CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050680/S002

STATISTICAL REVIEW(S)

FEB 2 4 1998

Statistical Review and Evaluation

NDA #:	50-680/S-002 Amendment 5
Applicant:	Pharmacia & Upjohn 7000 Portage Road Kalamazoo, MI 49001-0199
Name of Drug:	Cleocin® 3 Vaginal Cream (clindamycin phosphate 2%)
Documents Reviewed:	Technical Report and supporting appendices (Volumes 22.1-22.8) dated August 28, 1997
Type of Report:	Statistical Review
Indication:	Treatment of bacterial vaginosis
Medical Reviewer:	Dr. Joe Winfield (HFD-590)

I. Introduction

The purpose of this submission is to amend NDA 50-680 Supplement 002 in response to a not-approvable letter dated May 7, 1996. This submission is a controlled clinical trial conducted in Europe in patients with bacterial vaginosis (BV) treated with either a 7-day or a 3-day regimen of Cleocin® vaginal cream (Protocol M/115/0048).

The objectives of the original protocol were to compare the safety and efficacy of a 3-day course of once daily clindamycin vaginal cream (CVC) versus a 7-day course in the prevention of recurrence of BV after its successful treatment, and to obtain information about the frequency of recurrence of BV over a longer period of follow-up. However, according to the sponsor, the data collected also supports the objective of determining if a 3-day regimen of clindamycin vaginal cream given once daily is therapeutically equivalent to a 7-day regimen in the treatment of BV. This is the primary objective of the analyses carried out for this submission.

This Phase IV trial was a double-blind, multicenter, prospective, randomized study. Patients with a clinical diagnosis of BV were randomized within each center to treatment with clindamycin vaginal cream for either 3 or 7 days. Thirty-six centers from 16 countries were used to enroll a total of 581 subjects. The duration of the study was 3 months. Subjects were evaluated at baseline, 10 day follow-up, 30 day follow-up, and 90 day follow-up. Clinical efficacy was to be evaluated at the day 10 follow-up visit, while the incidence of recurrence of BV was to be evaluated at the day 30 and 90 follow-up visits.

Reviewer's Comment: The sample size determined for this study was based on the rate of recurrent BV (at the Day 30 follow-up visit) present in the two study populations. Assuming a rate of 27% for recurrent BV, an alpha level of 0.05, power of 0.90, and a minimum clinically significant difference of 15%, 156 patients per treatment were necessary. To allow for dropouts, a total of 500 patients were to be enrolled. Based on 200 patients per treatment and assuming cure rates from the power to conclude equivalence within ±20% and ±10%, respectively, is >90%. Thus, the sample size is adequate to determine equivalence of the two treatment groups based on cure rates.

The clinical diagnostic criteria for BV as described in the protocol were:
- an increased, thin, homogenous, malodorous vaginal discharge
- vaginal fluid of pH > 4.5
- fishy amine odor after adding 10% KOH solution to vaginal fluid
- clue cells in vaginal fluid on microscopic examination.

Patients were to be evaluated for efficacy using the following outcome criteria:

Cured- all 4 diagnostic criteria resolved

Improved- only 3 of the 4 diagnostic criteria resolved

Failure- only 2 or fewer diagnostic criteria resolved.

Patients who attended the day 10 visit but did not complete the course of medication due to an adverse event related to study medication were considered *side effect failures*. An overall outcome rating was to be determined based on the criteria in Table 1.

Table 1
Criteria for Evaluation of Overall Outcome Rating

Day 10		Day 30		Day 90 Response	Overall outcome
Response	Action	Response	Action		
cured	continue	cured	continue	cured	cured
improved	continue	improved	continue	improved	improved
				failure (recurrence)	recurrence
				cured/improved but history of BV after Day 30	recurrence
		failure (recurrence)	STOP	patient out of trial	recurrence
failure	STOP	patient out of trial			failure

In addition to the above efficacy evaluations, the FDA recommended that efficacy data be analyzed using tests for vaginal fluid odor and clue cells as the only criteria for evaluation of clinical status. A cure was defined as the resolution of both amine odor and clue cells and any other result was considered a failure. Status was assigned as non-assessable if insufficient data were available to determine cure or failure. An overall outcome rating of cure, failure, or non-assessable was determined as defined in Table 2.

Table 2
Criteria for Evaluation of Overall Outcome Rating
Based on FDA Recommended Efficacy Criteria

Day 10	Day 30	Overall Outcome
Cure	Cure Failure Non-assessable	Cure Failure Non-assessable
Failure (including side-effect failure)	Any status	Failure
Non-assessable	Cure Failure Non-assessable	Non-assessable Failure Non-assessable

The results of the FDA requested analyses are affected by the fact that visit attendance was based on the four protocol-specified criteria. Thus, patients who would be considered cured based on the FDA criteria but were assessed as failed under the original criteria were not required to return for the next follow-up visit, and patients who were improved according to the protocol-specified criteria, and so attended the next follow-up visit, could be failures according to the FDA criteria.

The medical reviewer defined clinical response in two additional ways. The first defines a clinical cure as no clue cells, no odor, and pH < 4.7. The second definition ignores pH and defines a clinical cure as no clue cells and no odor. This definition differs slightly than the sponsor definition including the clue cell and odor only in that failures at day 10 were carried forward to day 30.

II. Efficacy Evaluation

For this review, the primary efficacy variable is clinical response at day 30. For completeness, the sponsor's overall outcome will also be presented. The modified intent-to-treat population consists of all patients who had a recorded dosing start date or a completed Day 10 follow-up visit ME profile. Patients were included in the evaluable population if they attended the Day 10 visit and the Day 30 visit was at least 14 days following the Day 10 visit, had not menstruated at the follow-up visit, had not received other antibiotics prior to the assessment, and had not douched during protocol therapy or within 2 days prior to the follow-up visit.

- Patient Demographics

Five hundred eighty-one patients were enrolled in the study. The modified intent-to-treat population consisted of 534 patients, 261 patients randomized to the CVC 3-day treatment group and 273 patients randomized to the CVC 7-day treatment group. The following table contains the demographic characteristics by treatment group for the patients included in the MITT population. As can be seen from Table 3, distributions of these variables are similar across the two treatment groups (p>.62). The descriptive

variable, race, is evaluated using Fisher's Exact test based on white, black and all other races. Age is evaluated using a one-way ANOVA.

