due to menopause. The efficacy of synthetic conjugated estrogens A, vaginal cream 1g (0.625mg) was demonstrated in pivotal trial DR-CEN-302.

1.1 Recommendation on Regulatory Action

Sufficient evidence is provided to conclude that synthetic conjugated estrogens, A vaginal cream 1g (0.625mg synthetic conjugated estrogens, A) provides relief in the treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy due to menopause that begins at week 2-3 and is maintained through treatment week 12. In reviewing this submission, this reviewer observes very little clinical difference between the 2g and 1g dosage in trial DR-CEN-302. Therefore, this reviewer can not recommend, nor does the sponsor seek approval of the 2g dose, because it provides *no clinical benefit* to the patient in regards to either efficacy or safety. Safety of this product is not a major concern; serious and common adverse events are lower than Cenestin® (synthetic conjugated estrogens, A tablets) 0.3 mg per day.

1.2 Recommendation on Postmarketing Actions

Based upon the clinical and safety data present in this submission, this reviewer recommends that the sponsor study a 0.5g (0.375mg synthetic conjugated estrogens, A) vaginal cream dose to demonstrate a lowest effective dose or an ineffective dose.

1.2.1 Risk Management Activity

No additional risk management is deemed necessary. Synthetic conjugated estrogens, A vaginal cream 2g and 1g was studied in pivotal study DR-CEN-302. The 1g dosage appears to be an effective dose of synthetic conjugated estrogens, A which produces lower serum estrogen levels than the approved Cenestin 0.3mg oral tablet.

1.2.2 Required Phase 4 Commitments

A Phase 4 commitment should be required to demonstrate whether the 0.5g (0.375mg synthetic conjugated estrogens, A cream) dosage is the lowest effective dose of synthetic conjugated estrogens, A cream. This is recommended because the onset of efficacy occurs at week 2 ($p < 0.0012$) for the 1g (0.625mg synthetic conjugated estrogens, A) and efficacy continues through the twelfth week of treatment.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor Duramed Research Inc. has submitted study DR-CEN-302 to support approval of synthetic conjugated estrogens, A cream for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. This submission is in response to a not-approvable letter sent to the sponsor on April 25, 2005. Study DR-CEN-302 is a randomized, multicenter, double-blind, placebo controlled trial to compare the effects of 12 weeks of treatment with synthetic conjugated estrogens, A vaginal cream vs. placebo vaginal cream on vulvovaginal atrophy in healthy postmenopausal women. At a meeting on July 18, 2005 the Agency indicated to Duramed that a well-controlled trial demonstrating statistical significance for all three co-primary endpoints as outlined in the Guidance "Estrogen and Estrogen/Progestin Drugs Products to treat vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms would be necessary. Study DR-CEN-302 is the sponsor's response to that meeting.

1.3.2 Efficacy

The sponsor studied synthetic conjugated estrogens, A cream 2g and 1g versus matching placebo vaginal cream to demonstrate the efficacy of conjugated estrogens, A cream over 12 weeks of treatment. Study DR-CEN-302 results demonstrate efficacy at week 12 for both dosages of synthetic conjugated estrogens, A. The group receiving the 2g or the group receiving the1g vaginal cream, when compared to their respective placebo groups at week 12, demonstrated a significant increase in the percentage of vaginal superficial cells ($p < 0.0001$); significant decrease in the vaginal parabasal cells ($p < 0.0001$); a significant decrease in the vaginal pH ($p < 0.0001$); and a significant reduction in the *individual* most bothersome symptom(s) (MBS) of vaginal dryness ($p = 0.0002$ and $p = 0.0016$) and vaginal pain during intercourse ($p < 0.0001$, and $p = 0.0002$ for the 2g and 1g, respectively, respectively).

1.3.3 Safety

The safety of synthetic conjugated estrogens, A cream 2g and 1g is supported by study DR-CEN-302. Additional safety support was also demonstrated in study DP3-2002-002 (original submission) and a Phase 1 study 231-03 that was used to support synthetic conjugated estrogens, A cream in the original submission of June 25, 2004. Approximately 622 subjects (synthetic conjugated estrogens, A cream 2g [161], synthetic conjugated estrogens, A vaginal cream 1g [150], 2g placebo [156], 1g placebo [155]) were randomized and treated with one of these four vaginal creams.

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The criteria used to assess the safety of synthetic conjugated estrogens, A cream 2g and 1g were adverse events (AEs), vital signs, general physical examination, breast and gynecological examinations, assessment of bleeding, body weight, and laboratory assessments. Safety assessments also included transvaginal ultrasound and endometrial biopsy at the screening visit and at the end treatment visit.

No new safety concerns were observed in study DR-CEN-302. Adverse events coding using the Medical Dictionary for Regulatory Activities (MedDRA) was employed.

1.3.4 Dosing Regimen and Administration

Synthetic conjugated estrogens, A cream 1g should be applied _____
for the first 7 days of treatment and two times a week _____ b(4)

1.3.5 Drug-Drug Interactions

Drug interactions are well defined for this class of estrogen products. No special studies were conducted with synthetic conjugated estrogens, A cream 2g or 1g in regards to drug interactions that are not presently included in the estrogen class label.

1.3.6 Special Populations

No special populations were studied with this product.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

See Original review by Dr. van der Vlugt on April 25, 2005 for a *detailed history* of this product.

• Proposed Trade Name:	Bijuva vaginal cream
• Established name:	Synthetic conjugated estrogens, A cream
• Chemical name:	Synthetic conjugated estrogens, A
• Pharmacologic class:	Estrogen
• Proposed Indication:	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause

Cenestin® (synthetic conjugated estrogens A) tablet is an approved oral drug product that contain the following nine substances in combination: sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, 17β-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium17β- estradiol sulfate. Cenestin 0.45mg, 0.625mg, 0.9mg, and 1.25mg tablets are administered orally in a continuous daily regimen for the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause. Cenestin 0.3mg tablet, administered orally in a continuous daily regimen, is also approved f*or the treatment of moderate to severe vulvar and vaginal atrophy (VVA) associated with the menopause.*

Synthetic conjugated estrogens, A vaginal cream is a new dosage form with the active ingredient ——————. Synthetic conjugated estrogens A, vaginal cream also contains the *same* nine estrogenic substances in combination as the Cenestin tablets and contains the following inactive ingredients: benzyl alcohol, —wax, cetyl alcohol, cetyl esters wax, glycerin, glyceryl monostearate, light mineral oil, methyl state, propylene glycol monosterate, sodium hydroxide, sodium lauryl sulfate, and sodium phosphate dibasic anhydrous. b(4)

The established name of the drug substance is synthetic conjugated estrogens, A vaginal cream. The Division of Medication Errors and Technical Support (DMETS) *did not* recommend the use of the proprietary name, Bijuva in the first review cycle. The primary reason was possible confusion of this product (Consult #04-0105) with the marketed product Enjuvia™. This was conveyed to the sponsor in the not-approval letter of March 17, 2005.

2.2 Currently Available Treatment for Indications

See Original review by Dr. van der Vlugt on April 25, 2005 for list of approved products for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

See Original review by Dr. van der Vlugt on April 25, 2005.

2.4 Important Issues With Pharmacologically Related Products

See Original review by Dr. van der Vlugt on April 25, 2005.

2.5 Presubmission Regulatory Activity

See Original review by Dr. van der Vlugt on April 25, 2005. Also note that this submission is a direct response to the not-approvable letter of March 17, 2005. In this letter the sponsor was asked to demonstrate a statistically significant result on the most bothersome symptom (MBS). Duramed evaluated a composite MBS and the individual MBS and has submitted data that supports a statistically significant and clinically significant meaningful effect on the individual MBS.

2.6 Other Relevant Background Information

See Original review by Dr. van der Vlugt on April 25, 2005. Since the original review of Dr. van der Vlugt there has been one product approved in the Division for the treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy due to menopause. The product is Enjuva™ (synthetic conjugated estrogens, B 0.3mg tablets) and it was approved on April 23, 2007.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See original CMC review dated April 18, 2005.

3.2 Animal Pharmacology/Toxicology

See Original Pharmacology/Toxicology review dated February 24, 2005. During this review cycle there was one major CMC issue that arose. Duramed changed the analytical method for Free Steroids from USP procedure (based on GC) to an in-house (based on HPLC). The comparison of these two methods showed that the new procedure yielded results — times lower than the previous method. The sponsor was asked to resolve the differences in the analytical methods. The sponsor responded by showing that Free

b(4)

 b(4)
Steroids are "not lost" during the extraction period; that this new method lowered the Free Steroids limit — .imes (from 3% to — %.)

Additional minor deficiencies included: lack of ID test on release specifications, incorrect Total Yeast and Mold limit on specifications, and use of response factor in the analytical method, although an official USP standard already exists. Presently, two minor issues are being addressed concerning the label, an incorrect DLDE table and the lack of water in the SPL labeling. These minor issues will be resolved within the following week.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of data used in this review is the clinical trial conducted by the sponsor. The sponsor conducted study DR-CEN-302 "A Randomized, Multicenter, Double-Blind, Placebo Controlled Trial to Compare the Effects of 12 Weeks of Treatment with DR-2041 Vaginal Cream vs. Placebo Cream on Vulvovaginal Atrophy in Healthy Postmenopausal Women." This study randomized and treated a total of 622 subjects; subjects were randomized in a 1:1:1:1 blinded fashion to 2g synthetic conjugated estrogens, A, matching placebo to the 2g dose, 1g synthetic conjugated estrogens and a matching placebo to the 1g dose for twelve weeks of double-blind treatment. The mean age of subjects was 59.4 years of age.

There is no foreign history of any dosage form of synthetic conjugated estrogens, A. There are no withdrawn marketing authorizations for any reason.

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The following reviewer generated table summarizes the pivotal trial (DR-CEN-302) and the pK trial study #10716214:

4.2 Table of Clinical Studies

Table 1:. Table of Clinical Studies

Study Title	Number of Subjects on Active Drug	Number of Subjects on Placebo	Safety Evaluations	Duration (Days)
Phase III Study DR-CEN-302 entitled "A Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial to Compare the Effects of 12 Weeks of Treatment with DR-2041 Vaginal Cream vs. Placebo Cream on Vulvovaginal Atrophy in Healthy Postmenopausal Women."	2g Synthetic Conjugated estrogens, A (149) 1g Synthetic Conjugated Estrogens A (138)	2g Placebo (140) 1g Placebo (141)	Pre-Screening, Screening Baseline (1) Weeks 2, 3, 4, 8, 12	84
Study (# 10716214) compared the Pharmacokinetics of Synthetic Conjugated Estrogens A 0.625mg/g and 1.25mg/g Vaginal Cream to Cenestin® (Synthetic Conjugated Estrogens, A) 0.3mg tablets in Postmenopausal Females	60 subjects, 20 per group	N/A	1g Synthetic Conjugated Estrogens A on Days 1,2,3,4,5,6,7,10, 13,17,20,24, 27; 2g Synthetic Conjugated Estrogens A on Days 1,2,3,4,5,6,7,10, 13,17,20,24, 27; or one Cenestin 0.3mg tablet administered once a day for 27 consecutive days	27 days

4.3 Review Strategy

This review was conducted utilizing the following strategy:

- An overview of the total clinical documents with emphasis on protocol DR-CEN-302. This is the primary efficacy study reviewed to support the indication of treatment of moderate to severe vulvar and vaginal atrophy.
- Review of study # 10716214; a pharmacokinetic study to demonstrate that at steady state, the systemic exposure to equilin (total and unconjugated), estradiol(unconjugated) and estrone(total and unconjugated) are significantly

lower following biweekly administration of synthetic conjugated estrogens cream at dose levels of 0.625mg/g or 1.25mg/g compared to Cenestin 0.3mg per day.

- Review electron format (a CD ROM is provided in Module 1 that contains Labels and Labeling; Case Report Tabulations are also presented).

4.4 Data Quality and Integrity

In the previous review cycle for synthetic conjugated estrogens, A the reviewing medical officer requested an audit and two sites were identified for inspection by the Division of Scientific Investigations (DSI). These audits were deemed acceptable. In this review cycle no DSI audit is being sought. The reason for not seeking a DSI audit is that previous acceptable DSI audits were done for a previous Phase 3 study, this product is not a NME, data appears to be appropriately analyzed and reviewed source documents were found to be consistent with what was presented in the text of the document.

4.5 Compliance with Good Clinical Practices

Two studies performed (DR-CEN-302 and protocol # 10716214) were performed in accordance with regulation pertaining to Good Clinical Practice (GCP) (International Conference on Harmonization; Good Clinical Practice; Consolidation Guideline, Notice of Availability, Fed, Reg. 25692, May 1997) and the Declarations of Helsinki (Revised Edinburgh, Scotland 2000). Adequate informed consent was obtained, there were no site-specified issues identified by this reviewer; protocol violations were appropriately identified and this study is acceptable to world-wide standards.

This study's protocol was reviewed by the appropriate Institutional Review Board (IRBs).

4.6 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with clinical investigators as recommended by the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. There were no questions raised about the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A part of the complete response to the not approvable letter of April 2005 the sponsor conducted a pharmacokinetic study to demonstrate whether synthetic conjugated estrogens A, 1g or 2g dosages produced lower systemic absorption than a daily oral dose of 0.3mg SCE-A tablets.

Study 10716214 was a randomized, multiple-dose, three-treatment parallel design study that was performed from June 3, 2007 and August 8, 2007. The study is entitled "A study

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to Compare the Pharmacokinetics of Synthetic Conjugated Estrogens A, (synthetic conjugated estrogens, A) 0.625mg/g Vaginal Cream to Cenestin® (synthetic conjugated estrogens, A) 0.3mg tablets in Postmenopausal Females". The primary objective of this study was to compare the pharmacokinetic profile of two different doses (0.625mg and 1.25mg) of synthetic conjugated estrogens A, vaginal cream when given at intervals over a 27-day period compared to Cenestin 0.3 mg tablet taken once a day for 27 days in postmenopausal women.

The study was conducted with 60 (59 completing) healthy post menopausal female subjects in accordance with the Protocol No. 10716214 (Revision 1). All procedures were conducted on an in-patient and out-patient basis.

