CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-574**

STATISTICAL REVIEW(S)

OCT 26 1998

Statistical Review and Evaluation

NDA#:	20-574 (Resubmission)
Applicant:	Schering-Plough HealthCare Products, Liberty Corner, New Jersey
Name of Drug:	Gyne-Lotrimin 3™ 3-day Vaginal Cream (2% clotrimazole) for Over-the-Counter Use.
Documents Reviewed:	Volume 1.44 of 1.68 (Statistical Section from original application); Volumes 2.1, 2.7, 2.8, 2.9 of 2.9 from the Resubmission; Volumes 1 and 2 of Bridge Study CTZ 97-01.
	Medical Officer's Review
Indication:	Vulvovaginal candidiasis
Type of Review:	Clinical/Statistical
Medical Input:	Dr. Joseph Winfield, HFD-590

A. INTRODUCTION

In the original submission, the sponsor submitted results from three (US and Canadian) clinical trials (Protocols 92-11, 93-34 and 93-40) to support the claim for efficacy and safety of Gyne-Lotrimin 3™ 3-Day Vaginal Cream. Studies 93-34 and 93-40 were considered pivotal. Study 92-11 was discontinued prematurely because of a high rate of negative vaginal cultures for Candida at study entry; data from this study were subsequently used for safety assessment only. Since only one of the pivotal studies (#93-40) was determined to support the effectiveness of 3-day 2% clotrimazole cream therapy, the sponsor withdrew NDA 20-574, on 1/29/1996.

In the resubmission of NDA 20-574 on 11/25/1997, the sponsor submitted results from i) studies 93-34 and 93-40 combined as a single pivotal study, (ii) a new pivotal study, 95-50, of a 2% 3-Day clotrimazole cream that had been conducted by Taro Pharmaceuticals U.S.A., Inc., and shortly thereafter, (iii) a bridging study CTZ 97-01 for demonstration of the therapeutic equivalence of the Taro and SPHCP 2% products used for 3 days. The Taro 3-day 2% product

has been marketed in Canada as a prescription therapy (7 years) and as an over-the-counter product (2 years). SPHCP had acquired the rights to use the results of the Taro study #95-50. The reanalysis of the 93-34/93-40 study and the Taro study used the criteria agreed upon by the Agency at a 4/3/1996 meeting with SPHCP.

Study 93-34 was a physician-blinded, randomized, parallel-group study with 4 treatment arms initially. Patients (all from US investigational sites) were treated with 1%, 2% or 4% clotrimazole cream used once daily for 3 days, or 1% clotrimazole cream used for 7 days (standard treatment). After an interim look, the 3-Day 4% treatment arm was closed to further recruitment. Patients were seen on admission, followed up at 14-17 days and 28-31 days post therapy. All medications were self-administered.

Study 93-40 was a physician-blinded, randomized, parallel-group study with three treatment arms. Patients (all from Canadian investigational sites) were treated with 1%, or 2% clotrimazole cream used once daily for 3 days, or 1% clotrimazole cream used for 7 days (standard treatment). Patients were seen on admission, followed up at 14-17 days and 28-31 days post therapy. All medications were self-administered.

Study 92-11 had the same design as #93-34. Patients were seen on admission, and follow-up evaluations were made on days 1-2, 6-8, and 26-30 days. As already noted, this study was ended prematurely, and resulting data from this study were used only for safety assessment.

For the current review, efficacy analyses from studies 93-34 and 93-40 combined (that is, pooled together, and excluding the 4% 3-Day treatment arm from the 93-34 study) are assessed according to FDA's current evaluability criteria. The appropriateness of pooling the studies was reviewed. Safety data from studies 92-11, 93-34 and 93-40 are examined.

Study 95-50 (the Taro study) was a partially-blinded, randomized, parallel-group study, with 5 treatment arms. Patients (all from Canadian investigational sites) were treated with 1-day oral fluconazole [redacted] 1-day clotrimazole 500 mg vaginal tablet [redacted] 7-day 1% clotrimazole cream (Schering), 3-day 2% clotrimazole cream (Taro) or 1-day 2% clotrimazole cream (Taro). Patients were seen on admission, followed up at 14-17 days and 35-42 days post therapy. All medications were self-administered.