Table 3
Patient Demographics

	CVC 3-day	CVC 7-day	P-value
# Patients	261	273	
Age mean (sd) min, max	34.7 (9.4)	35.1 (10.2)	0.6253
Race (N)			0.8276
White	226	240	
Black	28	26	
Oriental/Asian	5	2	
Other	2	4	
Not Allowed to Ask	0	1	

- Analysis Results

Table 4 summarizes clinical response based on four diagnostic criteria at Day 30 for evaluable patients carrying forward failures at Day 10. Also included in the table is the 95% confidence interval about the difference between treatments in the percentage of cured/improved response rates. This confidence interval is the reverse of what the sponsor reported because the sponsor calculated the difference as standard treatment minus test treatment rather than test treatment minus standard treatment. Since the lower limit of the confidence interval lies within the lower bound of -20%, the cured/improved rates are therapeutically equivalent between treatment groups. A total of 83.2% of patients in the CVC 3-day group were cured or improved compared to 87.2% of patients in the CVC 7-day group.

Table 4
Clinical Response at Day 30 for Evaluable Patients
Based on Four Diagnostic Criteria

Outcome at Day 30	CVC 3-Day (N=202)	CVC 7-Day (N=218)	95% CI (3-day minus 7-day)
Cured	136 (67.3%)	145 (66.5%)	(-11.3%, 3.3%)
Improved	32 (15.8%)	45 (20.6%)	
Failed at Day 10	20 (9.9%)	16 (7.3%)	
Side-effect failure at Day 10	1 (0.5%)	0	
Failed (Recurred)	13 (6.4%)	12 (5.5%)	

A summary of the clinical response based on four diagnostic criteria at Day30 for MITT patients carrying forward failures at Day 10 is presented in Table 5. For this population, 84.9% of the patients in the CVC 3-day group and 88.3% of the patients in the CVC 7-day group were cured or improved. Even though the cure/improved rate for the CVC 7-day group was higher than the CVC 3-day group, these rates are therapeutically equivalent as seen from the 95% confidence interval.

Table 5
Clinical Response at Day 30 for MITT Patients
Based on Four Diagnostic Criteria

Outcome at Day 30	CVC 3-Day (N=225)	CVC 7-Day (N=240)	95% CI (3-day minus 7-day)
Cured	152 (67.6%)	161 (67.1%)	(-10.0%, 3.2%)
Improved	39 (17.3%)	51 (21.2%)	
Failed at Day 10	20 (8.9%)	16 (6.7%)	
Side-effect failure at Day 10	1 (0.4%)	0	
Failed (Recurred)	13 (5.8%)	12 (5.0%)	

Overall clinical outcome based on four diagnostic criteria for evaluable patients is summarized in Table 6. A total of 74.6% of the patients in the CVC 3-day groups were cured or improved compared to 75.4% of the patients in the CVC 7-day group. The treatments are therapeutically equivalent as seen from the 95% confidence interval for the difference between treatments in the percentage of cured/improved response rates. This analysis excluded non-assessable patients.

Table 6
Overall Clinical Outcome for Evaluable Patients
Based on Four Diagnostic Criteria

Overall Outcome	CVC 3-Day (N=193)	CVC 7-Day (N=207)	95% CI (3-day minus 7-day)
Cured	123 (63.7%)	127 (61.4%)	(-9.8%, 8.2%)
Improved	21 (10.9%)	29 (14.0%)	
Recurred	28 (14.5%)	35 (16.9%)	
Failed	20 (10.4%0	16 (7.7%)	
Side-effect failure	1 (0.5%)	0	
Non-Assessable	15	12 (5.0%)	

Tables 7 and 8 include summaries of clinical response for evaluable patients based on amine odor and clue cells only for Day 30 and overall, respectively. Based on the 95% confidence intervals, the cure rates for the two treatment groups are therapeutically equivalent.

Table 7
Clinical Response at Day 30 for Evaluable Patients
Based on Amine Odor and Clue Cells Only

Outcome at Day 30	CVC 3-Day (N=182)	CVC 7-Day (N=202)	95% CI (3-day minus 7-day)
Cured	161 (88.5%)	181 (89.6%)	(-7.9%, 5.7%)
Failed	21 (11.5%)	21 (10.4%)	

Table 8
Overall Clinical Response for Evaluable Patients
Based on Amine Odor and Clue Cells Only

Outcome at Day 30	CVC 3-Day (N=199)	CVC 7-Day (N=216)	95% CI (3-day minus 7-day)
Cured	161 (80.9%)	181 (83.8%)	(-9.7%, 6.9%)
Failed	37 (18.6%)	35 (16.2%)	
Side-effect failure	1 (0.5%)	0	
Non-assessable	14	19	

The medical reviewer defined 219 patients in the CVC 3-day group to be evaluable for efficacy and 230 patients in the CVC 7-day group to be evaluable. The following table includes the cures rates for each treatment group as determined by no presence of clue cells and odor regardless of pH level. The cure rates are also determined by no presence of clue cells and odor and a pH level less than 4.7. Also included in the table are weighted 95% confidence intervals about the difference of the cure rates for the two treatment groups (CVC 3-day minus CVC 7-day). The weighted confidence intervals (Cochran -Mantel-Haenszel) adjust for variation among investigators. Since the lower limit of the confidence intervals lies within the lower bound of -20.0%, the cure rates are therapeutically equivalent between treatment groups.

Table 9
Cure Rates at Day 30 (MO Defined)

Criteria to Determine Cure	CVC 3-Day	CVC 7-Day	Weighted 95% CI (3-day minus 7-day)
Clue and odor only	189/219 (86.3%)	203/230 (88.3%)	(-8.6%, 4.6%)
pH, clue, and odor	162/219 (74.0%)	168/230 (73.0%)	(-7.6%, 9.6%)

It was noted by the medical reviewer that certain investigators had 100% evaluability and cure rates using the MO defined cure. This holds for both the 3-day and 7-day treatment groups for a majority of these investigators. An analysis was performed removing the subjects from investigators whose influence on the cure rates may be the largest. The results of this analysis (not shown) lead to slightly wider confidence intervals but the lower bound still lies within the -20.0% limit to claim equivalence.