In study 10716214 subjects were randomized to one of three dosing regimens: 1 gram (0.625 mg) of synthetic conjugated estrogens, A vaginal cream applied intra-vaginally on Days 1, 2, 3, 4, 5, 6, 7, 10,13,17,24, and 27; or 2 gram (1.25mg) of synthetic conjugated estrogens, A vaginal cream applied intra-vaginally on Days 1, 2, 3, 4, 5, 6, 7, 10, 13,17, 24 and 27; or one Cenestin® 0.3 mg tablet administered once a day for 27 consecutive days.

At conclusion of the study (day 29) for all dose groups, each subject with a uterus received a 14-day course of Prometrium® (progesterone, USP) 200mg/day as a single 200 mg capsule at bedtime for 14 days. If the subject had a nut allergy, a 14-day course of Provera® (medroxyprogesterone acetate) USP 10mg/ay was provided as an alternative.

Blood samples were collected from 48 hours prior to initial study dosing (Day -2) for baseline levels and at multiple occasions during the study until 48 hours after the final study dosing (Day 29). The sample for all subject completing the study were shipped to the attention of _____ for determination of unconjugated estradiol, unconjugated estrone, unconjugated equilin, total estrone, and total equilin concentrations. b(4)

Statistical and Pharmacokinetic analyses were performed by _____ b(4)

The following is a summary table of the mean pharmacokinetic parameters (AUC and C_{max}) at day 27 comparing Bijuva vaginal cream and a Cenestin oral tablet:

Table 2:.Mean Pharmacokinetic parameters at Day 27 comparing Bijuva vaginal cream and a Cenestin oral tablet:

Product	Unconjugated Estrogen	AUCweekly (pg.hr/mL)	*P-values*
(A) Bijuva®, 1 gm (0.625 mg) Vaginal Cream	Equilin	66.84	0.4948 (A vs. B) <0.0001 (A vs. C)
	Estrone*	1246.35	0.3749 (A vs. B) <0.0001 (A vs. C)
	Estradiol*	350.23	0.9438 (A vs. B) 0.0055 (A vs. C)
(B) Bijuva®, 2 gm (1.25 gm) Vaginal Cream	Equilin	171.67	<0.0001 (B vs. C)
	Estrone*	1635.65	<0.0001 (B vs. C)
	Estradiol*	357.53	0.0060 (B vs. C)
(C) Cenestin®, 0.3 mg Oral Tablet	Equilin	1860.38	
	Estrone*	4335.47	
	Estradiol*	648.13	

*Baseline Corrected

Product	Unconjugated Estrogen	Cmax (pg/mL)	*P-values*
(A) Bijuva®, 1 gm (0.625 mg) Vaginal Cream	Equilin	5.49	0.1918 (A vs. B) 0.0020 (A vs. C)
	Estrone*	23.99	0.2082 (A vs. B) 0.0003 (A vs. C)
	Estradiol*	7.90	0.9201 (A vs. B) 0.4465 (A vs. C)
(B) Bijuva®, 2 gm (1.25 gm) Vaginal Cream	Equilin	11.45	0.0574 (B vs. C)
	Estrone*	31.44	0.6712 (B vs. C)
	Estradiol*	7.74	0.5027 (B vs. C)
(C) Cenestin®, 0.3 mg Oral Tablet	Equilin	20.09	
	Estrone*	46.83	
	Estradiol*	6.65	

*Baseline Corrected

For AUC note the weekly values for the two Bijuva vagina cream doses are statistically significant less than the values for the oral Cenestin by approximately 1/3. Also note

values for estradiol are approximately ½ that of oral Cenestin. For C_{max} the 1g dosage is statistically significant in regards to estrone and equilin, but not for estradiol when compared to oral Cenestin; for the 2g dosage statistical significance is not achieved for estrone, estradiol or equilin when compared to oral Cenestin.

5.2 Pharmacodynamics
No pharmacodynamic data was generated by the conduct of Phase 1 Study 231-01 to study the mechanism of action of synthetic conjugated estrogens, a vaginal cream.

5.3 Exposure-Response Relationships

See original Clinical Pharmacology review dated April 19, 2005. In the original review data was presented on two dosing regimens: daily dosing, cyclic 28-day, 2g daily dosing, 1-week no dosing regimen *or* twice weekly regimen, daily 2g dosing for 7 days, then 2g dosing twice weekly. Note the sponsor does not seek approval of the 2g dosing regimen in this review cycle.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication being sought in this re-submission is the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause for synthetic conjugated estrogen, A vaginal cream 2g (1.25mg of synthetic conjugated estrogen) and 1g (0.625 mg synthetic conjugated estrogen). NDA 21-788 (submitted March 13, 2008, received March 18, 2008) is a *complete response* to a not-approvable letter sent to Duramed on April 25, 2005 and addresses deficiencies outlined in that not-approvable letter. In this submission synthetic conjugated estrogen, A vaginal cream, 2g or 1g was applied twice weekly to the vagina for a total of 12 weeks of therapy.

6.1.1 Methods

Study DR-CEN-302 was a randomized, multicenter, double-blind, placebo controlled trial to compare the safety and efficacy of synthetic conjugated estrogens, A vaginal cream vs. placebo vaginal cream for 12 weeks of treatment on the symptoms of vulvar and vaginal atrophy (VVA) in healthy postmenopausal women." The Agency recommends, per its 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendation for Clinical Evaluation" (referred to elsewhere in this document as the Agency's 2003 draft clinical evaluation guidance document), to conduct one or more placebo-controlled trials to support efficacy."

In addition to primary study DR-CEN-302 the sponsor has submitted a pharmacokinetic study DR-CEN-10X, which is entitled "A study to Compare the Pharmacokinetics of Synthetic conjugated estrogens, A 0.625mg/g Vaginal Cream and Cenestin® (synthetic

conjugated estrogens, A) 0.3 mg Oral Tablets," to compare the pharmacokinetic profile of two different doses (0.625 and 1.25mg) of synthetic conjugated estrogens, A vaginal cream when given at various intervals over a 27 day period compared to Cenestin® 0.3mg tablets taken once a day for 27 days in postmenopausal women.

6.1.2 General Discussion of Endpoints

The general method used to review hormones in the treatment of moderate to severe vulva atrophy has been to review clinical trial data accrued during 12 weeks of treatment. The Agency's 2003 draft clinical evaluation guidance document recommends the co-primary endpoints of change in vaginal superficial and parabasal cells, change in vaginal pH and change in the patient self-identified most bothersome symptom to evaluate the treatment of moderate to severe symptoms of vulvar and vaginal atrophy resulting from estrogen deprived changes in the genitourinary tract. Estrogen deprivation causes profound changes in the genitourinary tract, and up to 40% of postmenopausal women have symptoms associated with these changes. The vagina mucosa and vulvar skin become thinner, the labia flatten and shrink, and the clitoris, uterus, and ovaries decrease in size. The endocervical glandular tissue becomes less active and mucus secretion decreases. The vaginal epithelium becomes dry and atrophic, which may cause inflammation, discomfort, itching and dyspareunia. The vagina becomes less distensible and elastic and is easily traumatized. A lateral wall vaginal cytology smear (allowing the cytologic examination of vaginal mucosa epithelial cells) demonstrates an increased proportion of parabasal vaginal epithelial cells and a decreased proportion of superficial vaginal cells. Vaginal pH is increased from the normal in reproductive age women of 3.5 to 4.0 (a pH which favors lactobacilli) to 6.0 to 8.0 (a pH which favors pathogenic organisms). A vaginal ultrasonography of the uterine lining will demonstrate endometrium thinning to $\leq$5 mm, signifying decreased estrogen stimulation.

Oral formulations of synthetic conjugated estrogens (CE) have been shown to restore vaginal cytology to a premenopausal state and to improve urogenital atrophy and dryness. In the original NDA submission, a placebo-controlled phase 3 study of 278 subjects was conducted to address an indication for treatment of vulvar and vaginal atrophy. Twice-weekly synthetic conjugated estrogens A, vaginal cream (2g equivalent to 1.25mg SCE-A) significantly increased the vaginal maturation index and decreased vaginal pH. However, the study was not specifically designed nor powered to evaluate individual most bothersome symptoms (MBS). This current study, DR-CEN-302 was conducted to more clearly evaluate the effect of synthetic conjugated estrogens, A vaginal cream on reducing the severity of the individual patient-reported MBS.

Per the Agency's 2003 draft clinical evaluation guidance document, the Division recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that:

a) have appropriate inclusion and exclusion criteria,
b) conduct appropriate study analyses, and

c) evaluate the following co-primary endpoints:

- The mean change from baseline to Week 12 in the vaginal maturation index (defined as a change in both superficial and parabasal cells). For study inclusion, study participants would have no greater than 5% superficial cells on the vaginal smear at baseline. The primary efficacy analysis should show a statistical significant increase in superficial cells and a statistically significant decrease in parabasal cells.
- The mean change from baseline to Week 12 in vaginal pH. For study inclusion, study participants should have a vaginal pH > 5.0 at baseline. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- The mean change from baseline to Week 12 in the moderate to severe symptom self identified by the subject as being the MBS to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis would show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome.

  The recommended subject self-assessed symptoms of vulvar atrophy include:

  1. Vaginal dryness (categorized as none, mild, moderate or severe).
  2. Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate, or severe).
  3. Dysuria (categorized as none, mild, moderate or severe).
  4. Vaginal pain associated with sexual activity (categorized as none, mild, moderate or severe).
  5. Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate or severe).

6.1.3 Study Design

Study DR-CEN-302 was a randomized, multicenter, double-blind, placebo controlled trial to compare the safety and efficacy of synthetic conjugated estrogens, A vaginal cream vs. placebo vaginal cream for 12 weeks of treatment. A total of 1,538 subjects were screened and 622 were randomized and treated. After the screening period, subjects were randomized in a 1:1:1:1 blinded fashion to 2g synthetic conjugated estrogens, A vaginal cream or its matching placebo, or 1g synthetic conjugated estrogens, A vaginal cream or its matching placebo for twelve weeks of double-blind treatment.

6.1.4 Efficacy Findings

The primary objective of study DR-CEN-302 was to evaluate the safety and efficacy of two doses of synthetic conjugated estrogens, A vaginal cream, administered twice weekly

compared to placebo vaginal cream, administered twice weekly for the treatment of vulvovaginal atrophy following 12 weeks of treatment.

The secondary objective was to observe the incidence and severity of treatment-emergent adverse events while using either of the two doses of synthetic conjugated estrogens, A vaginal cream.

This study was conducted at 88 centers within the US. The first subject was enrolled on August 28, 2006 and the final enrolled subject completed treatment on September 25, 2007. Duramed Research, Inc was responsible for all aspects of the study including clinical operations, monitoring, data management, statistics, and auditing. Duramed Research transferred the obligation for central laboratory activity to _____ and obligations for labeling, storage and distribution of investigational product was transferred from Duramed Research, Inc. to _____ b(4)

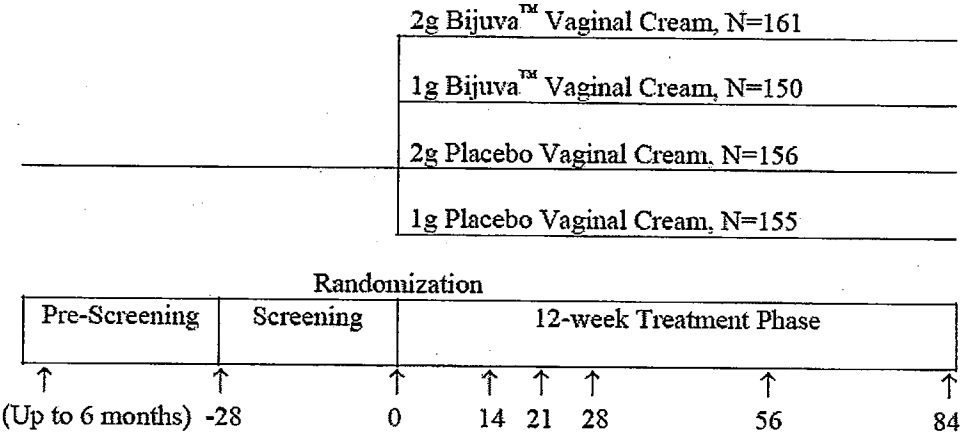
The study included two phases: a screening period of up to four weeks and a 12-week double-blind treatment period. There were a total of seven study visits for subjects not using hormone therapy (HT) at the initial visit or eight study visits to accommodate an hormone therapy (HT) washout period (if necessary) in cases where the subject was using HT at the initial visit.

Enrolled subjects were 30-80 years of age, naturally or surgically postmenopausal, with or without hysterectomy and/or oophorectomy, experiencing moderate to severe symptoms of vulvar and vaginal atrophy (as scored on a subject self-assessment questionnaire) and provided consent. Subjects 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. The following figure 2 shows the study design and schedule of assessments as well as a schematic flow chart of study DR-CEN-302:

Reviewer's Comment
This reviewer notes the inclusion of women who are age 30 and older. Even though a 30-40 year old woman might have undergone an oophorectomy and may be diagnosed as postmenopausal by hormonal levels, it is unlikely that she would immediately begin having symptoms of VVA. Symptoms of VVA generally occur within 5-10 years after the onset of menopause.