Study CTZ 97-01 (the Bridging study) was a blinded parallel group study to compare two treatments: the 2% 3-day clotrimazole vaginal cream manufactured by Taro, and the 2% 3-day clotrimazole vaginal cream manufactured by SPHCP. The study was conducted at 8 clinical sites in Canada. All medications were self-administered. Patients were seen on admission, and followed up at 21 days after starting treatment. At 5 weeks after enrollment, patients were contacted by phone to assess any return of symptoms.

For this Application, the primary efficacy analysis for Studies 93-34 and 93-40 is aimed at the assessment of therapeutic equivalence between the 3-Day 2% and the 7-Day 1% SPHCP products. The primary efficacy analysis for Study 95-50 for this Application is aimed at assessing therapeutic equivalence between the 3-Day 2% Taro product and the 7-Day 1% SPHCP product. Finally, the aim of the efficacy analysis for Study 97-01 is to assess therapeutic equivalence between the 3-Day 2% Taro product and the 3-Day 2% SPHCP product.

In addition to the primary efficacy analyses, this review examines the following secondary analyses: comparison of the 3-Day 1% and the 7-Day 1% SPHCP products from Studies 93-34 and 93-40 combined, and comparison of the 1-Day 2% Taro product and the 7-Day 1% SPHCP product from Study 95-50. Data from patients in the 95-50 study who were treated with 1-day oral fluconazole [redacted] or 1-day clotrimazole 500 mg vaginal tablet [redacted] have not been examined.

Baseline Consistency

Studies 93-34 and 93-40: there were no apparent differences at baseline between treatment arms with respect to age, race, disease severity, oral contraceptive usage, diabetic status, or prior history of monilial infection (all p-values > 0.10). The rates of prior monilial infection were 69% and 72% for studies 93-34 and 93-40, respectively.

Study 95-50: there were no apparent differences at baseline between treatment arms with respect to age, race, disease severity, diabetic status, or prior history of monilial infection; the rate of patients with prior monilial infection was 67%. The proportion of patients receiving the 3-Day 2% Taro product who use oral contraceptives, 26%, was significantly higher than the proportions receiving the 7-Day 1% SPHCP product (12%) or 1-Day 2% Taro product (17%) (p-value of chi-square test = 0.054).

Study CTZ-9701: there were no apparent baseline inconsistencies between the two treatment groups with respect to patient race, age or diabetic status. There were no significant differences between treatment groups in the proportion of patients with Candida albicans at study entry, or past history of monilial infection (rate = 67% overall). There were no significant differences between treatment groups in the average scores of the following clinical signs and symptoms: itching, burning, vulvar excoriation, vaginal edema and discharge. Patients in center 2, however, who were randomized to the Taro product had significantly greater average scores than those randomized to the Schering product for: vulvar erythema, vulvar edema, vulvar excoriation, and the total score of all of these signs and symptoms. These findings were evidenced by significant

center*treatment interactions. No treatment differences were seen for the other 7 centers. Note that center 2 had only 10 patients, 5 in each treatment group, and contributed 7% of the total number, thus this finding may be regarded as inconclusive.

B. EFFICACY EVALUATION

The primary efficacy variable is the therapeutic cure rate. A patient is said to be therapeutically cured if she is cured both clinically and microbiologically.

Criteria for assessing efficacy

Evaluation of efficacy was carried out in as similar fashion as possible across the four studies, which had somewhat different designs. The definitions and criteria were based on current FDA's current evaluability criteria in consultation with the Medical Officer.

The following criteria were used for the studies 93-34, 93-40 and 95-50 for which there were 2 visits (Visits 2 and 3) post-treatment for assessment of signs, symptoms and microbiological response to treatment:

Mycological cure: negative culture and negative KOH for Candida at Visits 2 and 3; if the results disagree, the culture result is used, but if the culture result is missing, the KOH result is used.

Clinical cure: Patient had improved signs (erythema, edema, excoriation) and symptoms (itching/irritation (1 symptom) and burning) at Visit 2, and only one or two signs and symptoms categorized as mild at Visit 3. Vaginal discharge was not included as a sign. The sign/symptom score is the average of all non-missing measurements. To count as improvement, the mean score at Visit 2 had to be strictly less than that at Visit 1 (baseline).