Reviewer's Comment: The 3-day duration of treatment with CVC has been shown to be therapeutically equivalent to the 7-day treatment with CVC regardless of the definition of a clinical cure. Since there is some concern about the high cure rates for individual investigators, it may be prudent to point this out in the 'clinical trials' section of the label, if deemed informative to physicians.

III. Safety Evaluation

Medical event (ME) data are summarized in Table 10. Of the 534 patients who received CVC, 169 (31.6%) reported a total of 243 medical events. The 3-day treatment group reported slightly more drug-related ME's than the 7-day treatment group and the two severe drug-related ME's reported were experienced by patients treated with CVC for 3 days.

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Table 10
Medical Event Summary

	CVC 3-Day (N=261)	CVC 7-Day (N=273)
Patients (%) with ME's		
All ME's	80 (30.7%)	89 (32.6%)
Drug-related ME's	27 (10.3%)	18 (6.6%)
Total # ME's Reported		
All ME's	119	124
Drug-related ME's	28	20
Dropouts Due to ME	10	5

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The most common ME's reported were vaginal moniliasis, moniliasis, vulvovaginal disorder, and bacterial vaginosis. The most frequent drug-related ME's were those affecting the urogenital system. Six patients in the 3-day group and 2 patients in the 7-day group dropped out of the study due to a drug-related ME. None of the ME's that led to patient dropouts were serious.

Table 11 summarizes the ME's reported in 1% or more of patients in either treatment group.

Table 11
Medical Events Reported by ≥ 1% of Patients

Body System	Event	CVC 3-Day (N=261)	CVC 7-Day (N=273)
Body	Generalized abdominal pain	4 (1.5%)	1 (0.4%)
	Flu syndrome	5 (1.9%)	2 (0.7%)
	Headache	5 (1.9%)	1 (0.4%)
	Abnormal microbiological test	2 (0.8%)	5 (1.8%)
	Moniliasis	8 (3.1%)	13 (4.8%)
	Trauma	5 (1.9%)	0
	Upper respiratory infection	3 (1.1%)	0
Digestive	Diarrhea	2 (0.8%)	3 (1.1%)
Respiratory	Pharyngitis	3 (1.1%)	1 (0.4%)
Urogenital	Bacterial vaginosis	7 (2.7%)	8 (2.9%)
	Cystitis	3 (1.1%)	1 (0.4%)
	Vulvovaginal disorder	10 (3.8%)	10 (3.7%)
	Urinary tract infection	5 (1.9%)	6 (2.2%)
	Menopause	0	3 (1.1%)
	Metrorrhagia	1 (0.4%)	3 (1.1%)
	Vaginal moniliasis	18 (6.9%)	24 (8.8%)
	Unintended pregnancy	3 (1.1%)	1 (0.4%)
	Vaginitis/vaginal infection	3 (1.1%)	2 (0.7%)

Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

1. *Using a definition of clinical cure based on all four diagnostic criteria or based on amine odor and clue cells including or excluding pH level, clindamycin vaginal cream 2% administered for 3 days has been shown to be therapeutically equivalent to clindamycin vaginal cream 2% administered for 7 days.*

2. *Both clindamycin vaginal cream regimens appear to be safe. There are no significant differences in the incidence of medical events between the two treatment regimens, although drug-related medical events were reported slightly more among the patients treated for 3 days.*

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This review contains 8 pages.

STATISTICAL REVIEW AND EVALUATION

NOV 30 1995

NDA#:	50-680/S-002
Applicant:	The Upjohn Company
Name of Drug:	CLEOCIN® vaginal cream (clindamycin phosphate 2%)
Drug Class:	3-S
Indication(s):	Bacterial vaginosis.
Type of Review:	Clinical.
Documents Reviewed:	Volumes 1.23 though 1.38, stamp dated May 8, 1995; Amendment #3, stamp dated June 30, 1995; Amendment #4, stamp dated July 10, 1995.
Medical Officer:	Dr. Joseph Winfield, HFD-520

I. INTRODUCTION

Bacterial vaginosis (BV) is a common disease, accounting for approximately 40% of all cases of vaginal infection in women. Clinically, it is characterized by the presence of vaginal discharge that (1) is thin, homogeneous, and malodorous, (2) gives off a fishy-amine odor when mixed with 10% potassium hydroxide (KOH), (3) has pH>4.5, and (4) contains clue cells on microscopic examination. The current approved regimen for treating bacterial vaginosis with CLEOCIN®, or 2% clindamycin vaginal cream (CVC), is 5 g (containing approximately 100 mg of clindamycin phosphate) intravaginally once daily, preferably at bedtime, for 7 days. The aim of the current submission is to show that the above treatment regimen may be shortened to 3 days. The sponsor contends that the shortened treatment regimen will improve compliance and perhaps reduce the risk of side effects, while maintaining the same level of efficacy. To support these claims, data from three studies are discussed. The two pivotal studies, protocols M/1115/0027 and M/1115/0020 (referred to hereafter as studies 0027 and 0020, respectively), are both multi-center, randomized, controlled, Phase III clinical trials. Study 0020 compares 3 day treatment with CVC to 7 day treatment with CVC, while study 0027 compares 3 day treatment with CVC to placebo (vehicle). The third study, protocol M/1115/0021 (referred to hereafter as study 0021), is a single-center, randomized, controlled, clinical Phase II/III pilot study which compared 3 day treatment with CVC to placebo. All three studies are discussed in Section II, and then conclusions which may be conveyed to the sponsor are given in Section III.

Note: This reviewer's comments and analyses may be found either under the "Comments" section of each study review or throughout the main text in italics.

II. EVALUATION

A. Pivotal Study 0020

Methods

This was a multicenter (10 investigators; 9 in the U.S., 1 in Canada), randomized, controlled, observer-blinded comparison of 3 versus 7 day treatment of bacterial vaginosis with 2% CVC.