Figure 1: 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)

Figure 2:. Schematic Flow Chart

Figure 2 Study Schematic – Flow Chart

	Pre-Screening[1]	Screening[2]	Baseline[3]	Treatment				
Visit	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6[4]**
Day	**Variable Duration**	**-28**	**0[5]**	**14**	**21**	**28**	**56**	**84**
History and Physical								
Informed Consent	X[1]	X[2]						
Vital Signs/Height/Weight[6]	X	X	X	X	X	X	X	X
Medical History	X[1]	X[2]						
Physical Examination		X						X
Gynecological Examination[7]		X						X
Laboratory Parameters								
Serum Chemistry Panel[8]	X	X						X
Hematology[9]		X						X
Urinalysis		X						X
Serum lipid profile[10]		X						X
Serum FSH and Estradiol Levels		X						
Urine Pregnancy Test[11]		X	X					
Procedures								
Mammogram[12]		X[2]						
TVU/Endometrial Biopsy[13]		X						X
Pap Smear		X						
Vaginal Cytology[14]		X		X	X	X	X	X
Vaginal pH		X		X	X	X	X	X
Investigator Assessment of Atrophy[15]		X	X	X	X	X	X	X
Assessments								
Self-Assessment of Atrophy[16]		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X
Study Medication Compliance				X	X	X	X	X
Distribution/Collection								
Dispense/Collect Study Medication			X	X	X	X	X	X
Dispense progestin[17]							X	

[1]For Subjects requiring washout of hormone therapy, the initial evaluation will be considered a "pre- screening" visit (Visit -1). At Visit -1, HT washout subjects will sign the informed consent form, provide medical history, will have vital signs taken and serum chemistry done and will begin the required washout period (see exclusion criterion E2). After completion of the HT washout period, the subject will return to the clinic to complete the remainder of the Visit 0 procedures.
[2] At the Screening Visit, subjects not requiring washout will complete all study procedures with the exception of assessing adverse events. Subjects returning to the study site at the end of washout will not repeat the informed consent process (unless the informed consent form has been amended since the previous visit), or medical history. Washout subjects will be assessed for adverse events at the Screening Visit. Subjects will have a mammogram done (for women over 40 unless the subject can provide documented results of normal mammogram within 9 months of the anticipated date for conclusion of the Visit 0 procedures).
[3]The Baseline Visit (Visit 1) will occur no more than 4 weeks after the Screening Visit provided results of all required screening tests and procedures have been received and reviewed to ensure eligibility for randomization
[4]Visit 6 End of Treatment (or Early Termination).
[5]Day 0 is defined as the first day that study medication is taken. Subjects will be required to begin dosing at the Randomization Visit.
[6]Height is measured at Visit 0, Screening, only.
[7]Includes breast and pelvic examination.
[8]Serum chemistry tests include: glucose, creatinine, uric acid, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase, potassium, sodium, chloride, carbon dioxide (CO_2), calcium, phosphorous, magnesium, total protein, albumin, and total bilirubin.
[9]Hematology tests include: complete blood count (CBC) with an automated differential.
[10]Serum lipid profile includes: Lipid Profile Panel standardized measurement of fasting (≥12 hours) total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol, and triglycerides.
[11]Urine pregnancy test for females of childbearing potential (non-sterilized), results must be negative for continued eligibility in the study.
[12]Mammogram is required for all women aged 40 and over. A negative mammogram will be required (documented results of a previous NORMAL mammogram within 9 months is acceptable).
[13]A transvaginal ultrasound (TVU) will be performed at Screening (Visit 0) on subjects that have undergone a hysterectomy, unless a copy of the surgical record is provided to the Investigator. An endometrial biopsy and TVU will be done during the Screening Period and at the final study visit on all subjects with a uterus. Biopsy results at screening must be "normal" for continued eligibility for the study. Documented results of a previous normal biopsy within 6 months of Screening are acceptable.
[14]For assessment of vaginal cytology, the number of parabasal, intermediate, and superficial cells will be counted and the percentage of each cell type will be calculated. The Maturation Index of the vaginal mucosa will be calculated from these percentages according to the following equations: Maturation Index Score = (% parabasal cells x 0.0) + (% intermediate cells x 0.5) + (% superficial cells x 1.0). Study sites will receive results of vaginal cytology sampling from the Screening Visit, in order to assess subject eligibility for the study. Thereafter, sites will be blinded to these results.
[15]Investigator assessment of vaginal atrophy will be completed with categories including vaginal atrophy, color of the vaginal epithelium, and dryness; vaginal tissue integrity/friability; and vaginal tissue petechiae.
[16]Subjects will complete a written assessment of vaginal atrophy that will include answering questions regarding vaginal dryness and itching and problems with intercourse. At the Randomization Visit the subject will indicate which symptom is the single most bothersome and the most bothersome symptom must be rated as moderate or severe.
[17]A 14-day course of Prometrium® or medroxyprogesterone acetate will be provided to all subjects with an intact uterus at Visit 5 or early discontinuation from the study.

In addition to the routine study procedures described above, additional procedures performed at the end of study (Day 84/Visit 6 or early termination visit included physical examination, gynecological examination (including breast and pelvic examination), clinical laboratory test (including chemistry hematology, fasting serum lipid profile, urinalysis), *transvaginal ultrasound (TVU) and endometrial biopsy on all subjects with a uterus.*

All subjects with a uterus were provided with a 14-day course of Promethium® or medroxyprogesterone acetate (MPA™) at visit 5 (Day 56). Subjects were instructed to take Prometrium 300 mg daily, beginning on the day immediately following the last dose of study medication. Subjects with a peanut allergy received a 14-day course of MPA and were instructed to take one 10mg tablet daily, beginning on the day immediately following the last dose of medication.

Reviewer's Comment

The sponsor elected to treat all subjects with a uterus immediately after the last dose of synthetic conjugated estrogens, A cream with a 14-day course of a progestin. This is appropriate since it is not known how much unopposed estrogen is being absorbed from the vagina and what effect the absorbed estrogen might have on the endometrium.

A Randomization Visit (Study Visit 1) occurred no more than four weeks after the Screening Visit (Visit 0) and after all results of screening evaluations were available. Subjects who met all entry criteria following completion of the screening procedures were randomized in a 1:1:1:1 fashion to one the following four blinded treatment groups:

- Treatment Group 1: 2g Bujiva™ vaginal cream containing 1.25 mg SCA-A, applying once daily for the first days the two times/week
- Treatment Group 2: 1g Bujiva™ vaginal cream containing 1.25 mg SCA-A, applying once daily for the first days the two times/week
- Treatment Group 3: Placebo Vaginal Cream matching Group 1, applying once daily for the first 7 days then two times/week
- Treatment Group 4: Placebo Vaginal Cream matching Group2, applying once daily for the first 7 days then two times/week
-

Regardless of treatment group, subjects began study drug dosing at the Randomization Visit and were instructed to take each dose of study medication at approximately the same time each day for the first 7 days and two times (Tuesday and Friday) for the remainder of the 12-week treatment period. This treatment regimen is identical to 2 of 5 treatment regimens used in study DP3-2002-002. In study DP3-2002-002 a 2g (1.25mg) dose was used against matching placebo for either 2g daily for 21 days followed by 7 days without active treatment ***or*** 2g daily for one week followed by 2g twice weekly for 11 weeks of treatment. A fifth dosing regimen was Premarin® vaginal cream for 21 days followed by 7 days without treatment.

Study Population

Reviewer's Comment

Study design and the schedule of assessments appear adequate to assess symptoms of vulvar and vaginal atrophy.

Inclusion Criteria

1. Naturally **or** surgically postmenopausal women, with or without an intact uterus, age 30 to 80 years, inclusive. Postmenopausal was defined as (all timing calculation from the Screening Visit [Visit 0]):
    a. At least 12 months natural spontaneous amenorrhea, or
    b. At least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, **or**
    c. Six months spontaneous amenorrhea with serum FSH concentrations >40 mIU/mL, **or**

d. For hysterectomized subjects without bilateral oophorectomy: serum FSH concentrations >40 mIU/mL AND estradiol concentrations of <20 pg/ml.

2. On self-assessment of vaginal atrophy (Vaginal Atrophy/Sexual Function Questionnaire) at the Randomization Visit, the subject rated at least one symptom as moderate or severe and had to identify, among those symptoms rated moderate or severe, the one considered by the subject to be the most bothersome.
3. No greater than 5% superficial cells on vaginal smear (subjects qualified for randomization based on the Screening Visit evaluation. Continued participation in the study was dependent on the Randomization Visit cytology evaluation also meeting this criterion).
4. Vaginal pH >5.0 at the Randomization Visit.
5. Have had a normal (atrophic, proliferative, or secretory) endometrial biopsy without evidence of endometrial hyperplasia or cancer (for subjects with an intact uterus).
6. Subjects >40 years of age had a negative mammogram performed at the Screening Visit (Visit 0) (or must have provided the investigator with documentation of a normal mammogram performed within 9 months of Visit 0) and had a normal clinical breast examination at Visit 0.
7. Normally active and otherwise judged to be in good health by the investigator on the basis of medical history, physical examination and routine laboratory tests.
8. Able to complete all study procedures, including the required questionnaires and all study visits.
9. Able to understand and provide signed informed consent.

Exclusion Criteria

1. Known sensitivity or contraindications to natural or synthetic estrogens or progestins,
2. Any estrogen, progestin, or selective estrogen receptor modulator (SERM) therapy within the following times prior to the Screening Visit (Visit 0):
    a. Four-week washout for vaginal and transdermal (rings, creams, gels) estrogen or estrogen/progestational products
    b. Eight-week washout for oral estrogen and/or progestational therapy
    c. Eight-week washout for SERMs (e.g., Raloxifene)
    d. Three-month washout for progestational implants, estrogen, or estrogen/progestational injectable drug therapy
    e. Six-month washout for estrogen pellet therapy or progestational injectable drug therapy.
    f. Use or consumption of any nutritional supplements or food products with estrogenic or potential estrogenic activity within 30 days of the Screening Visit,
3. Low-grade squamous intraepithelial lesion (LSIL) or worse on screening Pap smear; any other abnormal finding on the Pap smear that the investigator considered clinically significant [such as "atypical squamous cells cannot exclude HSIL" (ASC-H), "atypical glandular cells" (AGC)]; or any Pap result that would

necessitate further evaluation by biopsy and/or colposcopy. Any screening Pap with "atypical squamous cells of undetermined significance" (ASC-US) had "reflex" HPV testing done on the Pap sample. If the HPV testing was negative for high-risk types, the subject could be enrolled; if the HPV testing was positive, a colposcopy was required and the subject was NOT eligible for enrollment.

4. History or current diagnosis of endometrial hyperplasia,
5. Recent history (within 1 year) of vaginal bleeding of unknown cause,
6. Recent history or recent diagnosis (within 2 years) of endometriosis,
7. History or current diagnosis of thrombophlebitis, thromboembolic events, stroke, amaurosis fugax, or transient ischemic attack,
8. History or current diagnosis of congestive heart failure, myocardial infarction, known coronary artery disease, undiagnosed chest pains, or any heart disease requiring antiarrhythmics or digitalis,
9. Fasting triglyceride level greater than 350 mg/dL,
10. Known or suspected pregnancy,
11. Uncontrolled or insulin-requiring diabetes mellitus (DM); patients on a stable dose (>90 days) of oral requiring the use of hypoglycemic medications are eligible,
12. Uncontrolled or untreated hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or both, using the mean of three readings taken at least one minute apart with the subject in a sitting position). Subjects with hypertension adequately controlled by medication were allowed to enter the study only if the dose of antihypertensive therapy had remained constant for at least 3 months,
13. History of breast cancer or estrogen-dependent neoplasia (e.g., endometrial cancer),
14. History of malignancy within the past 5 years, with the exception of basal cell or squamous cell carcinoma of the skin curatively treated by surgery, or localized gynecologic cancer treated by surgery or other appropriate procedure,
15. Recent history of (within six months prior to Visit 0) or current significant gastrointestinal, endocrine (e.g., hyperthyroidism or uncontrolled hypothyroidism), renal, pulmonary, hepatic, or biliary disease,
16. Clinically significant migraine headaches, asthma, epilepsy, or other conditions aggravated by fluid retention (to be determined by the Investigator),
17. Clinically significant mental illness (to be determined by the Investigator),
18. Recent history of (within past 12 months) or strong potential for alcohol or substance abuse. Alcohol abuse was defined as >14 drinks per week (1 drink =12 oz beer, 5 oz wine, or 1 ½ oz distilled spirits),
19. Clinically significant abnormal laboratory values at Screening (Visit 0) (including, but not limited to, serum creatinine > 2 mg/dL, serum total bilirubin > 2X upper limit of normal [ULN], ALT or AST >1.5X ULN),
20. Participation in another clinical trial or exposure to any investigational agent within 30 days prior to Screening (Visit 0)
21. A condition the Investigator believed would interfere with her ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk, and

22. Current diagnosis of vaginal infection.

Subjects were to be discontinued from the study if any of the following occurred:

- A condition which, in the opinion of the investigator, contraindicated the use of estrogen and/or progestin
- Subject requested withdrawal from the study
- Adverse event which made subject continuation impossible or inadvisable
- Subject lost to follow-up
- Subject discovered after randomization not to have met the protocol entrance criteria (e.g., more than 5% superficial cells on vaginal smear taken at Randomization Visit)
- Subject refused to cooperate with required study procedures
- Use of estrogens, other than study drug
- Use of progestins
- Use of any additional experimental drug or device
- Unstable doses of antihypertensive medication
- Use of hypoglycemic medication
- Use of anti-arrhythmic medication
- Use of vaginal lubricants or moisturizers, and
- Use of nutritional supplements or food products with estrogenic or potential estrogenic activity (e.g., soy products, black or blue cohosh, red clover, flaxseed, dong quai, ginseng, ginkgo, licorice, evening primrose, kava and vitex).

Inclusion and exclusion criteria are consistent with previous studies of estrogen products for the treatment of vulvar and vaginal atrophy.

Treatment Compliance

Overall study compliance was calculated as the percentage of expected cream taken, expressed as a value between 0% and 100%. The actual weight of study medication taken was calculated as the weight of tubes dispensed minus the weight of tubes returned. The weight of expected usage was derived from the number of days between the first dose date and the last dose date (as recorded on the CRF).

Non-compliance was defined as compliance of less than 80% or greater than 120% of expected usage.

Efficacy and Safety Variables

Efficacy Variables

Primary Efficacy Variables

- The mean change in the maturation index between Baseline (Randomization Visit (Day 0) and End of Treatment (Day 84) additionally, the mean changes in the percentage of parabasal and superficial cells from Baseline to End of Treatment were evaluated).
- The formula for the Maturation Index is:

- Maturation Index = (% Parabasal cell x 1.0) +
- (% Intermediate Cells x 0.5) + (%Superficial cells x 1.0)

- The mean change in vaginal pH between baseline and End of Treatment,
- The mean change in severity between the Baseline and End of Treatment for the moderate to severe symptom that has been identified at Baseline by the subject as being the most bothersome. The most bothersome symptom (MBS) was derived from the subject self-assessment of vaginal atrophy, that consisted of 5 questions concerning 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). The subject then classified the MBS as the single symptom rated as either moderate or severe at baseline that she considered the most bothersome from among all symptoms rated moderate or severe. The six symptoms considered for determination of the MBS were:
    - Vaginal Dryness
    - Vaginal Irritation/Itching
    - Vaginal Soreness
    - Pain during intercourse (could be score as 7 ["N/A]
    - Bleeding after intercourse (could be score as 7 ["N/A].