Therapeutic cure: Patient had both a clinical and mycological cure.

The following criteria were used for study 97-01 for which there was only one post-treatment visit (Visit 2) for assessment of signs, symptoms and laboratory evidence of Candida, plus a follow-up telephone call at 5 weeks to assess symptoms.

Mycological cure: negative culture and negative KOH for Candida at Visit 2.

Clinical cure: Patient had improved signs (erythema, edema, excoriation) and symptoms (itching/irritation (1 symptom) and burning) at Visit 2, and no return of signs by the follow-up call except for "mild" itching. Vaginal discharge was not included as a sign.

Therapeutic cure: Patient had both a clinical and mycological cure.

Results

Cure Rates

Tables 1-5 give cure frequencies for Studies 93-34, 93-40, 93-34 and 93-40 combined, 9550, and 9701. Appendix Tables A1-A5 give cure frequencies provided by the Sponsor for Studies 93-34, 93-40, 93-34 and 93-40 combined, 9550, and 9701. For Studies 95-50 and 97-01, the Sponsor's rates are closely similar to those given here in Tables 4 and 5. For Studies 93-34 and 93-40, however, the cure rates reported by the Sponsor are different from those given in Tables 1-3, due to inconsistencies and unnecessary elimination of data. This was attributable to the criteria for evaluating cure having changed over time since these old studies were conducted. Recent consultations between the Medical Officer and the Sponsor have resolved the inconsistencies between the rates reported here and those provided in the NDA.

For each study, the evaluated patients are those enrolled patients who were included because they were eligible at baseline and were not excluded after baseline for any of the following reasons: protocol violations, follow-up visits "out-of-window", dropouts, lost-to-follow-up, adverse events, patient request, investigator request, abnormal laboratory results including Pap smears, and reasons labeled "other" by the Sponsor. For therapeutic, clinical, and microbiological cure, and for each treatment group, the numbers given in the Tables are $N_1 / N_2 / N_3$ where N_1 = number of patients cured, N_2 = number of patients not cured, N_3 = number of patients with missing result. The total numbers of evaluable patients are $N_1 + N_2 + N_3$.

Table 1: Study 93-34

	Group A Schering 7-Day 1%	Group C Schering 3-Day 2%	Group B Schering 3-Day 1%
Therapeutic Cure	49/60/0	52/56/1	39/66/5
Clinical Cure	95/13/1	88/16/5	82/21/7
Microbiological Cure	53/56/0	57/51/1	43/62/5
Total evaluable	109	109	110
Total enrolled	137	131	138

Table 2: Study 93-40

	Group A Schering 7-Day 1%	Group C Schering 3-Day 2%	Group B Schering 3-Day 1%
Therapeutic Cure	60/47/1	51/58/1	55/53/7
Clinical Cure	100/6/2	99/7/4	105/7/3
Microbiological Cure	62/45/1	52/57/1	55/52/8
Total evaluable	108	110	115
Total enrolled	131	131	133

Table 3: Studies 93-34 and 93-40

	Group A Schering 7-Day 1%	Group C Schering 3-Day 2%	Group B Schering 3-Day 1%
Therapeutic Cure	109/107/1	103/114/2	94/119/12
Clinical Cure	195/19/3	187/23/9	187/28/10
Microbiological Cure	115/101/1	109/108/2	98/114/13
Total evaluable	217	219	225
Total enrolled	268	262	271

Table 4: Study 95-50

	Group C Schering 7-Day 1%	Group D Taro 3-Day 2%	Group E Taro 1-Day 2%
Therapeutic Cure	47/30/0	48/26/0	43/29/0
Clinical Cure	71/7/0	67/7/0	65/7/0
Microbiological Cure	49/25/0	49/20/0	42/27/0
Total evaluable	77	74	72
Total enrolled	87	90	87

Table 5: Study 97-01

	Taro 3-Day 2%	Schering 3-Day 2%
Therapeutic Cure	43/23/0	42/26/0
Clinical Cure	49/17/0	53/15/0
Microbiological Cure	51/15/0	51/17/0
Total evaluable	66	68
Total enrolled	74	73