Women aged 16 to 60 were included in the study if they had a clinical diagnosis of BV (vaginal discharge with pH>4.5, clue cells, and an amine odor after adding 10% KOH to vaginal discharge), and a gram stain of vaginal fluid smear consistent with a diagnosis of BV (significant reduction in the number of normally occurring *Lactobacillus* morphotypes concurrent with an increase in the *Gardnerella vaginalis/Bacteroides* and *Mobiluncus* morphotypes). Some of the reasons for exclusion from the study were: pregnant or breast-feeding; allergy to clindamycin; systemic or vaginal antimicrobial therapy in the 2-week period before the study; history of antibiotic-associated colitis or of frequent periodic diarrhea; use of non-protocol antibiotics; positive culture for *N gonorrhea*; positive KOH smear for *C albicans*; positive wet mount or culture for *T vaginalis*; positive rapid diagnostic test or culture for *C trachomatis*; clinical evidence of active genital herpes viral infection; atrophic vaginitis; anticipated menstruation during the treatment period or at follow-up visit; or unwilling to stop douching during therapy.

At visit 1, patients were randomized (in blocks of six within center) to receive once daily doses of 5 grams of 2% CVC intravaginally at bedtime, for either 3 or 7 consecutive days. Compliance with taking study medication was checked by the use of patient diaries and by inquiring about dates of treatment. Visit 2, the only follow-up visit, was scheduled for 21-35 days after the completion of treatment. This evaluation included a pelvic examination; description of vaginal fluid and tests for pH, odor, and clue cells; gram stain of vaginal fluid; and patient evaluation of efficacy (cure, improved, failure). If signs or symptoms of vulvovaginitis were present at follow-up, tests or cultures for *C. albicans* and *T. vaginalis* were performed.

The primary efficacy parameter at visit 2, the follow-up visit, was clinical response. Patients were categorized as follows: (1) **clinical cure** -- a return to normal of all 3 diagnostic criteria (i.e., vaginal fluid pH≤4.5, absence of clue cells, and no odor using the KOH test); (2) **improvement** -- a return to normal of 2 of the 3 diagnostic criteria; (3) **(clinical) failure** -- a return to normal of 1 or none of the diagnostic criteria; or (4) **side effect failure** -- the patient was unable to complete therapy due to drug-related adverse medical events. Secondary efficacy parameters were gram stain outcome (success, improvement, failure) and patient's evaluation of efficacy (cured, improved, failure). Safety evaluations included collection of medical event data and determination of the incidence of post-treatment vaginitis.

Reviewer's Comments: The definition of clinical response in this study varies from that given in studies 0027 and 0021, where patients who present with clue cells are considered

failures regardless of their outcome on the other two variables, pH and odor. In addition, in studies 0027 and 0021, gram stain outcome and presence/absence of vaginal discharge are included in the definition of clinical response. This is discussed in the Comments section below, and some analyses are presented which are more consistent with those performed in studies 0027 and 0021.

All subjects who received study medication were included in the safety analyses and the intent-to-treat (ITT) analysis of the primary efficacy variable. In addition, per-protocol analysis was used to examine the primary efficacy variable, as well as the secondary efficacy variables. Patients were evaluable for the per-protocol analyses if they met the following criteria: met all inclusion and exclusion criteria at study entrance; received 3-4 days (3-day regimen) or 6-9 days (7-day regimen) of treatment; had no menses during protocol therapy or at the follow-up visit; had no additional systemic or vaginal antimicrobial therapy during the study (unless the subject was a clinical or side effect failure); returned for visit 2 (except for clinical or side effect failures); no douching during treatment or within 2 days of visit 2; started protocol therapy within 14 days after study eligibility tests were done; and had no other reason for which the investigator and study monitor would consider the patient nonevaluable. Patients who developed a genital infection other than BV during the study were considered evaluable if the diagnostic criteria for BV were not compromised by the concomitant infection and if treatment for the concomitant infection was not begun before the follow-up evaluation.

All statistical tests were two-sided, and declared significant if $p \leq 0.05$, or marginally significant if $0.05 < p \leq 0.10$. Clinical response at follow-up was treated as continuous (cure = 1, improved = 2, failure = 3) and analyzed using analysis of variance to test for investigator-by-treatment interaction. In the absence of a qualitative interaction, Fisher's exact test was used to test for treatment effect. Fisher's exact test was also used to test for a difference between treatment groups in cure rate, presence of amine odor, presence of clue cells, vaginal pH (≤ 4.5, > 4.5), and any other categorical variables. Other continuous variables were analyzed using one-way ANOVA to investigate treatment effect.

Reviewer's Comments: Since the sample size is not small, there is no reason to use Fisher's exact test when analyzing categorical variables in this study. In my analysis of categorical study variables presented in the Comments section below, I will use Pearson's chi-square test to test for general differences between the treatment groups. In addition, for ordinal categorical variables such as clinical response (where the outcomes, cure, improved, and failure, are ordered), I will use the Mantel-Haenszel test to test for monotonicity (i.e., does a patient tend to score "higher" on one treatment group than another?).

Results

Four hundred and eleven patients were enrolled in the study by 10 investigators, 207 on the 3-day and 204 on the 7-day treatment regimen. Enrollment at the different centers varied from 14 to 98 patients. Of the 411 patients enrolled, 409 received at least one dose of study medication and are included in the safety and ITT analyses (2 patients in the 3-day group received no study drug). There were 259 subjects evaluable for the per-protocol analyses, 131 (63%) in the 3-day group and 128 (63%) in the 7-day group. Of

the 150 patients who were not evaluable, 16 needed additional antibiotic therapy (8 in each treatment group), 26 were noncompliant with the dosing regimen (11, or 5.4%, in the 3-day and 15, or 7.4%, in the 7-day group), 33 had a follow-up visit that was not 21-35 days post-therapy (16 in the 3-day and 17 in the 7-day group), 62 had protocol violations (did not have clinical BV, gram stain not compatible with BV, tested positive for *C. trachomatis* or *N. gonorrhea*, were not between the ages of 16 and 60, douched during study, or had menses during study), 5 were lost to follow up (3 in the 3-day group and 2 in the 7-day group), and 8 left for "other" reasons (1 in the 3-day group and 7 in the 7-day group).

Both treatment groups were similar at baseline with regard to demographics, sexual history, and pelvic/vaginal infection history. Patients ranged in age from 17 to 58 years. Approximately 56% were white, 33% black. The average weight was 145 pounds. No relevant difference between the two groups was found in medical history.