Secondary Efficacy Variables

The mean change in severity of each MBS symptom, between Baseline (Randomization Visit [Day 0]) and End of Treatment (Day 84). In this analysis, the number of subjects considered for each symptom equaled the number of subjects who reported the symptom as the MBS; the required sample size for each MBS symptom evaluation could not be determined *a priori.*

The mean change and percent change in the primary efficacy variables and the first secondary efficacy variable noted above between Baseline and Days 14, 21, 28, 56 and 84 (Percent change was assessed for vaginal pH and MBS but was not assessed for maturation index).

Mean change in the percent of intermediate cells between Baseline and Days 14, 21, 28, 56 and 84.

The mean change in severity of Subject and Investigator Assessments of Vaginal Atrophy between Baseline and Days 14, 21, 28, 56 and 84. The individual investigator assessments were made using the same 0 (none), 1 (mild), 2 (moderate) and 3 (severe) rating scale as used for the subject assessment and evaluated the following:

- Vaginal atrophy
- Vagina color
- Vaginal rugosity
- Blanching of tissue (with pressure)
- Vaginal tissue integrity
- Vaginal tissue petechiae

- The proportion of subjects reporting a reduction in each Subject Self-Assessed symptoms from moderate or severe severity at baseline to mild or none at end of treatment.

The 2003 draft clinical evaluation guidance document recommends that data demonstrate an increase in vaginal superficial cells and a decrease in vaginal parabasal cells, a reduction in vaginal pH and a reduction in the severity of the subject's designated MBS are the most appropriate measurement for assessment of new treatments for vulvar and vaginal atrophy. Per the sponsor, the change in the investigator's assessment of vaginal atrophy is also considered to be an important independent assessment of each subject's condition.

Safety Evaluations
Safety was assessed by evaluation of treatment-emergent adverse events (TEAEs), standard laboratory test results, physical examinations (including breast and pelvic exams), vital signs, and endometrial biopsy (screening and end of study for non-hysterectomized subjects).

Statistical Methods Planned in the Protocol and Determination of Sample Size

A statistical analysis plan (SAP) was prepared and submitted to FDA (SAP dated 8/31/07). The SAP was a companion of the statistical methods section of the study protocol and provided a comprehensive description of the subject cohorts, methods and data analyses that were to be used. If differences existed in descriptions or explanations provided in the protocol and the SAP, the SAP took precedence. No changes were made to the planned analysis.

Subject Cohorts
Four cohorts were defined for analysis: Safety, ITT (Intent-to-Treat), MITT (Modified Intent-to-Treat) and PPC (Per-Protocol Completers). Determination of each subject's qualification for inclusion in the Safety, ITT and MITT cohorts was made prior to unblinding the randomization codes. The qualification for the PPC cohort was determined after locking the database and unblinding the treatment in order to calculate study medication compliance according to the treatment assignment. The criteria for the makeup of each cohort are detailed as follows:

- *Safety cohort:* Included all randomized subjects who received at least one dose of the study medication. This is the cohort for all safety assessments such as adverse events and laboratory results.
- *ITT cohort:* All subjects who had been randomized to treatment received at least one dose of study medication and for whom there was a *baseline assessment and at least one post-randomization assessment* of maturation index, vaginal pH, and severity of MBS. For the determination of baseline assessments of superficial and parabasal cytology, vaginal pH and the MBS, if actual baseline values for these variables were missing or were otherwise not obtained, the Screening visit values were considered to be

the baseline values. In addition, any subject with a last observed post-randomization rating of "7" (i.e. not applicable) implied that the *environment for recording that rating no longer applied* (e.g. pain during intercourse cannot be properly rated if the subject has not engaged in intercourse).

- *MITT cohort:* that subject of the ITT cohort which met the study protocol requirements at baseline of 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. Per the 2003 draft clinical evaluation guidance document concerning the definition of vulvovaginal atrophy for the purpose of evaluating the efficacy of a new treatment, *the MITT cohort served as the primary cohort for inferences from the primary and secondary analyses since it incorporated this definition.*
- *PPC cohort*: that subset of subjects from the MITT cohort that had completed the full term of study participation (12 weeks) and who had no significant protocol violations recorded that my influence the evaluation of the response. Subjects could be excluded from the PPC for the following reasons:
  - Violations of inclusion or exclusion criteria
  - Non-compliance by the subject, including but not limited to:
  - Missing appointments
  - Less than 80% or greater than 120% compliance with the study medication
  - Use of prohibited medications during the study.

Reviewer's Comment:
The sponsor's used a subset of the ITT to make the MITT which was not properly defined. The sponsor added to the traditional ITT the following phrase "a *baseline assessment and 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";* this results in a lesser number of subjects in the sponsor's ITT (N = 568) and the MITT cohort (N =556). The difference between a traditional ITT and the sponsor's ITT cohort is 54 (8.7%) subjects (1g synthetic conjugated estrogens A,[12], 1g placebo [14], 2g synthetic conjugated estrogens A,[12] and 2g placebo[16], respectively). Because study results from a traditional ITT, the sponsor's ITT, and the MITT cohort were similar, highly significant and *not* marginally significant, and the number of subjects eliminated in each study group (ITT, MITT) is not too different from each other, results are *unlikely* to be sufficiently different in the final analyses to alter a decision on efficacy. (See table 18)

Statistical Considerations:
A two-sided significance of $\alpha = 0.05$ was used test the hypothesis:

H0: The mean (or mean rank) change from Randomization Visit (Day 0, Baseline) to End of Treatment for subjects receiving each of the active

vaginal creams will be equal to the change for subjects receiving the respective placebo.

In order to control the overall Type I error rate of 5%, the analysis of the active treatment groups compared to their respective placebo control groups incorporated a step-down testing procedure. Each active treatment group was compared to its respective placebo group utilizing an alpha = 0.05 level of significance for each comparison within the step-down paradigm. However, only if the higher 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 group.

A two-way analysis of covariance (ANCOVA) model was used to analyze the data with the baseline value as the covariate, including tests for treatment, site, and treatment-by-site interaction.

The last-observation-carried-forward (LOCF) procedure was used to impute post-baseline efficacy data for all time points beyond which data were available.

An ANCOVA model was employed to assess the significance of differences between the active and placebo groups. The initial model included terms for baseline, treatment, site and treatment by-site interaction. If the interaction term was found to significantly contribute to the model ($p \leq 0.05$), the nature of the interaction (quantitative vs. qualitative interaction) and the appropriateness of inferences made regarding the treatment effects were investigated. If the interaction was found to be inconsequential in nature (this would be described as part of the results obtained for each analysis) or the p-value for the interaction test was > 0.05, the interaction term was eliminated from the ANCOVA model resulting in a final model testing the effects of baseline, treatment and site.

Prior to running the initial ANCOVA model, the MITT cohort was used to assess those sites that did not have enough subjects to "stand alone" in the analysis, defined as at least three subjects in each treatment group. This number was chosen as a good minimum for the calculation of a within-site-treatment-group-observed variance. All sites that did not meet this criterion were pooled into one "super site" prior to the analysis. This "super site" was then used in the analysis of all primary and secondary efficacy endpoints. Among the 88 sites that screened subjects, 81 sites enrolled subjects who were randomized to treatment and only 80 sites provided data for the efficacy analyses had insufficient numbers of subjects per treatment group and were therefore pooled together for all analyses involving tests of site effect or treatment-by-site interaction.

For each of the co-primary efficacy endpoints superficial and parabasal vaginal cells, vaginal pH and self-identified MBS, the assumption of normality was examined by applying the *Shapiro-Wilk* test to the residuals from the initial ANCOVA model

containing the tests of main effects and the interaction term. If the assumption of normality ($p > 0.05$) was substantially violated, then the change from baseline data for the endpoint in question was ranked across treatment groups and the analysis was then performed on the ranked data.

Safety Analysis
Safety and tolerability were assessed through the reporting of treatment-emergent AEs, standard laboratory test results, physical and gynecological examinations (including breast and pelvic exams), vital signs, *TVU and endometrial biopsy (performed at Screening and End of Treatment for subjects with a uterus).*

Determination of Sample Size
The sample size for this study was calculated using results from a previous study of synthetic conjugated estrogens, A vaginal cream using a similar study design and study endpoints. Of the co-primary endpoints of change in superficial and parabasal vaginal cells, change in vaginal pH and change in the severity of the MBS, the *one requiring the largest sample size* to provide 90% power for statistical testing of the null hypothesis of no difference between means *was change in severity of the MBS.* A sample size of *111 per treatment group* would have 90% power to detect a difference in means of 0.350 assuming that the common standard deviation is 0.800, based on a two group t-test with $\alpha = 0.05$ two-sided significance level. Approximately 600 subjects were planned for randomization into this study to provide a sufficient number of subjects for the goal of 120 patients per treatment group completing the 12-week treatment period.

Changes in the Conduct of the Study or Planned Analyses

1. The sponsor submitted protocol Amendment 1 (Dated 12/05/06) included that the visit for dispensing the second tube for subjects in the 2g groups was changed from Visit 5 (Week 8) to Visit 3 (Week 3); the visit for providing Prometrium or MPA was changed from Visit 6 (Week 12 or EOT) to Visit 8 (Week 8).
2. This study was conducted as a special protocol assessment (SPA) to the original study, received by the Division on November 9, 2005 following a meeting with the sponsor on July 18, 2005. In the original statistical plan for this study, the MBS co-primary endpoint analysis was specified as the overall change in MBS severity across patients regardless of symptom. In the Division's response to the sponsor the *co-primary endpoints consists of an evaluation of each individual MBS symptom, e.g. vaginal dryness, vaginal soreness, etc. In addition, inclusion of urinary symptoms in the subject self-assessment questionnaire was not recommended.*

Disposition of Subjects
A total of 1,538 subjects were screened for participation in this study. Of those subjects, 622 were randomized and treated with one of following treatments:

- 2g synthetic conjugated estrogens, A vaginal cream, containing 1.25 mg synthetic conjugated estrogens, A (SCEA), administered twice weekly (*N=161*)

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{Phill H. Price, M.D.}
{NDA 21-788}
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- 2g placebo vaginal cream matching 2g synthetic conjugated estrogens, A vaginal cream *(N=156)*
- 1g synthetic conjugated estrogens, A vaginal cream, containing 0.625 mg (SCE-A) administered twice weekly *(N=150)*
- 1g placebo vaginal cream matching 1g synthetic conjugated estrogens, A vaginal cream *(N=155)*

Note, in the following summary tables (Bujiva 2g and 1g) is used by the sponsor instead of the established name synthetic conjugated estrogens, A

Table 3:.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

Note in table 3 that 62 (10%) subjects did not complete this study. The largest number of subjects who discontinued was due to subject request 26 (4.2%) and that 23 of the 26 subjects who discontinued in this category were in the placebo groups; one half (13/26) discontinued due to lack of efficacy. Also note that 12 (1.9%) of subjects discontinued due to an adverse event and two thirds of this total (8/12) were in the active treatment groups. Additionally 10 (1.6%) discontinued due to lost to follow-up and 5 (0.8%) were due to non-compliance with the protocol.

There were 6 protocol deviations. Protocol deviations were captured but did not necessarily exclude a subject from the PPC cohort. For the ITT cohort, subjects were excluded only if they lacked valid data at Baseline and End of Treatment for any or all of the three co-primary endpoints. For the *MITT cohort,* subjects were excluded only if the baseline value obtained for any or all of the co-primary efficacy endpoints *did not meet the criteria specified in the current FDA guidance* (i.e., a superficial cell count $\leq 5\%$, vaginal pH > 5 and at least one patient-assessed moderate or severe symptom identified as MBS at baseline).

The following table 4 summarizes the respective cohorts (note MITT cohort):

Table 4:. Summary of Subject Cohorts

Screened = 1538 Subjects	2g Bijuva	1g Bijuva	2g Placebo	1g Placebo	Total
Safety (Treated Subjects)	161	150	156	155	622
Intent-to-Treat (ITT)	149 (92.5%)	138 (92.0%)	140 (89.7%)	141 (91.0%)	568 (91.3%)
Modified Intent-to-Treat (MITT)	146 (90.7%)	135 (90.0%)	135 (86.5%)	140 (90.3%)	556 (89.4%)
Exclusion from MITT*	3 (1.9%)	3 (2.0%)	5 (3.2%)	1 (0.6%)	12 (1.9%)
A: Baseline Superficial Cells > 5%	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.2%)
B: Baseline pH ≤ 5	1 (0.6%)	1 (0.7%)	3 (1.9%)	0 (0.0%)	5 (0.8%)
C: Baseline MBS Not Moderate or Severe	2 (1.2%)	2 (1.3%)	1 (0.6%)	1 (0.6%)	6 (1.0%)
A or B	1 (0.6%)	1 (0.7%)	4 (2.6%)	0 (0.0%)	6 (1.0%)
A or C	2 (1.2%)	2 (1.3%)	2 (1.3%)	1 (0.6%)	7 (1.1%)
B or C	3 (1.9%)	3 (2.0%)	4 (2.6%)	1 (0.6%)	11 (1.8%)
Per Protocol Completers (PPC)	105 (65.2%)	60 (40.0%)	97 (62.2%)	81 (52.3%)	343 (55.1%)
Exclusion from PPC*	41 (25.5%)	75 (50.0%)	38 (24.4%)	59 (38.1%)	213 (34.2%)
Did Not Complete Study**	7 (4.3%)	6 (4.0%)	13 (8.3%)	12 (7.7%)	38 (6.1%)
Violation of Inclusion or Exclusion Criteria	0 (0.0%)	2 (1.3%)	0 (0.0%)	1 (0.6%)	3 (0.5%)
Use of Prohibited Medications***	0 (0.0%)	1 (0.7%)	1 (0.6%)	0 (0.0%)	2 (0.3%)
Did Not Meet HT Wash-out Requirement	4 (2.5%)	3 (2.0%)	4 (2.6%)	2 (1.3%)	13 (2.1%)
Non-Compliance with Study Medications	32 (19.9%)	64 (42.7%)	21 (13.5%)	45 (29.0%)	162 (26.0%)

** A subject may be excluded due to more than one deviation.*
*** Completers with < 70 days of treatment exposure were excluded from the PPC cohort.*
**** Based on verified list of prohibited medications.*
Note: Numbers in parentheses are percentages of treated subjects for each and total treatment groups.