Comparisons in cure rates between treatment arms

The primary efficacy comparison is between the 2% 3-Day treatment and the 1% 7-Day treatment (reference), and also between the 2% 3-Day products manufactured by Taro and SPHCP. As secondary analyses, the statistical comparisons between the SPHCP 3-Day 1% and

7-Day 1% products (Studies 93-34 and 93-40), and between the Taro 1-Day 2% and SPHCP 7-Day 1% products (Study 95-50) are given. The confidence intervals given throughout are 95% confidence intervals with Yates' correction.

The cure rates analyzed are the number of patients cured divided by the number of evaluable patients.

Studies 93-34 and 93-40 combined: No evidence was found to suggest that Studies 93-34 and 93-40 could not be combined. The studies had the same design except for the extra arm in the 93-34 study (receiving the 4% product) which was discontinued. The total number of patients enrolled per treatment arm and the fraction of patients evaluable were similar across studies:

Study	Group A (7-day 1%) enrolled/evaluable	Group C (3-Day 2%) enrolled/evaluable	Group B (3-Day 1%) enrolled/evaluable
93-34	137 (80%)	131 (83%)	138 (80%)
93-40	131 (82%)	131 (84%)	133 (86%)

Further, the differences in cure rates between the 3-day 2% product and the 7-day 1% product, and between the 3-day 1% product and the 7-day 1% products, did not differ between the two studies. This was evidenced by lack of a significant (at the 0.1 level) treatment-by-study interaction in logistic regression analyses.

Study	Type of cure	Group A (7-day 1%) cure rates %	Group C (3-Day 2%) cure rates %	Group B (3-Day 1%) cure rates %
93-34	Therapeutic	45.0	47.7	35.5
	Clinical	87.2	80.7	74.6
	Microbiological	48.6	52.3	39.1
93-40	Therapeutic	55.6	46.4	47.8
	Clinical	92.6	90.0	91.3
	Microbiological	57.4	47.3	47.8

Table 6 gives the summary of the comparisons of rates of microbiological, clinical and therapeutic cure. The confidence intervals are not adjusted for testing 2 groups versus one control.

For the **primary comparison** (2% 3-Day vs. 1% 7-Day product), equivalence is seen for therapeutic cure, clinical cure and microbiological cure. However, the cure rate for therapeutic cure for the SPHCP 3-Day 2% product is less than 50%.

For the secondary comparison (1% 3-Day vs. 1% 7-Day product), equivalence is seen for therapeutic cure, clinical cure and microbiological cure. The rates for therapeutic and microbiological cure are less than 50% for the SPHCP 3-Day 1% product.

TABLE 6
Studies 93-34 and 93-40 combined. Analysis of cure rates from Table 3.

Type of Cure	Treatment and Cure (%) Test	Treatment and Cure (%) Control	
	SPHCP 3-Day 2% cream Cure (%)	SPHCP 7-Day 1% cream Cure (%)	95% Confidence Intervals n_t, n_c (95% C.I.) p_t, p_c
Therapeutic Cure	103/219 (47%)	109/217 (50%)	$_{219,217}$(-0.1304,0.0664) $_{47\%,50\%}$
Clinical Cure	187/219 (85%)	195/217 (90%)	$_{219,217}$ (-0.1110,0.0215) $_{85\%,90\%}$
Microbiological Cure	109/219 (50%)	115/217 (53%)	$_{219,217}$ (-0.1306, 0.0661) $_{50\%,53\%}$
	SPHCP 3-Day 1% cream Cure (%)	SPHCP 7-Day 1% cream Cure (%)	95% Confidence Intervals n_t, n_c (95% C.I.) p_t, p_c
Therapeutic Cure	94/225 (42%)	109/217 (50%)	$_{225,217}$ (-0.1817, 0.0126) $_{42\%,50\%}$
Clinical Cure	187/225 (83%)	195/217 (90%)	$_{225,217}$(-0.1354, 0.0003) $_{83\%,90\%}$
Microbiological Cure	98/225 (44%)	115/217 (53%)	$_{225,217}$(-0.1917, 0.0029 $_{44\%,53\%}$

The 95% confidence intervals are given as n_t, n_c (95% C.I.) p_t, p_c, where n_t, n_c are the numbers in the test group and control groups, respectively, and p_t, p_c are the success rates in the test and control groups, respectively.
Rate is number of successes/number of evaluable patients

Study 95-50: Table 7 gives the summary of the comparisons of cure rates as derived by the statistical reviewer. Again, the reported confidence intervals are not adjusted for testing 2 groups versus one control.