The table below summarizes clinical response at visit 2 (the primary efficacy variable) for the evaluable patient population. Using ANOVA, no significant differences were found in clinical response by treatment, investigator, or treatment-by-investigator interaction (p-values of 0.35, 0.31, and 0.71, respectively). Thus, Fisher's exact test is used to test for treatment differences. The difference in the distribution of outcomes was marginally statistically significant (p = 0.068).

CLINICAL RESPONSE -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Cure	77 (58.8)	80 (62.5)
Improvement	29 (22.1)	36 (28.1)
Failure	25 (19.1)	12 (9.4)

Reviewer's Comments: Using the Pearson chi-square test to examine general differences between 3- and 7-day treatment, a p-value of 0.069 is obtained, suggesting that there is a marginal difference between the two groups. This difference is not monotone, however, as suggested by the p-value = 0.14, obtained using the Mantel-Haenszel test. These results are explained by examining the individual rates of cure, improvement, and failure. Cure rates for the two regimens are comparable (p = 0.54; 95% confidence interval for the proportion cured on 3-day minus the proportion cured on 7-day of [-0.16, 0.09]), as are the rates of improvement (p = 0.26; 95% confidence interval of [-0.17, 0.05]). However, the 3-day treatment group has a statistically higher failure rate than the 7-day group (p = 0.02; 95% confidence interval for the proportion of failures on 3-day minus the proportion of failures on 7-day of [0.01, 0.19]).

There was no significant difference between treatment groups in the number of patients with normal pH (p = 1.0) or absence of amine odor at follow-up (p = 0.32); however, there was a statistically significant difference in the number of patients with clue cells in the vaginal fluid (p = 0.004). Clue cells were absent in only 74% of the patients treated for 3

days, compared with 88% of patients treated for 7 days.

There were no differences between treatment groups for either of the secondary efficacy variables, vaginal fluid gram stain outcome at follow-up and patient evaluation of efficacy ($p=0.20$ and $p=0.27$, respectively).

When the clinical response of all patients is considered, there is a higher percentage of failures in both treatment groups as the table below shows. In this population, there is no difference in outcome by treatment ($p=0.61$, using Fisher's exact test). The 95% confidence interval for the proportion cured on 3-day minus the proportion cured on 7-day is (-0.12, 0.08), suggesting no difference. The analysis of variance of clinical response found no significant treatment or treatment-by-investigator effect ($p=0.50$ and $p=0.30$, respectively). There was a significant investigator effect ($p=0.01$), however, since the ANOVA was to be used only to test for an interaction this finding is not pursued by the sponsor.

Reviewer's Comments: In my analysis, I used the Cochran-Mantel-Haenszel procedure to test for treatment differences in clinical outcome, while controlling for investigator differences. Using this approach, there was still no significant treatment difference ($p=0.210$).

CLINICAL RESPONSE -- ALL PATIENTS

OUTCOME	3-DAY (N=205) n (%)	7-DAY (N=204) n (%)
Cure	100 (48.8)	103 (50.5)
Improvement	41 (20.0)	46 (22.5)
Failure*	64 (31.2)	55 (27.0)

*Failures include patients who were lost to follow-up or who took additional antibiotics.

Since this drug applies only to women, and was tested on a fairly homogeneous group of patients with respect to age (17-58 years old), the only subgroup variable which is examined for treatment differences is race. In the evaluable patient group, blacks appear to have a larger difference in the number of failures on 3- versus 7-day treatment compared to whites and others (a higher and lower number of failures on 3- and 7-day treatment compared to the other races, respectively). There is no obvious explanation for this difference. Since it is not duplicated in either the intent-to-treat population in this study, or in the two placebo-controlled studies (in these, no difference is found across races in response to treatment with 3 day CVC and placebo), it is probably just an artifact of multiple comparisons. The reviewing medical officer concurs with this assessment. Results for this study are given below by race for both patient groups, evaluable and intent-to-treat (i.e., all).

CLINICAL RESPONSE BY RACE -- EVALUABLE PATIENTS

		3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)	p-value'
White	Cure	42 (59.2)	49 (65.3)	0.57
	Improvement	16 (22.5)	17 (22.7)	
	Failure	13 (18.3)	9 (12.0)	
Black	Cure	23 (52.3)	24 (58.5)	0.052
	Improvement	11 (25.0)	15 (36.6)	
	Failure	10 (22.7)	2 (4.9)	
Other	Cure	12 (75.0)	7 (58.3)	0.50
	Improvement	2 (12.5)	4 (33.3)	
	Failure	2 (12.5)	1 (8.3)	

' Based on Fisher's exact test.

CLINICAL RESPONSE BY RACE -- ALL PATIENTS

		3-DAY (N = 205) n (%)	7-DAY (N = 204) n (%)	p-value'
White	Cure	59 (51.8)	62 (55.4)	0.80
	Improvement	21 (18.4)	21 (18.8)	
	Failure*	34 (29.8)	29 (25.9)	
Black	Cure	29 (39.7)	33 (47.8)	0.21
	Improvement	17 (23.3)	20 (29.0)	
	Failure*	27 (37.0)	16 (23.2)	
Other	Cure	12 (66.7)	8 (34.8)	0.11
	Improvement	3 (16.7)	5 (21.7)	
	Failure*	3 (16.7)	10 (43.5)	

*Failures include patients who were lost to follow-up or who took additional antibiotics.
' Based on Fisher's exact test.

Medical event (ME) data are summarized in the following table. Of the 409 patients who received CVC, 117 (29%) reported a total of 163 medical events. Note that, as expected, there are fewer drug-related ME's in the 3-day treatment group.