As the primary analysis cohort the efficacy of each synthetic conjugated estrogens, A 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 (6) synthetic conjugated estrogens, A 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 and one had a baseline pH > 5. In the remaining 6 subjects 4 were excluded in the active treatment groups (2 each for synthetic conjugated estrogens A, 2g and 1g) and 2 were in the placebo groups. Given the sample size calculated for this study, the numbers of analyzable subjects in both the MITT and ITT cohorts were similar and both are considered adequate with the protocol-specified sample size requirement.

Subject Disposition
A total of 1,538 subjects were screened in this study. Of those screened, 622 were randomized and treated with one of the following treatments:

- 2g synthetic conjugated estrogens, A vaginal cream, containing 1.25 mg synthetic conjugated estrogens, A (SCE-A), administered twice weekly (N=161)
- 2g placebo vaginal cream matching 2g synthetic conjugated estrogens, A vaginal cream (N=156)
- 1g synthetic conjugated estrogens, A vaginal cream, containing 0.625 mg SCE-A, administered twice weekly (N=150)
- 1g placebo vaginal cream matching 1g synthetic conjugated estrogens, A vaginal cream (N=155).

Analysis for both efficacy and safety does not suggest any aberrant, erroneous, or suspicious data points that could have changed any inferences presented in the results section of this report. However, one case of missing data and a number of cases where medication kits were incorrectly shipped are noted below:

Subject 0051/51004 was treated but could not be included in the evaluations of either safety or efficacy because of no information regarding her assigned treatment and because no post-baseline CRF pages could be retrieved.

Twenty-six (26) sites involved subjects who received study medication kits that had originally been labeled for other sites. [redacted] the unused medication kits to sites were enrollment rate exceed the number of originally allocated study kits. Since both the original shipping and re-shipping of study medications took place according to the randomization blocks and all individuals involved in this study were blinded to the study treatment, the balance of integrity of randomization was preserved across all sites throughout the study. b(4)

The following table 5 shows demographic and other baseline characteristics of subjects entered into the study:

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Table 5:. Subject Demographic and Baseline Characteristics (MITT) Cohort

	2g Bijuva (N=146)	1g Bijuva (N=135)	2g Placebo (N=135)	1g Placebo (N=140)	Total (N=556)
Race					
African-American	13 (8.9%)	10 (7.4%)	10 (7.4%)	5 (3.6%)	38 (6.8%)
Asian	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	4 (0.7%)
Caucasian	122 (83.6%)	112 (83.0%)	120 (88.9%)	126 (90.0%)	480 (86.3%)
Hispanic	10 (6.8%)	11 (8.1%)	3 (2.2%)	7 (5.0%)	31 (5.6%)
Other	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	3 (0.5%)
***Age* (yrs)**					
Mean (Std)	59.3 (6.10)	60.0 (6.48)	58.3 (5.96)	59.9 (6.78)	59.4 (6.36)
Median	59.1	58.9	57.3	59.2	58.5
(Min, Max)	(42.7, 77.6)	(47.0, 76.3)	(42.8, 75.9)	(41.6, 76.3)	(41.6, 77.6)
***Weight* (lbs)**					
Mean (Std)	153.9 (28.74)	156.1 (31.47)	155.2 (30.63)	154.8 (28.27)	155.0 (29.70)
Median	148.0	150.0	152.0	149.5	150.0
(Min, Max)	(94.0, 282.0)	(101.0, 282.0)	(93.0, 290.0)	(108.0, 242.0)	(93.0, 290.0)
***Body Mass Index* (kg/m^2)** *					
N	137	130	127	134	528
Mean (Std)	26.5 (5.39)	27.0 (5.30)	26.9 (5.34)	26.8 (4.61)	26.8 (5.16)
Median	25.7	25.7	25.8	26.5	25.8
(Min, Max)	(17.3, 48.2)	(18.6, 50.1)	(17.9, 46.9)	(18.3, 42.2)	(17.3, 50.1)
***Systolic Blood Pressure* (mmHg)** **					
N	145	135	135	140	555
Mean (Std)	120.9 (12.63)	119.8 (12.20)	119.7 (12.45)	120.6 (14.75)	120.3 (13.03)
Median	120.0	120.0	120.0	120.5	120.0
(Min, Max)	(90.0, 158.0)	(90.0, 142.0)	(88.0, 149.0)	(90.0, 189.0)	(88.0, 189.0)
***Diastolic Blood Pressure* (mmHg)** **					
N	145	135	135	140	555
Mean (Std)	75.6 (8.85)	73.3 (8.66)	74.8 (8.25)	75.2 (7.89)	74.8 (8.45)
Median	78.0	74.0	75.0	76.0	76.0
(Min, Max)	(50.0, 98.0)	(50.0, 88.0)	(50.0, 90.0)	(58.0, 99.0)	(50.0, 99.0)
***Heart Rate* (beat/min)** **					
N	145	135	135	140	555
Mean (Std)	70.4 (9.73)	71.2 (9.14)	71.8 (9.18)	70.9 (8.92)	71.1 (9.24)
Median	70.0	70.0	72.0	72.0	70.0
(Min, Max)	(48.0, 92.0)	(52.0, 97.0)	(50.0, 96.0)	(46.0, 99.0)	(46.0, 99.0)
Uterus Present					
Yes	92 (63.0%)	85 (63.0%)	83 (61.5%)	87 (62.1%)	347 (62.4%)
No	54 (37.0%)	50 (37.0%)	52 (38.5%)	53 (37.9%)	209 (37.6%)
Time Since Last Menses (months)					
Mean (Std)	158.5 (98.13)	155.6 (105.72)	142.7 (103.12)	157.2 (106.42)	153.6 (103.23)
Median	141.0	140.0	116.0	128.5	129.0
(Min, Max)	(12.0, 488.0)	(13.0, 456.0)	(13.0, 502.0)	(9.0, 491.0)	(9.0, 502.0)

**Twenty-eight subjects didn't report height, therefore were excluded from the BMI's calculation.*
***One subject without baseline blood pressures and heart rate was excluded from the calculations.*

Overall, there were no major differences seen across treatment groups. Ages ranged from 41 to 77 years with a mean age of 59.4 years. The majority of subjects were Caucasian 480 (86.3%); African American 38 (6.8%), Hispanic 31 (5.6%) and a very small number

of Asians comprised the remaining subjects in the study. Weights ranged from 93 to 290 pounds with a mean of 155.0 pounds; the BMI ranged from 17.3 kg/m^2 to 50.1 kg/m^2. Mean time since the last menses was 153.6 months (12.8 years). More than half of the subjects 347 (62.4%) had a uterus present.

Compliance was calculated based on available information from the CRFs. Mean percent compliance for the 12-week treatment period was virtually the same between each synthetic conjugated estrogens, A dose and its matching placebo. Mean compliance both within and across treatment groups was well over 97%.

Table 6 is a summary of the actual use amounts of study medications:

Table 6:. Summary of Actual Use (grams) of Study Medications (MITT Cohort)

	2g Bijuva	1g Bijuva	2g Placebo	1g Placebo	Total
N	145	134	133	138	550*
MEAN	57.25	32.35	54.87	31.16	44.06
STD	12.54	7.93	13.07	7.86	16.20
MIN	9.40	8.80	7.00	11.50	7.00
MAX	109.20	54.90	109.10	55.60	109.20
MEDIAN	58.20	32.70	55.50	30.95	41.70

**Subjects with missing drug compliance due to tubes not returned or lost-to-follow-up were not presented.*

Summary statistics based on the actually used amount of study medication provided additional measurement of subject compliance. Subjects who were taking synthetic conjugated estrogens A, 1g vaginal cream who did not meet the dose compliance criterion of between 80% and 120%, used on average 32.3g in the 1g synthetic conjugated estrogens A, 1g group compared to 57.3g in the synthetic conjugated estrogens A, 2g group. Placebo groups used slightly lesser amounts per gram of medication

Analysis of Efficacy

Analysis of Primary Efficacy Variables

The statistical analyses of the co-primary efficacy variables (change in superficial and parabasal vaginal cells, vaginal pH, and the most bothersome symptom) incorporated a *step-down test procedure* comparing the active treatment groups to their respective groups. Because statistically significant comparisons were first observed in the 2g dose groups for these co-primary endpoints, the testing procedure was also conducted for the 1g dose groups and results for both the higher and lower dose groups are presented in parallel in the following efficacy sections. For each co-primary endpoint measure, the baseline-adjusted means are displayed with p-values obtained from the main effect model with baseline as the covariate.

Maturation Index

The mean change from baseline to Week 12 in the maturation index was one of the co-primary efficacy endpoints reported in protocol CEN-302. The numbers of parabasal, intermediate and superficial cells were counted in the vaginal cytology smear and the percentage of each cell type was calculated. The percentages were then used in the following equation to determine the maturation index value:

> Maturation index = (% parabasal cells x 0) + (% intermediate cells x 0.5) + (superficial cells x 1.0)

The following table 7 shows the baseline distribution of the MBS, vaginal pH, and vaginal Cytology in the MITT:

Table 7:. Baseline distribution of the MBS, Vaginal pH, and Vaginal Cytology in the MITT

	2g Bijuva (N=146)	1g Bijuva (N=135)	2g Placebo (N=135)	1g Placebo (N=140)	Total (N=556)
Most Bothersome Symptoms					
Vaginal Dryness	76 (52.1%)	60 (44.4%)	70 (51.9%)	72 (51.4%)	278 (50.0%)
Vaginal Irritation/Itching	10 (6.8%)	23 (17.0%)	15 (11.1%)	22 (15.7%)	70 (12.6%)
Vaginal Soreness	3 (2.1%)	6 (4.4%)	3 (2.2%)	5 (3.6%)	17 (3.1%)
Dyspareunia	57 (39.0%)	45 (33.3%)	47 (34.8%)	41 (29.3%)	190 (34.2%)
Bleeding After Intercourse	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Vaginal pH					
N	146	135	135	140	556
Mean (Std)	6.3 (0.65)	6.3 (0.67)	6.3 (0.62)	6.3 (0.63)	6.3 (0.64)
Median	6.5	6.5	6.1	6.1	6.5
(Min, Max)					
***Superficial Cells* (%)**					
N	146	135	135	140	556
Mean (Std)	1.0 (1.52)	1.1 (1.62)	1.1 (1.56)	1.3 (1.71)	1.1 (1.61)
Median	0.0	0.0	0.0	0.0	0.0
(Min, Max)					
***Parabasal Cells* (%)**					
N	146	135	135	140	556
Mean (Std)	42.6 (30.98)	38.5 (32.54)	40.4 (33.83)	37.6 (31.86)	39.8 (32.26)
Median	43.5	32.0	31.0	30.5	32.0
(Min, Max)					
Maturation Index					
N	146	135	135	140	556
Mean (Std)	29.2 (15.68)	31.3 (16.53)	30.3 (17.19)	31.8 (16.16)	30.7 (16.37)
Median	29.5	34.5	35.5	35.3	34.0
(Min, Max)					

b(4)

Reviewer's Comment
Note 'N' for the MBS as compared to the 'N' for other primary efficacy variables is reduced because the MBS was followed for each individual MBS symptom from baseline to week 12, *whether or not* the symptom was still considered the subject's most bothersome symptom.

The following table 8 shows the summary statistics for the co-primary endpoints (MITT Cohort, LOCF). This summary table is taken for the primary statistical reviewer. This table incorporates four tables from the sponsor into one:

Table 8:. Summary statistics of the 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)

Reviewer's Comment
Note the similarities between Table 7 and Table 8. However, the Ns are different for the MBS in Table 7; Table 6 describes summary statistics in more detail.

Table 9:. Maturation Index: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva	146	29.20	33.27	1.191	24.36	<.0001
2g Placebo	135	30.34	8.91	1.222		
1g Bijuva	135	31.31	31.46	1.221	26.3	<.0001
1g Placebo	140	31.84	5.16	1.205		

Change = Change in Maturation Index (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

Note the synthetic conjugated estrogens, A 2g cream increased the final maturation index by a mean of 33.3 compared to 8.9 for 2g placebo cream ($p < 0.0001$); similarly, the 1g synthetic conjugated estrogens, A cream increased the final maturation index by a mean of 31.4 compared to 5.1 for the 1g placebo cream following 12 weeks of treatment. Similar statistical significant increase ($p < 0.001$) in the maturation index was also shown in the ITT and PPC cohorts).

In reviewing products used to treat VVA the Agency's recommendation is that data should demonstrate a statistically significant increase in the percentage of superficial cells and a statistically significant decrease in percentage of parabasal cells. The following two tables (Tables 10-11) show results specifically related to the percentages of superficial cells and parabasal cells that changed from baseline:

Table 50:. Superficial Cells: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva	146	0.97	26.79	1.237	21.79	<.0001
2g Placebo	135	1.08	5.00	1.271		
1g Bijuva	135	1.13	25.16	1.270	22.05	<.0001
1g Placebo	140	1.31	3.11	1.256		

Change = Change in Superficial Cells (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

Table 61:. Parabasal Cells: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva	146	42.56	-39.82	1.796	-26.97	<.0001
2g Placebo	135	40.41	-12.85	1.844		
1g Bijuva	135	38.51	-37.75	1.842	-30.55	<.0001
1g Placebo	140	37.64	-7.20	1.818		

** Change = Change in Parabasal Cells (Day 0 to Day 84 [or End-of-Treatment]).*
*** Difference = Difference between active treatment group and matching placebo.*
**** P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

Medical Officer's Comments

Overall, there is a statistically significant improvement in the maturation index when compared to placebo for both the 2g and 1g synthetic conjugated estrogens, A dosages. In addition, table 9 and 10 demonstrated a statistically significant increase in superficial cells and a corresponding statistically significant decrease in parabasal cells between baseline and week 12. The change in the percentage of superficial and parabasal cells represent a shift toward a more thickened vaginal mucosa consistent with reproductive aged women.