TABLE 7
Study 95-50: Analysis of Cure Rates from Table 4

Type of Cure	Treatment and Cure (%) Test	Treatment and Cure (%) Control	
	TARO 3-Day 2% cream Cure (%)	SPHCP 7-Day 1% cream Cure (%)	95% Confidence Intervals n_t, n_c (95% C.I.) p_t, p_c
Therapeutic Cure	46/73 (63%)	40/70 (57%)	$_{73,70}$(-0.1156, 0.2330) $_{63\%,57\%}$
Clinical Cure	61/73 (84%)	59/70 (84%)	$_{73,70}$ (-0.1416, 0.1272) $_{84\%,84\%}$
Microbiological Cure	48/73 (66%)	44/70 (63%)	$_{73,70}$ (-0.1421, 0.2000) $_{66\%,63\%}$
	TARO 1-Day 2% cream Cure (%)	SPHCP 7-Day 1% cream Cure (%)	95% Confidence Intervals n_t, n_c (95% C.I.) p_t, p_c
Therapeutic Cure	40/71 (56%)	40/70 (57%)	$_{71,70}$(-0.1858, 0.1697) $_{56\%,57\%}$
Clinical Cure	62/71 (87%)	59/70 (84%)	$_{71,70}$ (-0.0989, 0.1597) $_{87\%,84\%}$
Microbiological Cure	42/71 (59%)	44/70 (63%)	$_{71,70}$ (-0.2121, 0.1381) $_{59\%,63\%}$

The 95% confidence intervals are given as n_t, n_c (95% C.I.) p_t, p_c, where n_t, n_c are the numbers in the test group and control groups, respectively, and p_t, p_c are the success rates in the test and control groups, respectively.
Rate is number of successes/number of evaluable patients.

For the **primary comparison** (2% 3-Day Taro vs. 1% 7-Day SPHCP product), equivalence is seen for therapeutic, clinical and microbiological cure. All cure rates are greater than 50%.

For the secondary comparison (Taro 2% 1-Day product vs. SPHCP 1% 7-Day product), the rates show equivalence for therapeutic cure and clinical cure, but not for microbiological cure since the lower bound of the confidence interval less than -0.2.

The Sponsor's analysis did not give the same confidence intervals as those reported here since they did not use Yates' correction.

Study 97-01: Table 8 gives the summary of the comparisons of cure rates between the SPHCP and Taro 3-Day 2% products as derived by the statistical reviewer.

TABLE 8
Study 97-01: Analysis of Cure Rates from Table 5

Type of Cure	Treatment and Cure (%)	Treatment and Cure (%)	
	SPHCP 3-Day 2% cream	TARO 3-Day 2% cream	95% Confidence Intervals n_t, n_c (95% C.I.) p_t, p_c
Therapeutic Cure	42/68 (62%)	43/66 (65%)	68,66 (-0.2118, 0.1440) 62%,65%
Clinical Cure	53/68 (78%)	49/66 (74%)	68,66 (-0.1223, 0.1963) 78%,74%
Microbiological Cure	51/68 (75%)	51/66 (77%)	68,66 (-0.1819, 0.1365) 75%,77%

The 95% confidence intervals are given as n_t, n_c (95% C.I.) p_t, p_c, where n_t, n_c are the numbers in the test group and control groups, respectively, and p_t, p_c are the success rates in the test and control groups, respectively.

Equivalence is seen for clinical cure and microbiological cure, but not for therapeutic cure since the lower bound of the confidence interval is less than -0.2. The therapeutic and microbiologic cure rates for the Taro product are greater than those of the SPHCP product. All cure rates are greater than 50%.