MEDICAL EVENT SUMMARY

	3-DAY (N = 205)	7-DAY (N = 204)
Patients (%) with ME's All ME's Drug-related ME's	 58 (28.3) 35 (17.1)	 59 (28.9) 46 (22.5)
Total # of ME reports All ME's Drug-related ME's	 78 40	 85 58
Patients w/ serious ME's	0	1
Patient dropouts due to ME	2	3
Deaths	0	0

The most frequently reported drug-related ME in both treatment groups was vaginitis. The serious ME reported in the 7-day group was strep throat, for which the patient was hospitalized (and dropped from the study) 16 days after treatment was completed. This was assumed to be unrelated to study medication. Of the two patients who dropped out due to ME's in the 3-day group, one had abdominal cramping (judged unrelated to study drug as it began 2 days prior to beginning treatment) and one developed yeast vaginitis (judged related to study drug; this patient's BV was cured). Of the two other 7-day patients who dropped out due to ME's, one developed a urinary tract infection 15 days after completing therapy (judged unrelated to study drug) and one developed vulvar itching, redness, and edema (judged possibly related to study drug; BV was cured).

The following table compares ME's that occurred with a frequency of 1% or more in either treatment group.

MEDICAL EVENTS OCCURRING IN 1% OR MORE OF PATIENTS

	3-DAY (N = 205) n (%)	7-DAY (N = 204) n (%)
Vaginitis/vulvovaginitis	32 (15.6)	39 (19.1)
Yeast/fungal infection – vagina	1 (0.5)	5 (2.5)
Nausea	1 (0.5)	5 (2.5)
Abdominal pain	4 (2.0)	2 (1.0)
Vaginal/vulvovaginal itching & vulvar pruritis	5 (2.4)	4 (2.0)
Headache	2 (1.0)	3 (1.5)

Of 58 patients tested for *C. albicans* and *T. vaginalis* in the 3-day group (the sponsor does not indicate how these patients were chosen, other than to say that some of them were

symptomatic for vaginitis), 13 tested positive for *C. albicans* and none tested positive for *T. vaginalis*. Of 60 patients tested in the 7-day group, 20 had *C. albicans* and 1 had *T. vaginalis*.

Comments

The sponsor argues that a 3-day course of treatment for bacterial vaginosis with clindamycin will maintain the same level of effectiveness as the currently approved 7-day course, while improving safety. It is true that safety is somewhat improved by shortening the duration of treatment. However, it is unclear whether the 3-day course is maintaining the same level of efficacy as the 7-day course. The distribution of clinical response as defined by the sponsor in evaluable patients is marginally statistically significantly different ($p = 0.069$ for Pearson's chi-square test, suggesting a general association between treatment and outcome), with patients on 3 days of treatment failing more often, 19% versus 9% for 7 days ($p = 0.02$). While no data on resistance is presented, in view of the significant 19% versus 9% failure rate consideration must be given to the possiblility of emerging resistance were 3 day therapy to be used in place of the current 7 day therapy.

When individual parameters are considered for the evaluable patient population (clue cells, pH, odor, discharge, gram stain, and patient's evaluation of therapy), the only statistically significant treatment difference is in the proportion of patients who still have clue cells approximately 1 month after treatment, 26% of patients treated for 3 days, compared to 12% of patients treated for 7 days. This difference is highly statistically significant ($p = 0.004$). Since patients were classified as failures in studies 0027 and 0021 when clue cells were present, this difference suggests that 3-day treatment with CVC is statistically inferior to 7-day treatment. Whether this difference is clinically significant will have to be determined by the medical officer. Tables 1 through 6, which can be found in Appendix 1, illustrate how patients fared on the individual variables for 3 versus 7 days of treatment.

If clinical outcome is defined as it was in studies 0027 and 0021, there is no significant treatment difference. That is, if **success** is defined as normal gram stain, clue cells, pH, odor, and discharge; **improved** is defined as normal gram stain and clue cells, and ≤ 2 of pH, odor, and discharge normal; and **failures** are everyone else, then the outcome is that given in Table 7 for the evaluable patient population (chi-square p-value = 0.87; Mantel-Haenszel $p = 0.61$) and that given in Table 8 for the intent-to-treat patient population (chi-square $p = 0.75$; Mantel-Haenszel $p = 0.46$). Using this definition, however, success rates are fairly low in both treatment groups. For the evaluable patients, only 41% of patients treated for 3 days and 44.5% of patients treated for 7 days were successes.

The medical officer, Dr. Winfield, suggested two alternative definitions of clinical response using the 3 variables chosen by the sponsor: clue cells, pH, and odor. The first is as follows: **success** is normal clue cells, pH, and odor; **improved** is either pH and clue cells or odor and clue cells normal (i.e., if clue cells are present, the patient is counted as a failure); and **failure** is everyone else. Tables 9 and 10 present the results of this analysis for evaluable and ITT patients, respectively. In this case, clinical outcome is highly statistically significantly different for 3- versus 7-day treatment (with patients treated for 3 days performing worse than patients treated for 7 days) in the evaluable group (chi-square $p = 0.006$; Mantel-Haenszel $p = 0.074$), and marginally statistically significantly different

(again 3-day patients are performing worse) in the ITT group (chi-square p = 0.053; Mantel-Haenszel p = 0.18). The second alternative definition suggested by Dr. Winfield ignores outcome on pH and considers patients to either have been cured or not (i.e., there is no improved category). In this case, **successes** are those patients who have normal odor and clue cells, and **failures** are everyone else. Treatment differences are again highly statistically significantly different for the evaluable patient population (chi-square p = 0.005; Mantel-Haenszel p = 0.005; 95% confidence interval for the proportion cured on 3 days of treatment minus the proportion cured on 7 days of treatment = [-0.25, -0.04]), and marginally statistically significantly different for the intent-to-treat patient population (chi-square p = 0.052; Mantel-Haenszel p = 0.052). These results are given in Tables 11 and 12, respectively. Both approaches demonstrate that the 7 day therapy is statistically superior to the proposed 3 day therapy.

B. Pivotal Study 0027

Methods

Study 0027 was a multicenter (11 investigators, all in the U.K.), randomized, double-blind, controlled clinical trial comparing 3 day treatment of bacterial vaginosis with Cleocin to placebo.