Vaginal pH

The mean change from baseline to Week 12 in the vaginal pH was the second of the three co-primary efficacy variables reported in protocol CEN-302. Vaginal pH was measured by inserting a standardized pH paper into the vaginal and comparing the results to the manufacturer's color chart. To demonstrate effectiveness, the Agency recommends that the statistical analysis report a statistically significant lowering of vagina pH between baseline and Week 12.

The following table 12 shows the change from Baseline pH to the end of study results.

Table 72:. Vaginal pH: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Raw Data)***
2g Bijuva	146	6.35	-1.44	0.071	-1.06	<.0001
2g Placebo	135	6.30	-0.38	0.073		
1g Bijuva	135	6.32	-1.48	0.073	-1.17	<.0001
1g Placebo	140	6.27	-0.31	0.072		

Change = Change in Vaginal pH (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis. Normality test: p-value=0.0515.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

Note from the baseline pH to the end of treatment pH the 2g synthetic conjugated estrogens, A dose decreased the vaginal pH by -1.44 compared to -0.38 for the placebo dose correlating into a difference of -1.06. Note the 1g synthetic conjugated estrogens, A dose also decreased the vaginal pH by -1.48 compared to -0.31 for the placebo dose which correlates to a difference of -1.17. The p-value is significant at < 0.0001. A reduction in the vaginal pH to <5 represents a shift toward a more thickened vaginal mucosa that is consistent with reproductive aged women.

Medical Officer's Comments
Overall, there is a statistically significant improvement in the vaginal pH when compared to placebo for the 2g and 1g synthetic conjugated estrogens, A dosages. These findings represent a shift toward a more thickened (healthy) vaginal mucosa consistent with reproductive aged women.

Most Bothersome Symptom (Overall Analysis)
The most bothersome symptom (MBS) was derived from the subject self-assessment of vaginal atrophy, which consisted of five questions concerning the severity of individual symptoms graded on a scale of 0 -3 (corresponding to, respectively, None, Mild, Moderate, or Severe) or 7 for N/A (non-applicable). The subject then classified the MBS *as the single symptom rated as either moderate or severe at baseline that she considered the most bothersome from among all symptoms rated moderate or severe.* (These symptoms are Vaginal Dryness, Vaginal Irritation/Itching, Vaginal Soreness, Pain during Intercourse and Bleeding after Intercourse.) *The severity of the MBS was then followed through to the end of treatment, whether or not the symptom was still considered the subject's most bothersome symptom.*

At baseline for the MITT Cohort (N = 556), the breakdown of symptoms chosen as the most bothersome was comparable across treatment groups and distributed as *278* (50%)

vaginal dryness, *70* (12.6%) vaginal irritation or itching, *17* (3.1%) vaginal soreness, *190* (34.2%) pain during intercourse, and *1* (0.2%) bleeding after intercourse.

The following sponsor's table 13 shows results from the *overall* MBS from baseline to end of treatment (MITT Cohort)

Table 83:. Overall Most Bothersome Symptom: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	146	2.61	-1.77	0.085	-0.67	<.0001
2g Placebo	135	2.59	-1.10	0.087		
1g Bijuva	135	2.62	-1.71	0.087	-0.6	<.0001
1g Placebo	140	2.55	-1.11	0.086		

** Change = Change in the Severity of Most Bothersome Symptom (Day 0 to Day 84 [or End-of-Treatment]).*
*** Difference = Difference between active treatment group and matching placebo.*
**** P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis. Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).*

Medical Officer's Comments
Baseline values for the composite MBS are greater than 2.5 (moderate to severe) for all treatment groups. Note that the 2g synthetic conjugated estrogens, A dose decreased the composite MBS compared to placebo by a difference of -0.67 and the 1g synthetic conjugated estrogens A, dose decreased the MBS compared to placebo by a difference of -0.60. Both dosages demonstrate significant p-values <0.0001. The p-value for the composite MBS is *not unexpected since it does not say what symptoms are helped.* The primary intent was to change to an individual symptom.

More importantly to this review of symptoms associated with VVA is the MBS *not as a composite, but as the individual symptom* that is self identified by the subject at baseline to the end of treatment, *whether or not the symptom was still considered the subject's most bothersome symptom.*

The following four (Tables 14-17) *sponsor's tables* show the results for the individual MBS that was self-identified by the subject from baseline to the end of treatment:

Table 94:. Individual MBS Symptom-Vaginal Dryness: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	76	2.61	-1.84	0.114	-0.55	<.0001
2g Placebo	70	2.54	-1.29	0.114		
1g Bijuva	60	2.58	-1.65	0.123	-0.48	0.0012
1g Placebo	72	2.47	-1.17	0.113		

** Change = Change in the Severity of Individual MBS Symptom - Vaginal Dryness (Day 0 to Day 84 [or End-of-Treatment]).*

Table 105:. Individual MBS Symptom-Pain during Intercourse: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	57	2.68	-1.78	0.186	-0.89	<.0001
2g Placebo	47	2.72	-0.89	0.196		
1g Bijuva	45	2.71	-1.76	0.184	-0.82	<.0001
1g Placebo	41	2.76	-0.94	0.199		

** Change = Change in the Severity of Individual MBS Symptom - Pain during Intercourse (Day 0 to Day 84 [or End-of-Treatment]).*
*** Difference = Difference between active treatment group and matching placebo.*
**** P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis.*
Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).

Table 116:. Individual MBS Symptom-Vaginal Irritation/Itching: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	10	2.30	-1.36	0.297	-0.52	0.1847
2g Placebo	15	2.40	-0.84	0.269		
1g Bijuva	23	2.52	-1.43	0.230	-0.2	0.4746
1g Placebo	22	2.32	-1.23	0.218		

** Change = Change in the Severity of Individual MBS Symptom - Vaginal Irritation/Itching (Day 0 to Day 84 [or End-of-Treatment]).*

Table 127:. Individual MBS Symptom-Vaginal Soreness: Change from Baseline (Day 0) to End of Treatment (MITT Cohort)

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva	3	2.33	-4.17****	1.026	-2	0.0958
2g Placebo	3	2.33	-2.17	0.750		
1g Bijuva	6	2.67	-1.64	0.485	-1.12	0.1270
1g Placebo	5	3.00	-0.52	0.548		

Change = Change in the Severity of Individual MBS Symptom - Vaginal Soreness (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis. Note: 69 sites were pooled into one "super site" due to testing treatment-by-center interaction (< 3 subjects in one or more treatment arms).*
****Change > 3 due to covariate adjustment based on baseline severity and the site factor.*

Note in sponsor's Tables 14 and 15 that the mean severity at baseline and the change between baseline and the end of treatment for each individual symptom that was identified by the subject as the MBS. Also note that following 12 weeks of treatment that the number of subjects compared to the composite number are *markedly reduced* because subjects were followed throughout the trial for their MBS. For instance, for the MBS of vaginal dryness the number per treatment group ranged from 60-72 at baseline; for the individual MBS of pain on intercourse the number per treatment group ranged from 41 to 57. Following 12 weeks of treatment, 2g synthetic conjugated estrogens, A cream reduced the severity of vaginal dryness and pain during intercourse by a mean of 1.84 and 1.78, respectively, compared to 1.29 and 0.89, respectively for 2g placebo (with both p-values <0.0001); the 1g synthetic conjugated estrogens, A cream reduced the severity of these two most MBS by a mean of 1.65 and 1.76, respectively, compared to 1.17 and 0.94, respectively for 1g placebo cream ($p = 0.0012$) and <0.0001), respectively following 12 weeks of treatment.

Tables 16 and 17 show the change from baseline to the end of the study for vaginal irritation/itching and vaginal soreness. Note neither symptom demonstrated a statistically significance difference between synthetic conjugated estrogens, A 2g or 1g compared to placebo and there appears to be insufficient power to demonstrate a treatment effect for these two symptoms in this study.

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The following is a summary table of individual symptoms as classified by the subject as the MBS. Note in table 18 that there are slight differences in the change from baseline compared to the previous tables from the sponsor. See reviewer's comments regarding the slight differences noted after Table 19.

Table 138:. Analysis of Primary Endpoints: Change from Baseline (Day 0) to End of Treatment (MITT Cohort) (Statistical Reviewer's table)

Endpoint	Treatments	N	Baseline	LS Mean Change	Standard Error	Difference Trt-Pl	W-test P-Value	P-Value*
Vaginal Maturation 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			

Reviewer's comment

When comparing the previous summary tables (9-13) of the sponsor to summary table 18, small differences are noted in the *"difference (trt-Pl")* column between the sponsor and the Agency's statistical reviewer analyses, although *p-values remain essentially the same.* The small differences are observed because the Agency reviewed the data *in two parts:* high dose groups (2g synthetic conjugated estrogens A, vs. 2g placebo) and low dose groups (1g synthetic conjugated estrogens A, vs. 1g placebo). The step down procedure was applied. The sponsor placed four treatment arms in the same model at the start of their analyses; therefore, small differences are noted in different columns between tables.

In reviewing additional tables for the onset of statistical efficacy this reviewer notes the following results:

- For the maturation index (both 2g and 1g synthetic conjugated estrogens, A) the onset of statistical efficacy ($p < 0.0001$) regarding the difference between superficial cells and placebo treatment effect is shown as early as Day 14. The treatment effect is also shown for parabasal cells ($p < 0.0001$) at Day 14 and is maintained throughout the remainder visits to the end of the study.
- For vaginal pH (both 2g and 1g synthetic conjugated estrogens, A) the onset of statistical efficacy ($p< 0.0001$) is shown as early as Day 14 and is maintained to the end of the study.
- For the *overall* MBS (both 2g and 1g synthetic conjugated estrogens, A) the onset of statistical efficacy (2g and 1g, $p < 0.0001$ and $p = 0.0016$, respectively) is shown as early as Day 21 and is maintained to the end of the study.
- For the *individual* MBS symptom-vaginal dryness the onset of statistical efficacy (2g and 1g, synthetic conjugated estrogens, A $p =0.005$ and $p = 0.0065$, respectively) is shown as early as Day 21 and is maintained to the end of the study ((at Day 84 EOT, $p< 0.0001$and 0.0012 for the 2g and 1g, synthetic conjugated estrogens, A respectively).
- For the *individual* MBS symptom-pain during intercourse the onset of statistical efficacy (2g and1g, $p =0.0002$ and $p = 0.0030$, respectively) is shown as early as Day 21 and is maintained to the end of the study (at Day 84 EOT, $p< 0.0001$ for both synthetic conjugated estrogens, A dosages)
- For the *individual* MBS symptom—vaginal irritation/itching a statistical significant p- value is only shown at Day 28 for the 2g synthetic conjugated estrogens A. For the individual MBS symptom—vaginal soreness a statistical significant p-value is only shown on Day 56 for the 1g synthetic conjugated estrogens, A dose.

Subject Self-Assessment of Vaginal Atrophy

The sponsor also presented five *supporting tables* that summarize the statistical analyses performed on the change from baseline to each post-baseline visit during the 84-day double-blind phase of the study. These tables demonstrate that synthetic conjugated estrogens, A consistently demonstrate a larger mean reduction than the matching placebo in the severity of all *five subject-assessed symptoms* at Day 21, Day 28, Day 56, and Day

84 (Week 12 end of treatment). For the self assessed symptoms of vaginal dryness and pain during intercourse significant mean reduction in symptom severity were first observed for both synthetic conjugated estrogens, A dosages compared to its matching placebo by Day 21 and maintained through subsequent visits (for vaginal dryness statistical significance was shown by day 21 for both dosages and for pain on intercourse 2g synthetic conjugated estrogens, A statistical significance occurred on Day 14 and for the 1g synthetic conjugated estrogens, A statistical significance occurred on Day 21).

Investigator's Assessment of Vaginal Atrophy
The sponsor also presented seven supporting tables that assessed vaginal atrophy for the MITT cohort as determined during physical examination of the subject at scheduled visits. Factors assessed were vaginal color, vaginal dryness, decrease vaginal rugosity, blanching of tissue (with pressure), vaginal tissue integrity and vaginal tissue petechiae. For each of these measures and at each post-baseline visit (Day 14, Day 21, Day 28, Day 56 and Day 84 [end of treatment]), statistically significant reductions in severity favoring synthetic conjugated estrogens, A over placebo were observed. These findings support the subject self-assessed individual symptom analysis results and the analysis results for the MBS co-primary endpoint.

6.1.5 Clinical Microbiology
In the previous submission to Clinical Microbiology no deficiencies were noted. The previous NDA submission included data for Microbial Limits and Antimicrobial Effectiveness Testing (AET) in the Chemistry, Manufacturing and Controls section which were determined to be satisfactory.

6.1.6 Efficacy Conclusion

Two active treatment doses of synthetic conjugated estrogens, A (SCE-A) vagina cream, 1g containing 0.625mg SCE-A and 2g containing 1.25g SCE-A both administered once a day for seven days and then twice weekly for the remaining 11 weeks of treatment, when compared to placebo, were shown to be effective in the treatment of moderate to severe vaginal dryness and moderate to severe pain with intercourse, symptoms of vulvar and vaginal atrophy due to menopause. Consistent with the 2003 draft clinical evaluation guidance document statistically significant increases in vaginal superficial cells and a decreases in vaginal parabasal cells, and a significant decrease in vaginal pH were observed in 84 days (12 weeks) of treatment and a significant reduction in the symptom specific MBS was observed for vaginal dryness and pain with intercourse when compared to its corresponding placebo. In addition, secondary outcome measures assessed by the patient and the physician support the primary efficacy outcomes of significant differences between the treatment effect and placebo that begin at week 2-3 and are maintained until week 12.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In a phase 3 study protocol (DR CEN-302) a total of 622 subjects were randomized and treated with one of the four vaginal creams: 2g synthetic conjugated estrogens, A (N =161), 2g placebo (N = 156), 1g synthetic conjugated estrogens, A (N = 150) or 1g placebo (N = 155). The treatment period was 84 days and was preceded by a 28-day screening period (subjects on HT at first presentation for the study were required to have a 6-month washout period prior to the screening visit). The distribution of the extent of exposure in days for each treatment group was comparable for the four treatment groups. Safety and tolerability were assessed by comparisons between treatment groups of treatment-emergent adverse events (TEAEs), standard laboratory test results, vital signs, transvaginal ultrasound (TVU) and endometrial biopsy results (Day -28 and Day 84) or end of treatment for non-hysterectomized subjects.