The Sponsor's results in the NDA do not agree with those calculated here since Yates' correction was not used. Without Yates' correction, the lower bound of the confidence interval for therapeutic cure is greater than -0.2.

SAFETY EVALUATION

Studies 93-34 and 93-40 combined, and Study 92-11

The Sponsor reported the following adverse events, including those considered related to treatment, for the 3 databases of the original submission. The overall incidence of adverse events was similar across treatment groups in each study.

Study	7-Day 1% SPHCP	3-Day 1% SPHCP	3-Day 2% SPHCP	3-Day 4% SPHCP
	N/n/m	N/n/m	N/n/m	N/n/m
92-11	56 / 6 / 3	52 / 8 / 4	52 / 11 / 4	54 / 4 / 1
93-34	137 / 47 / 12	138 / 54 / 12	131 / 39 / 10	48 / 20 / 6
93-40	131 / 14 / 3	133 / 17 / 0	131 / 18 / 1	0 / 0 / 0

N=total, n = number with adverse events, m = number with adverse events probably or possibly related to treatment.

Somewhat different numbers were derived from tabulations of the data base in the current submission. The overall incidence of adverse events was similar across treatment groups in each study. The most severe adverse events were vulvovaginal burning and itching, which are also symptoms of the condition being treated.

Study	7-Day 1% SPHCP	3-Day 1% SPHCP	3-Day 2% SPHCP	3-Day 4% SPHCP
	N/n/m	N/n/m	N/n/m	N/n/m
92-11	no information	No information	no information	no information
93-34	137 / 50 / 20	138 / 47 / 25	131 / 41 / 12	48 / 22 /10
93-40	131 / 14 / 2	133 / 17 / 0	131 / 18 / 1	0 / 0 / 0

N=total, n = number with adverse events, m = number with adverse events probably or possibly related to treatment.

Tables 9 and 10 list all adverse events with a total occurrence of > 1% for Studies 93-34 and 93-40, respectively. The Medical Officer's report contains a discussion of adverse events possible related to treatment, so that is not done here. No treatment related problems were found.

Table 9. Adverse Event Frequencies: Study 93-34

Group		A		B		C		D	
	ARCD	N	%	N	%	N	%	N	%
Abdominal pain	2	4	2.920	1	0.725	3	2.290	2	4.167
Back pain	93	2	1.460	1	0.725	2	1.527	2	4.167
Bronchitis	131	1	0.730	2	1.449	0	0	0	0
Conjunctivitis	188	0	0	2	1.449	1	0.763	0	0
Diarrhea	235	3	2.190	1	0.725	1	0.763	3	6.250
Dizziness	238	1	0.730	2	1.449	1	0.763	0	0
Dysmenorrhea	250	5	3.650	3	2.174	3	2.290	1	2.083
Dyspepsia	252	1	0.730	1	0.725	1	0.763	0	0
Dysuria	257	2	1.460	0	0	1	0.763	3	6.250
Headache	378	12	8.759	15	10.870	18	13.740	11	22.917
Bacterial Inf	486	3	2.190	2	1.449	0	0	1	2.083
Viral infection	489	3	2.190	2	1.449	2	1.527	0	0
Leukorrhea	538	2	1.460	2	1.449	1	0.763	2	4.167
Menstrual dis.	564	2	1.460	0	0	2	1.527	0	0
Micturition freq.	570	1	0.730	2	1.449	1	0.763	1	2.083
Myalgia	586	2	1.460	2	1.449	2	1.527	1	2.083
Nausea	601	0	0	3	2.174	2	1.527	1	2.083
Pain NS	639	1	0.730	1	0.725	0	0	1	2.083
Pharyngitis	674	1	0.730	2	1.449	2	1.527	1	2.083
Pruritis gen.	709	1	0.730	4	2.899	5	3.817	1	2.083
Rash	729	2	1.460	1	0.725	0	0	0	0
Allergic rhinitis	763	1	0.730	0	0	2	1.527	0	0
Sinusitis	784	1	0.730	0	0	3	2.290	1	2.083
Skin disorder	790	1	0.730	1	0.725	2	1.527	0	0
Tooth disorder	871	0	0	2	1.449	2	1.527	1	2.083
URTI	902	6	4.380	3	2.174	3	2.290	0	0