Criteria for entry into the study were as follows: premenopausal women at least 18 years of age with a clinical diagnosis of BV (vaginal fluid pH > 4.5, clue cells, and an amine odor after adding 10% KOH to vaginal discharge); gram stain of vaginal fluid smear consistent with diagnosis of BV (significant reduction in the number of normally occurring *Lactobacillus* morphotypes concurrent with an increase in the *Gardnerella vaginalis/Bacteroides* and *Mobiluncus* morphotypes); and not menstruating at baseline nor expected to menstruate in the next 7 days. The reasons for excluding women from the study were: known allergy to clindamycin; not taking adequate contraceptive measures, pregnant, or breast feeding; presence of intrauterine contraceptive device; systemic or vaginal antimicrobial therapy within the previous 2 weeks; history of antibiotic-associated colitis, inflammatory bowel disease, or frequent periodic diarrhea; atrophic vaginitis; clinical evidence of genital herpes, cervical or vaginal vault warts, or symptoms suggestive of pelvic inflammatory disease; participation in any other clinical trials within the previous 3 months; women who had previously had a hysterectomy; any other serious or uncontrolled disease.

At visit 1, the first day of treatment, patients were randomly assigned to receive either 5 grams of 2% clindamycin vaginal cream or placebo, administered intravaginally at bedtime for 3 consecutive days. Follow-up visits were scheduled for days 7 and 28 (visits 2 and 3, respectively). The evaluable time window for visit 2 was between days 6 and 16; for visit 3 it was between days 17 and 42.

The primary efficacy variables at visits 2 and 3 were the rates for success, improvement, failure, medical event failure (at visit 2 only), and recurrence (visit 3 only). **Success** was defined as being asymptomatic for bacterial vaginosis (the sponsor does not explain how patients are determined to be symptomatic/asymptomatic for BV), normal gram stain, normal vaginal discharge, vaginal fluid pH ≤ 4.5, absence of clue cells, and a negative KOH

odor test (recall that the last three items are what constituted a "clinical cure" in study 0020, the primary efficacy variable there). **Improved** was defined as being asymptomatic for BV, absence of clue cells, normal gram stain, but persistence of one or more of the other 3 criteria for BV (abnormal vaginal discharge, pH>4.5, positive KOH odor test). **Failure** was defined as the presence of symptoms attributable to BV, a gram stain consistent with a diagnosis of BV, or the presence of clue cells. Patients who received alternative/additional antibiotic therapy after visit 2 were categorized as failures (for the purposes of the ITT analysis only), regardless of the outcome, at visit 3. **Medical event failure** was defined as attending visit 2, but failing to complete medication due to a medical event. **Recurrence** was a failure at visit 3, that had been categorized as success or improved at visit 2.

The secondary efficacy variables at visits 2 and 3 were gram stain (positive or negative), vaginal discharge (normal or abnormal), clinical response (cure, improvement, failure -- defined as in study 0020), and the components of "clinical response" (clue cells, vaginal fluid pH, and KOH odor test). In addition, in order to compare the results of study 0027 with study 0020, an "overall outcome" of cure, improved, failure, relapse, or unknown was determined for each patient at the end of the study as illustrated in the table below. There are several problems with this approach (see Comments below). All of the primary and secondary efficacy variables were considered categorical and analyzed using chi-square techniques. Continuous variables were analyzed using ANOVA. All statistical tests were two-sided and considered statistically significant at $p \leq 0.05$.

Visit 2 Assessment	Visit 3 Assessment	Overall Outcome
Success	Success	Cure
	Improved	Improved
	Failure	Relapse*
	Recurrence	Relapse**
	Missing/Did Not Attend	Unknown
Improved	Success	Cure
	Improved	Improved
	Failure	Failure
	Recurrence	Relapse**
	Missing/Did Not Attend	Unknown
Failure/ME Failure	Success	Failure***
	Improved	Failure****
	Failure	Failure
	Missing/Did Not Attend	Unknown
Missing/Did Not Attend	Success	Cure
	Improved	Improved
	Failure	Failure
	Missing/Did Not Attend	Unknown

*This would be "failure" in study 0020.

**Study 0020 is unable to determine recurrence rates, as they only have 1 follow-up visit.

***This would be "success" in study 0020.
****This would be "improved" in study 0020.

All patients who received at least one dose of study medication were included in the ITT analysis of safety and the primary efficacy variable. Per-protocol analysis was also used to examine the primary efficacy variable, as well as the secondary efficacy variables. Patients evaluable at visit 2 were those who met the baseline inclusion/exclusion criteria, did not have any other infections, did not menstruate during treatment, abstained from intercourse during treatment, completed study medication, and were present for visit 2. Patients who satisfied the above and had no antibiotic treatment since visit 2 were considered evaluable for visit 3.

Results

Of the 221 patients enrolled in the study, 141 (64%) completed the study (71 out of 107, or 66%, on CVC, and 70 out of 114, or 61%, on placebo). Of the 80 patients who did not complete the study, 25 (23%) from the CVC group and 29 (25%) from the placebo group were lost to follow-up. Other reasons for not completing the study in the CVC group were serious medical event (1), non-serious medical event (3), patient ineligible (1), protocol noncompliance (3), patient's request (2), and other (1). The placebo group had roughly the same number of dropouts for the reasons listed above, plus 7 patients (6%) who did not complete the study due to lack of efficacy.

In the CVC group, 96 patients attended visit 2 and 69 (64%) were evaluable for efficacy. The most common reasons for nonevaluability were: positive for *C. albicans*, *N. gonorrhea*, or *Chlamydia* (10.2%); did not attend the visit (9.3%); and menstrual period during treatment (6.5%). In the placebo group, 99 patients attended visit 2 and 66 (58%) were evaluable for efficacy. At visit 3, 69 CVC-treated patients attended (excluding patients who were prescribed alternative antibiotic therapy), and 52 (49%) were evaluable for efficacy. Nonevaluable patients either did not attend (13%), or had received alternative antibiotic therapy (4%). In the placebo group, 30 attended (again excluding patients prescribed alternative antibiotics), and 18 (16%) were evaluable.

Demographic characteristics were similar between the two treatment groups at baseline. Patients ranged in age from 18 to 49 years, with an average weight of 133 pounds. Approximately 82% were white, 16% black, 1% Asian, and 1% West Indian. Medical history was similar between the two groups with one exception. CVC patients had slightly fewer previous episodes of BV (an average of 1.4 episodes, versus 2.1 in the placebo group). This difference was not statistically significant ($p=0.16$).