Reviewer's Comment
A 6-month washout period is much longer than what is recommended in the guidance document unless the subject had received some long-term injectable/implant drug therapy.

7.1.1 Deaths

There were no deaths in study protocol DR CEN-302.

7.1.2 Other Serious Adverse Events

A total of 622 subjects were randomized and treated with one of the four vaginal creams: 2g synthetic conjugated estrogens, A 2g placebo , 1g synthetic conjugated estrogens, A or 1g placebo (N = 155). Adverse events were reported during the regularly scheduled visits to the investigational site. Site personnel recorded the information regarding each event on the adverse event (AE) page of the Case Report Form (CRF). TEAEs were AEs that began or worsened on or after the first dose through the date of study completion (including events that occurred within 14 days after the last dose). TEAEs were reported by 295 (47.4%) of the 622 subjects in the safety cohort. Although subjects in the synthetic conjugated estrogens, A vaginal cream groups reported an overall higher incidence of TEAEs than placebo subjects, the difference was *not* significant: 49.2% in the active treatment groups and 45.7% in the placebo groups reported TEAEs.

A total of 8 subjects experienced a serious adverse event (SAE) during the study, four placebo subjects, two active subjects and two subjects who were not randomized reported SAEs. One DVT/PE was observed in a placebo-treated subject.

The following table 19 shows the subjects who experienced a SAE:

Table 19:. Serious Adverse Events

Treatment	Subject	SAE Descripton	Causality	Ongoing?
	0027/27019*	DIVERTICULITIS	None	Resolved
		MILD PANCREATITIS	None	Resolved
	0097/97008*	CARDIAC CHEST PAIN	None	Resolved
		HYPERTENSION	None	Resolved
2g Bijuva	0084/84004	CHRONIC SINUSITIS	None	Resolved
1g Bijuva	0044/44006	VENTRICULAR TACHYCARDIA	None	Resolved
2g Placebo	0027/27041	DEEP VEIN THROMBOSIS	Possibly	Resolved
		PULMONARY EMBOLISM	Possibly	Yes
	0055/55003	CARDIAC CHEST PAIN	Possibly	Resolved
	0059/59013	HYPONATRAEMIA	None	Resolved
1g Placebo	0045/45018	HODGKIN'S DISEASE	None	Yes

**Not randomized, not treated.*

Note two subjects had SAEs who were not randomized. Also note subject (#0027/2741) in the placebo group who developed a DVT/PE. This subject was a 70year old Caucasian female with no previous history of vascular problems. She was on multiple medications including simvastatin, hydroxychloroquine, levothyroxine, Lyrica™, Vicodin™, Actonel™, Cymbalta™, docudate sodium and salsalate. The subject was randomized on April 26, 2007. She completed the study and stopped investigational product on July 17, 2007. At the final study visit on July 19, 2007 her laboratory results and physical examinations were unremarkable. On ——— she was admitted to the hospital with pain, soreness and swelling in her left leg. A venous doppler ultrasound revealed extensive venous thrombosis of the left superficial femoral, popliteal and calf veins. Per the ultrasound and CT scan, the subjects was diagnosed with DVT and PE (serious, severe, and possibly due to investigational product per the investigator). She was treated with Coumadin and breathing treatments. The subject was discharged on ———. At the time of discharge, the DVT was considered to have residual effects with treatment ongoing and the PE had not resolved with treatment ongoing.

b(6)

Subject (#44/44006) was a 49 year old Caucasian female with multiple medical problems including high cholesterol, acne, *hypothyroidism*, irritable bowel syndrome, hot flashes, night sweats, ovarian cysts, prolapsed bladder, anemia, joint pain, seasonal allergies, etc. Concomitant medication at the time of screening included levothyroxine. At the screening visit on November 10, 2006 her laboratory results and physical and gynecological examinations, including Pap smear were unremarkable.

The subject was randomized to 1g synthetic conjugated estrogens, A. She began therapy on December 1, 2006. On December 22, 2006 the subject experienced episodes of lightheadedness and felt her heart "skipped beats." She was placed on a Holter monitor by her cardiologist. The monitor recorded ventricular tachycardia (serious, and

severe).This was interpreted by the investigator as not related to investigational product. She was admitted to the hospital and a thallium stress test, ECG, and cardiac MRI were performed with normal results. An electrophysiology study was performed and revealed an "extra conduction pathway." The subject underwent a pathway ablation procedure. She was discharged on [redacted] and the event was considered resolved. b(6)

Medical Officer's Comment
The two most serious SAEs are presented above. It is the opinion of this medical officer that these adverse events do not appear to be related to active treatment.

7.1.3 Dropouts and Other Significant Adverse Events
The following table 20 shows subjects who discontinued from the study due to an adverse event. Table 21 differs from table 20 in that it records subjects who discontinued specially due to a medication related AE (rather than for any reason).

Table 140:. Adverse Events Leading to Study Discontinuation

Treatment	Site	Subject	AE Description	Severity
2g Bijuva	0012	12002	ABD BLOATING	Moderate
			ABD TENDERNESS	Mild
			ABD. CRAMPING	Mild
			PRESSURE IN LOWER ABD.	Moderate
	0033	33006	BACTERIAL VAGINOSIS	Mild
	0049	49033	BILATERAL BREAST SORENESS	Moderate
			BILATERAL LEG CRAMPS	Moderate
	0077	77005	VAGINAL IRRITATION	Moderate
	0081	81011	VAGINAL ITCHING	Moderate
1g Bijuva	0006	6004	ANTERIOR CHEST PAIN (NON CARDIAC)	Moderate
			HEADACHE	Moderate
			SHORTNESS OF BREATH	Moderate
			VAGINAL BURNING	Moderate
	0043	43009	FACIAL REDNESS	Mild
			FACIAL SWELLING	Mild
	0052	52016	YEAST INFECTION, VAGINAL ITCHING + BURNING	Moderate
2g Placebo	0052	52015	VAGINAL YEAST INFECTION	Moderate
	0078	78020	HEADACHE	Severe
1g Placebo	0033	33011	INCREASED HOT FLASHES	Mild
			INCREASED INSOMNIA	Mild
	0066	66015	POSTERIOR FORCHETTE FISSURE	Moderate

Two subjects discontinued due to AE but were not treated with study medication , therefore, not displayed.

A total of 12 subjects discontinued due to an AE. Of this total, eight subjects in the active groups (5 [2g synthetic conjugated estrogens, A vaginal cream], 3 [1g synthetic conjugated estrogens, A vaginal cream]) discontinued due to an AE compared to four subjects in the placebo groups. Two subjects also discontinued due to an AE, but were not treated with study medications.

Reviewer's Comment
Note a majority of subjects who discontinued did so because of vulvar/vaginal AEs. Fewer of the discontinuations were due to AEs at sites of the body (as a whole,) which are more identified with oral administration.

7.1.3.1 Overall profile of dropouts

The following table 21 summarizes the overall Profile of Dropouts and Subject Disposition:

Table 151:.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

Note that 26 (4.2%) subjects requested to be withdrawn; another 13 (2.1%) withdrew because of a lack of efficacy. As stated earlier *12 (1.9%)* of subjects withdrew due to an adverse event. Of these 12 subjects who discontinued due to an AE, six AEs were considered serious, four in the placebo groups and two in the active treatment groups.

7.1.3.2 Adverse events associated with dropouts

The following table 23 summarizes the overall incidence of *any* reported AEs, treatment-emergent AEs, treatment-related AEs, serious AEs (SAEs), and AEs that led to discontinuation by treatment group. Any AEs includes all adverse events reported from the beginning of the 28-day screening through the subjects' last report. AEs judged to be at least possibly related to study drug by the investigatory were considered to be treatment-related AEs.

Table 162: Adverse Event Summary (Safety Cohort)

	2g Bijuva (N=161)	1g Bijuva (N=150)	2g Placebo (N=156)	1g Placebo (N=155)	Total (N=622)
Total Number of AEs	170	180	159	135	644
Subjects with:					
Any AE	87 (54.0%)	83 (55.3%)	77 (49.4%)	72 (46.5%)	319 (51.3%)
Treatment-Emergent AE	79 (49.1%)	74 (49.3%)	74 (47.4%)	68 (43.9%)	295 (47.4%)
Treatment-Related AE	27 (16.8%)	15 (10.0%)	23 (14.7%)	16 (10.3%)	81 (13.0%)
SAE	1 (0.6%)	1 (0.7%)	3 (1.9%)	1 (0.6%)	6 (1.0%)
AE Leading to Discontinuation	5 (3.1%)	3 (2%)	2 (1.3%)	2 (1.3%)	12 (1.9%)

Again, note the 12 (1.9%) subjects who discontinued due to an AE and the 6 AEs that were considered serious, four in the placebo groups and two in the active treatment groups.

7.1.3.3 Other significant adverse events

Other treatment-emergent adverse events (Sponsor's table 47) that occurred in study protocol DR CEN-302 include six cases of flushing/hot flushes, four migraine headaches, six headache, three cases of application site irritation/pruritus, one night sweat, and two pruritis.

7.1.4 Other Search Strategies

There were no safety signals that arose from previous studies that required construction of any algorithm involving a combination of clinical findings as a marker for a particular adverse event.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In study protocol DR CEN-302, adverse events (AEs) were reported during the subject's regularly scheduled visits to the study centers (Study Visits 2-6). At scheduled visits, center personnel obtained and recorded results of vital signs and body weight, and queried the subject regarding adverse events, concomitant medication use and study medication compliance. The investigator (or qualified designee) obtained and recorded results of the vaginal pH, obtained a sample for vaginal cytology and examined the subject to complete the assessment of vaginal atrophy. In addition, at each of these visits, the subject completed the Vaginal Atrophy/Sexual Function Questionnaire.

Medical Officer's Comment
It should be noted that the use of recall data interviews may contribute to the under reporting of adverse events. Optimally the subject should be requested to record adverse events in a *daily diary* (as well as concomitant medication use), which is reviewed with the study coordinator at scheduled visits.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant reported the incidence of adverse events by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. While there may be many related terms that may be selected to describe an event in the MedDRA dictionary of preferred terms, there is no concern that the use of preferred terms resulted in a missed signal for the safety data.

7.1.5.3 Incidence of common adverse events

The following table 23 shows the incidence of TEAEs occurring in 3% or more of patients

Table 173: Adverse Events: Incidence of Treatment-Emergent Adverse Events occurring in 3% or more of Patients

MedDRA System Organ Class and Preferred Term	2g Bijuva (N=161)		1g Bijuva (N=150)		2g Placebo (N=156)		1g Placebo (N=155)		Total (N=622)	
	N	%	N	%	N	%	N	%	N	%
GASTROINTESTINAL DISORDERS										
ABDOMINAL PAIN	7	4.35	1	0.67	0	0.00	1	0.65	9	1.45
INFECTIONS AND INFESTATIONS										
UPPER RESPIRATORY TRACT INFECTION	6	3.73	7	4.67	6	3.85	7	4.52	26	4.18
URINARY TRACT INFECTION	5	3.11	3	2.00	6	3.85	2	1.29	16	2.57
VULVOVAGINAL MYCOTIC INFECTION	3	1.86	7	4.67	2	1.28	5	3.23	17	2.73
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS										
BACK PAIN	6	3.73	0	0.00	2	1.28	0	0.00	8	1.29
REPRODUCTIVE SYSTEM AND BREAST DISORDERS										
GENITAL PRURITUS FEMALE	5	3.11	4	2.67	1	0.64	0	0.00	10	1.61
NERVOUS SYSTEM DISORDERS										
HEADACHE	2	1.24	6	4.00	6	3.85	0	0.00	14	2.25
VASCULAR DISORDERS										
HOT FLUSH	2	1.24	5	3.33	5	3.21	2	1.29	14	2.25
HYPERTENSION	0	0.00	1	0.67	5	3.21	1	0.65	7	1.13

Note the incidence of TEAEs was comparable overall across treatment groups. A higher incidence rate of abdominal pain was reported for the active groups (8/33 [2.6%]) than for placebo (1/311 [0.3%]). While (no) back pain was reported in the low dose groups, a higher incidence rate was reported for the high dose synthetic conjugated estrogens, A group 6 (3.7%) when compared to the corresponding placebo group (2 [1.3%]). Nine (9) synthetic conjugated estrogens, A subjects (2.9%) and one placebo subject (0.3%) reported genital pruritus as an adverse event. The most commonly reported AE was upper respiratory tract infection (4.2%) for both placebo and synthetic conjugated estrogens, A. All other incidence rates of TEAEs were < 3% or similarly distributed across treatment groups

7.1.5.4 Common adverse event tables

The following table 24 shows the incidence of treatment-related adverse events (safety cohort):

Table 184:. Incidence of Treatment-Related Adverse Events (Safety Cohort)