A: 7-Day 1%, B: 3-Day 1%, C: 3-Day 2%, D: 3-Day 4%

Table 9. Adverse Event Frequencies: Study 93-34, continued

Group		A		B		C		D	
	ARCD	N	%	N	%	N	%	N	%
URI	909	3	2.190	5	3.623	3	2.290	1	2.083
Vag. Hemorrage	923	1	0.730	1	0.725	2	1.527	0	0
Vaginitis	924	14	10.219	12	8.696	9	6.870	1	2.083
Vomiting	946	2	1.460	0	0	0	0	1	2.083
Nasal cong'n	966	2	1.460	2	1.449	2	1.527	0	0
Lab. Test abn.	1298	0	0	1	0.725	2	1.527	2	4.167

A: 7-Day 1%, B: 3-Day 1%, C: 3-Day 2%, D: 3-Day 4%

Table 10. Adverse Event Frequencies: Study 93-40

Group		A		B		C	
	ARCD	N	%	N	%	N	%
Abdom. Pain	2	2	1.527	1	0.752	2	1.527
Cystitis	209	0	0	1	0.752	3	2.290
Dysmenorrhea	250	0	0	2	1.504	1	0.763
Headache	378	1	0.763	3	2.256	1	0.763
Migraine	571	1	0.763	1	0.752	1	0.763
Vomiting	946	0	0	0	0	3	2.290
Burning app.site	1463	2	1.527	0	0	1	0.763

A: 7-Day 1%, B: 3-Day 1%, C: 3-Day 2%,

Study 95-50

A database of adverse events was not provided. The Sponsor reported the following: There were 15 patients who reported adverse events in the 5 treatment groups. Six of these were possibly or probably related to study treatment: 5 treated with the vaginal tablet or the oral medication, and 1 with vaginal cream (Taro 1-Day 2% cream). Of the 9 patients with adverse events considered unrelated to study treatment, the numbers treated with vaginal cream were 3, 2, 1 with the SPHCP 7-Day 1%, Taro 3-Day 2%, and Taro 1-Day 2% creams, respectively. The adverse event rates were not significantly different among treatment groups.

Study 97-01.

A database of adverse events was not provided. The Sponsor reported the following: One patient was reported to have an adverse event that was considered remotely related to treatment: patient 805 (receiving Taro product) experienced an episode of heavy bleeding. The Sponsor reported that no serious drug-related events occurred, and, moreover, that no patient discontinued drug due to an adverse event. A review of the data showed that patient 1409

experienced a heart attack, which was not mentioned by the Sponsor. This patient was excluded after enrollment due to an "intercurrent illness" .

DISCUSSION

Consideration of multiple comparisons.

Studies 93-34, 93-40 and 95-50 were multiple arm studies: 3 (initially 4), 3, and 5 arms, respectively. For each study, in this review, 95% confidence intervals were calculated for 2 comparisons, both versus the same control. One of these in each case is considered primary and to be used for labelling, namely the 3-Day 2% cream (either SPHCP or Taro) versus the 7-Day 1% SPHCP cream. The question might be raised as to whether the confidence intervals should be adjusted (broadened) to take into account the fact that two comparisons were carried out versus the same control, and even the fact that there were 4 possible comparisons against the control in the 95-50 study. There is no textbook answer. At issue is the exact hypothesis(es) to be tested as specified at the study design stage, and the exact hypothesis(es) to be tested for this current evaluation of the NDA, and whether these can be different, as has happened. The original intentions apparently were of a multiple null hypothesis, although no mention of adjustment of the significance level has been found in the documents, whereas the current intentions are to focus on the primary comparison for efficacy, still using the whole data base for safety evaluation. This reviewer's choice is not to adjust for the multiple testing, since no specific claims are being made in this NDA for the secondary treatments, namely the 3-Day 1% SPHCP product or the 1-Day 2% Taro product. Also note that no attempt has been made to adjust for the fact that an interim look was made at the 93-34 data at which point the decision was made to discontinue recruitment to the 4% treatment arm, and not consider data from this arm in decisions as to efficacy.