MedDRA System Organ Class	2g Bijuva (N=161)		1g Bijuva (N=150)		2g Placebo (N=156)		1g Placebo (N=155)		Total (N=622)	
and Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
ANY AE										
Total Disorders	27	16.77	15	10.00	23	14.74	16	10.32	81	13.02
REPRODUCTIVE SYSTEM AND BREAST DISORDERS										
Total Disorders	15	9.32	8	5.33	5	3.21	4	2.58	32	5.14
GENITAL PRURITUS FEMALE	5	3.11	4	2.67	1	0.64	0	0.00	10	1.61
BREAST TENDERNESS	3	1.86	0	0.00	1	0.64	3	1.94	7	1.13
POSTMENOPAUSAL HAEMORRHAGE	2	1.24	0	0.00	2	1.28	0	0.00	4	0.64
VULVOVAGINAL DISCOMFORT	2	1.24	2	1.33	0	0.00	0	0.00	4	0.64
BREAST PAIN	1	0.62	3	2.00	0	0.00	0	0.00	4	0.64
GENITAL ERYTHEMA	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
PELVIC DISCOMFORT	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
VAGINAL SWELLING	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
BREAST MASS	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
GENITAL DISCHARGE	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
VAGINAL BURNING SENSATION	0	0.00	1	0.67	0	0.00	0	0.00	1	0.16
VAGINAL DISCHARGE	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
GASTROINTESTINAL DISORDERS										
Total Disorders	5	3.11	0	0.00	3	1.92	0	0.00	8	1.29
ABDOMINAL PAIN	3	1.86	0	0.00	0	0.00	0	0.00	3	0.48
ABDOMINAL DISTENSION	2	1.24	0	0.00	1	0.64	0	0.00	3	0.48
ABDOMINAL PAIN LOWER	2	1.24	0	0.00	1	0.64	0	0.00	3	0.48
ABDOMINAL DISCOMFORT	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
ABDOMINAL TENDERNESS	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
NAUSEA	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
INFECTIONS AND INFESTATIONS										
Total Disorders	3	1.86	2	1.33	2	1.28	5	3.23	12	1.93
VAGINAL CANDIDIASIS	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
VAGINITIS BACTERIAL	1	0.62	0	0.00	1	0.64	0	0.00	2	0.32
VULVOVAGINAL MYCOTIC INFECTION	1	0.62	1	0.67	0	0.00	4	2.58	6	0.96
GENITAL CANDIDIASIS	0	0.00	1	0.67	0	0.00	0	0.00	1	0.16
URINARY TRACT INFECTION	0	0.00	0	0.00	1	0.64	1	0.65	2	0.32
VULVITIS	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
INVESTIGATIONS										
Total Disorders	2	1.24	3	2.00	1	0.64	0	0.00	6	0.96
BLOOD CHOLESTEROL INCREASED	1	0.62	1	0.67	0	0.00	0	0.00	2	0.32

Table 24:. Incidence of Treatment-Related Adverse Events (Safety Cohort) (Continued)

MedDRA System Organ Class	2g Bijuva (N=161)		1g Bijuva (N=150)		2g Placebo (N=156)		1g Placebo (N=155)		Total (N=622)	
and Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
INVESTIGATIONS (cont'd)										
BLOOD CREATINE PHOSPHOKINASE INCREASED	1	0.62	1	0.67	0	0.00	0	0.00	2	0.32
CYTOLOGY ABNORMAL	0	0.00	1	0.67	0	0.00	0	0.00	1	0.16
URINE ANALYSIS ABNORMAL	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
VASCULAR DISORDERS										
Total Disorders	2	1.24	1	0.67	4	2.56	1	0.65	8	1.29
FLUSHING	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
HOT FLUSH	1	0.62	1	0.67	2	1.28	1	0.65	5	0.80
DEEP VEIN THROMBOSIS	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
HYPERTENSION	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS										
Total Disorders	1	0.62	1	0.67	2	1.28	0	0.00	4	0.64
MUSCLE SPASMS	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
AXILLARY MASS	0	0.00	1	0.67	0	0.00	0	0.00	1	0.16
BACK PAIN	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
PAIN IN EXTREMITY	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)										
UTERINE LEIOMYOMA	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
NERVOUS SYSTEM DISORDERS										
Total Disorders	1	0.62	4	2.67	4	2.56	1	0.65	10	1.61
MIGRAINE	1	0.62	1	0.67	1	0.64	1	0.65	4	0.64
DIZZINESS	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
HEADACHE	0	0.00	3	2.00	3	1.92	0	0.00	6	0.96
RENAL AND URINARY DISORDERS										
Total Disorders	1	0.62	0	0.00	0	0.00	1	0.65	2	0.32
MICTURITION URGENCY	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
POLLAKIURIA	1	0.62	0	0.00	0	0.00	0	0.00	1	0.16
BLADDER PAIN	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
CARDIAC DISORDERS										
ANGINA PECTORIS	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS										
Total Disorders	0	0.00	0	0.00	3	1.92	2	1.29	5	0.80
APPLICATION SITE IRRITATION	0	0.00	0	0.00	1	0.64	1	0.65	2	0.32
APPLICATION SITE PRURITUS	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
OEDEMA PERIPHERAL	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
SWELLING	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16

Error! Reference source not found.**Table 24:. Incidence of Treatment-Related Adverse Events (Safety Cohort) (Continued)**

MedDRA System Organ Class	2g Bijuva (N=161)		1g Bijuva (N=150)		2g Placebo (N=156)		1g Placebo (N=155)		Total (N=622)	
and Preferred Term	N	%	N	%	N	%	N	%	N	%
PSYCHIATRIC DISORDERS										
Total Disorders	0	0.00	0	0.00	2	1.28	1	0.65	3	0.48
INSOMNIA	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
LIBIDO INCREASED	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
TEARFULNESS	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS										
PULMONARY EMBOLISM	0	0.00	0	0.00	1	0.64	0	0.00	1	0.16
SKIN AND SUBCUTANEOUS TISSUE DISORDERS										
Total Disorders	0	0.00	1	0.67	0	0.00	3	1.94	4	0.64
ACNE	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
NIGHT SWEATS	0	0.00	0	0.00	0	0.00	1	0.65	1	0.16
PRURITUS	0	0.00	1	0.67	0	0.00	1	0.65	2	0.32

Reviewer's Comment
Note the overall low incidence of AEs for all treatment groups ranged from 10% to 16% and the 2g synthetic conjugated estrogens, A group and its corresponding placebo group are similar; smaller incidences are noted for the 1g dose and its corresponding placebo. This reviewer also notes *no* greater incidence of AEs compared to other vaginal products.

7.1.5.5 Identifying common and drug-related adverse events
A total of 81/622 (7.7%) TEAEs across the four treatment groups were felt to be treatment related AEs by study investigators. Across the two active group regimens and the corresponding placebo regimens the percentage of these AEs are similar.

7.1.5.6 Additional analyses and explorations

The low incidence of all adverse events and a minimal number of serious adverse events suggest that further evaluation of submitted data is not warranted.

7.1.6 Less Common Adverse Events

Under Reproductive System and Breast disorders, this reviewer notes two cases of postmenopausal hemorrhage in the 2g synthetic conjugated estrogens, A group and 2 cases in the 2g placebo group. Special attention was paid to the endometrium since this product is given as an unopposed estrogen. Unopposed estrogen use has been shown to increase the incidence of endometrial hyperplasia which is a precursor to endometrial carcinoma. In study DR CEN-302 the sponsor performed endometrial biopsies (EMB) at

the screening visit and at the end of treatment visit for patients in the safety cohort who had a uterus.

Results of EMB are reported in Sponsor's Table 9. Sponsor's Table 9 essentially follows recommendations for histologic descriptions as recommended when reading endometrial biopsy slides that has been outlined in the guidance document of 2003. Table 9 is too large to be reproduced therefore, the following text described findings.

At the screening visit, 324 of 384 (84.3%) randomized patients with a uterus had an endometrial biopsy performed, of which 283 (87.3) patients provided valid biopsy results and 41(12.7%) patients did not because of insufficient tissue obtained at baseline. For the 60 subjects with a uterus who did not have an EMB performed at the screening visit, the primary reason recorded was c*ervical stenosis* (or narrowed cervix) (47 [78.3%]). The other recorded reasons were prior biopsy (6), unsuccessful or aborted procedure (3), or waivers granted (4). A total of 272 patients had an EMB done at the screening visit also had an EMB done at the end of treatment; 227 subjects had valid biopsy results obtained at both screening visit and the end of treatment. *No findings among the successful entrance and exit biopsies were considered to be clinically significant.* One placebo patient (#30/30012) had an abnormal result (atrophic polyp) at day 84, while her baseline biopsy was normal atrophy. This reviewer notes that 32/42 patients who reported no EMB at the end of treatment refused because of patient discomfort. The remaining 10 patients reported a variety of reasons for not having a biopsy such as: "subject never returned or lost to follow-up" (2), "patient withdrawal of consent" (2), "unable to dilate cervix (or stenotic)" (2), "insufficient tissue or endometrial stripe < 2mm" (2), "too uncomfortable" (1) and "waiver granted" (1).

Reviewer's Comment
There were no clinically meaningful changes noted in exit biopsies from baseline.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Refer to the schematic flow chart (Figure 2) for breakdown of serum chemistry test, hematology test, serum lipid profiles and urine pregnancy test. Mammogram was required for all women aged 40 and over; a TVU was also performed at baseline.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons provide the best data for deciding whether there is a signal of a treatment effect of a drug on a laboratory test. In study DR-CEN-302 there appears to be no laboratory safety signal upon which to evaluate safety data.

7.1.7.3 Standard analyses and explorations of laboratory data

Laboratory tests were performed at the screening visit and/or randomization visit, and at the end of treatment. The baseline value was taken as the measurement at the randomization visit or at the screening visit when test were not performed at the randomization visit. All displays of the laboratory results compared the end of treatment value to the baseline value for the safety cohort. P-values presented for the means of each laboratory value were based on a one-way ANOVA across treatment groups from baseline, end of treatment and change from baseline to end of treatment.

Review of serum chemistry, serum lipid profile, hematology, and urinalysis demonstrate *no* changes that are clinically significant although there were minor changes that reached statistically significance in the bicarbonate and calcium levels when compared to placebo. Additionally minor changes were noted in the total cholesterol levels (either increase or decrease).

7.1.7.5 Special assessments

No special assessments for renal or hepatic toxicity are indicated for a vaginal estrogenic cream.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Two doses were studied in three pivotal phase 3 trials. From a clinical and safety viewpoint, there is *no* difference between synthetic conjugate estrogens, A vaginal cream 2g (1.25mg) and 1g (0.625mg) dosage. The sponsor identified no differences in the two dosages and is seeking to market the 1g (0.625mg) dosage only. The subject should insert 1g (1 applicator) intravaginally daily for one week followed by 1g (1 applicator) intravaginally twice per week

8.2 Drug-Drug Interaction

No drug-drug interactions were uncovered during two review trials.

8.3 Special Populations

Synthetic conjugate estrogens, A vaginal cream was investigated in postmenopausal women age 30 to 80, inclusive. No pharmacokinetic studies were conducted in other special populations, including patients with renal or hepatic disease.

8.4 Pediatrics

Synthetic conjugate estrogens, A vaginal cream are not indicated for use in a pediatric population.

8.5 Advisory Committee Meeting

No advisory committee meeting is being sought regarding synthetic conjugate estrogens, A vaginal cream.

8.6 Literature Review

There is no need to reference a literature review regarding synthetic conjugate estrogens, A vaginal cream; most pertinent data in the literature references oral synthetic conjugate estrogens A, tablets.

8.7 Postmarketing Risk Management Plan

There is no need to develop a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials that are not included in other sections of this review. Importantly, the generic name is synthetic conjugate estrogens, A vaginal cream. No agreement has been made between the Agency and Duramed regarding the proposed trade name Bijuva vaginal cream. In the previous review cycle, DMETS was not in agreement with the proposed name of Bijuva. It would seem that a more appropriate trade name would be Cenestin® vaginal cream to avoid confusion with other products.

9 OVERALL ASSESSMENT

In study DR-CEN-302 the sponsor has supplied sufficient evidence to support the concept that synthetic conjugate estrogens, A vaginal cream 1g (0.625mg) dose compared to placebo, is an effective dose in the treatment of moderate to severe vaginal dryness and moderate to severe pain with intercourse, symptoms of vulvar and vaginal atrophy in postmenopausal women. Statistically significant increases in vaginal superficial cells and a statistically significant decrease in vaginal parabasal cells, a significant decrease in vaginal pH and statistically significant reduction in the severity of the individual MBS of vaginal dryness and pain with intercourse was observed

For the maturation index and vaginal pH co-primary endpoints, as well as additional analyses for superficial cells and parabasal cells, statistical significance favoring the 1g synthetic conjugate estrogens, A vaginal cream dose was achieved by Day 14. For the MBS co-primary endpoints of vaginal dryness and pain with intercourse, statistical significance for the reduction in severity favoring the 1g dose was achieved by Day 21.

There is no data in either the prior submission or this present submission that supports the concept that the 1g is the lowest effective dose of synthetic conjugate estrogens, A vaginal cream.

9.1 Conclusions

This reviewer concludes that the 1g synthetic conjugate estrogens, A vaginal cream is an effective dose in the treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy due to menopause. There is no data in either the prior submission of June 25, 2004 or in this submission that support the concept that the 1g synthetic conjugate estrogen A, vaginal cream is the lowest effective dose to treat symptoms of vulvar and vaginal atrophy due to menopause. As per the recommended label the subject should initiate therapy using the one gram dose daily intravaginally for one week followed by one gram twice a week intravaginally.

9.2 Recommendation on Regulatory Action

A letter of approval should be sent to the sponsor.

9.3 Recommendation on Postmarketing Actions

Based upon the clinical and safety data presented in this submission, this reviewer recommends that the sponsor study the 0.5g (0.375mg/g) synthetic conjugate estrogens, A vaginal cream dose to demonstrate a lowest effective dose or an ineffective dose..

9.3.1 Risk Management Activity

No additional risk management is deemed necessary. Synthetic conjugated estrogens, A cream 1g was studied in pivotal study DR-CEN-302. The 1g dosage appears to be a low effective dosage of synthetic conjugated estrogens, A which produces lower serum estrogen levels than the approved 0.3mg Cenestin.

9.3.2 Required Phase 4 Commitments

A Phase 4 commitment is required to demonstrate if the 0.5g (0.375mg) dosage of synthetic conjugated estrogens A, cream is the lowest effective dose to treat moderate to severe symptoms of vulvar and vaginal atrophy given the fact that in study DR-CEN-302 the onset of efficacy occurred during week 2/3 ($p < 0.0012$) and that the treatment effect continued through week 12 of treatment.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

See Section 10.2

9.5 Comments to Applicant

10 APPENDICES

10.1 Review of Individual Study Reports

None

10.2 Line-by-Line Labeling Review

(See draft label to sponsor dated August 18, 2008 attached below)

b(4)

17 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Phill H. Price
9/11/2008 10:32:56 AM
MEDICAL OFFICER

Shelley Slaughter
9/11/2008 10:56:48 AM
MEDICAL OFFICER
I concur with the conclusions of Dr. Price that the data in the application for 1 gram of synthetic conjugated estrogens, A vaginal cream demonstrate acceptable efficacy and safety for this product and that approval is recommended.