For completeness, however, Bonferroni adjustment for 2 comparisons versus a single control did not change the conclusions for the primary comparison for the pooled 93-34 and 93-40 studies, or for the 95-50 study.

CONCLUSIONS

With respect to efficacy, the Sponsor found mycological, clinical and therapeutic equivalence between:

(i) the 3-Day 2% SPHPC and 7-Day 1% SPHCP therapies (Studies 93-34 and 93-40 combined).
(ii) the 3-Day 2% Taro and 7-Day 1% SPHCP therapies (Study 95-50).
(iii) the 3-Day 2% Taro and 3-Day 2% SPHCP therapies (Study 97-01).

In addition, the safety profiles were similar among treatments, and there are no safety issues due to the products.

The overall conclusions from the statistical review are as follows:

(i) The SPHCP 3-Day 2% and 7-Day 1% products are equivalent for Studies 93-34 and 93-40 combined, with respect to therapeutic, clinical and microbiologic cure. Note that the therapeutic cure rate was 47% for the SPHCP 3-Day 2% treatment.
(ii) The SPHCP 7-Day 1% and Taro 3-Day 2% products are equivalent in Study 95-50 with respect to therapeutic, clinical and microbiologic cure.
(iii) The SPHCP 3-Day 2% and Taro 3-Day 2% products are equivalent in Study 97-01 with respect to clinical and microbiologic cure, but the 95% confidence interval is (-0.2118, 0.1440) for therapeutic cure (rates 62% and 65% for the SPHCP and Taro products, respectively) indicating lack of equivalence.

The differences in confidence intervals with the Sponsor's findings for Studies 95-50 and 97-01 are due to the omission of the Yates correction, which was employed for this review.

There appear to be no safety problems with the products, nor differences in adverse event profiles between treatment groups.

/S/

Stella G. Machado, Ph.D.
Biostatistician, OB/QMR Staff

/S/

10/26/98

Concur: Aloka Chakravarty, Ph.D.
Biomedical Statistician, DOB III

APPENDIX TABLES

Cure rates for Studies 93-34, 93-40, 93-34 and 93-40 combined, 95-50 and CTZ97-01 as provided by the Sponsor.

Table A1: Study 93-34

	Group A Schering 7-Day 1%	Group C Schering 3-Day 2%	Group B Schering 3-Day 1%
Therapeutic Cure	46/41/17	48/34/21	39/41/23
Clinical Cure	74/13/17	68/14/21	60/20/23
Microbiological Cure	50/27/17	53/29/21	43/37/23
Total evaluable	104	103	103
Total enrolled	137	131	138

Table A2: Study 93-40

	Group A Schering 7-Day 1%	Group C Schering 3-Day 2%	Group B Schering 3-Day 1%
Therapeutic Cure	54/23/23	49/29/27	55/25/27
Clinical Cure	71/6/23	71/7/27	74/6/27
Microbiological Cure	56/21/23	50/28/27	55/25/27
Total evaluable	100	105	107
Total enrolled	131	131	133

Table A3: Studies 9334 and 9340 combined

	Group A Schering 7-Day 1%	Group C Schering 3-Day 2%	Group B Schering 1-Day 2%
Therapeutic Cure	100/64/40	97/63/48	94/66/50
Clinical Cure	145/19/40	139/21/48	134/26/50
Microbiological Cure	106/58/40	103/57/48	98/62/50
Total evaluable	204	208	210
Total enrolled	268	262	271

Table A4: Study 95-50

	Group C Schering 7-Day 1%	Group D Taro 3-Day 2%	Group E Taro 1-Day 2%
Therapeutic Cure	41/29/0	44/28/1	39/32/0
Clinical Cure	57/13/0	57/16/0	59/12/0
Microbiological Cure	44/26/0	48/24/1	42/29/0
Total evaluable	70	73	71
Total enrolled	87	90	87

Table A5: Study 97-01

	Taro 3-Day 2%	Schering 3-Day 2%
Therapeutic Cure	43/23/0	42/26/0
Clinical Cure	51/15/0	53/15/0
Microbiological Cure	51/15/0	51/17/0
Total evaluable	66	68
Total enrolled	74	73