The per-protocol and intent-to-treat analyses of the primary efficacy variable are summarized in the two tables below. Using both approaches, patients on CVC fare much better than those on placebo. The distribution of outcomes is statistically significantly different between CVC and placebo at both visits 2 and 3 (all 4 p-values <0.001, both per-protocol and ITT). When "success/improved" is compared to "failure/ME failure (visit 2 only)/recurrence (visit 3 only)", again CVC is statistically superior to placebo at both visits 2 and 3 (all p-values ≤ 0.002, using per-protocol or ITT). Finally, when "success" is compared to "improved/failure/ME failure (visit 2 only)/recurrence (visit 3 only)", CVC is

statistically superior to placebo at visits 2 and 3 (all p-values ≤ 0.003, using either the per-protocol or ITT sample). Results are similar across races (whites versus blacks), the only subgroup variable examined. They are also similar across centers.

ANALYSIS OF PRIMARY EFFICACY VARIABLE: PER-PROTOCOL

	VISIT 2		VISIT 3	
	CVC (N = 69) n (%)	PBO* (N = 66) n (%)	CVC (N = 52) n (%)	PBO* (N = 18) n (%)
Success	38 (55.1)	6 (9.1)	33 (63.5)	4 (22.2)
Improved	21 (30.4)	1 (1.5)	1 (1.9)	0 (0.0)
Failure	10 (14.5)	58 (87.9)	3 (5.8)	11 (61.1)
ME Failure	0 (0.0)	1 (1.5)	N/A**	N/A**
Recurrence	N/A**	N/A**	15 (28.8)	3 (16.7)

*PBO = Placebo.
**N/A = Not applicable.

ANALYSIS OF PRIMARY EFFICACY VARIABLE: INTENT-TO-TREAT

	VISIT 2		VISIT 3	
	CVC (N = 107) n (%)	PBO* (N = 114) n (%)	CVC (N = 107) n (%)	PBO* (N = 114) n (%)
Success	49 (45.8)	13 (11.4)	42 (39.3)	5 (4.4)
Improved	31 (29.0)	2 (1.8)	2 (1.9)	0 (0.0)
Failure	13 (12.1)	81 (71.1)	11 (10.3)**	61 (53.5)**
ME Failure	1 (0.9)	1 (0.9)	N/A#	N/A#
Recurrence	N/A#	N/A#	20 (18.7)	5 (4.4)
Missing/DNA@	13 (12.1)	17 (14.9)	32 (29.9)	43 (37.7)

*PBO = Placebo.
**Includes patients (8 CVC, 41 placebo) who received alternative antibiotics.
#N/A = Not applicable.
@ DNA = Did not attend.

Analysis of the secondary efficacy variables provides further support for the conclusion that CVC is more effective than placebo for 3-day treatment of bacterial vaginosis. The clinical response for both the per-protocol and ITT patient groups is summarized in the following table. Recall that this is chosen to be the primary efficacy variable in study 0020. In all cases, CVC is statistically superior to placebo (all p-values ≤ 0.001).

CLINICAL RESPONSE: PER-PROTOCOL

	VISIT 2		VISIT 3	
	CVC (N=69) n (%)	PBO* (N=66) n (%)	CVC (N=52) n (%)	PBO* (N=18) n (%)
Success	41 (59.4)	8 (12.1)	36 (69.2)	4 (22.2)
Improved	25 (36.2)	3 (4.5)	3 (5.8)	1 (5.6)
Failure	3 (4.3)	53 (80.3)	13 (25.0)	13 (72.2)
Missing	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)

*PBO = Placebo.

CLINICAL RESPONSE: INTENT-TO-TREAT

	VISIT 2		VISIT 3	
	CVC (N=107) n (%)	PBO* (N=114) n (%)	CVC (N=107) n (%)	PBO* (N=114) n (%)
Success	55 (51.4)	17 (14.9)	45 (42.1)	6 (5.3)
Improved	33 (30.8)	7 (6.1)	6 (5.6)	3 (2.6)
Failure	6 (5.6)	72 (63.2)	24 (22.4)	62 (54.4)
Missing/DNA**	13 (12.1)	18 (15.8)	32 (29.9)	43 (37.7)

*PBO = Placebo.

**DNA = Did not attend.

The other secondary efficacy variables were gram stain, vaginal discharge, clue cells, vaginal fluid pH, KOH odor test, and overall outcome. Significantly more patients in the placebo group had a positive gram stain at visit 2, compared to CVC (64.9% versus 4.7%; $p<0.001$). This difference remained at visit 3 (30.1% versus 14.1%; $p<0.001$). Vaginal discharge was present in more placebo than CVC patients at visit 2 (54.4% versus 10.3%; $p<0.001$) and visit 3 (21.9% versus 17.2%; $p=0.008$). Clue cells were present in more placebo patients at visit 2 (63.2% versus 3.7%; $p<0.001$) and visit 3 (30.1% versus 19.2%; $p<0.001$). Vaginal fluid pH remained greater than 4.5 in more placebo patients at visit 2 (63.2% versus 32.7%; $p<0.001$) and visit 3 (30.1% versus 17.2%; $p<0.001$). Finally, more placebo patients had a positive KOH test for odor than did CVC patients at visit 2 (50.9% versus 4.7%; $p<0.001$) and visit 3 (24.4% versus 12.5%; $p<0.001$). Patients were included in the "overall" evaluation if they met evaluability criteria for visits 2 and 3, or received alternative antibiotic treatment for BV. The overall outcome for evaluable patients is given in the following table. CVC patients perform significantly better than those who received placebo ($p<0.05$).

OVERALL OUTCOME -- EVALUABLE PATIENTS

OUTCOME	CVC (N=56) n (%)	PLACEBO (N=41) n (%)
Cure	30 (53.6)	1 (2.4)
Failure	11 (19.6)	37 (90.2)
Relapse	15 (26.8)	3 (7.3)

Medical event data are summarized in the following table. Of the 2 placebo patients who dropped out of the study due to a medical event, one had vaginal irritation and one had early menses and vulval warts. The reasons in the CVC group were deep vein thrombosis (pre-treatment), early menses and renal infection, early menses and vulvitis, and vulvo-vaginitis. Genital tract medical events were the most commonly reported in both groups. In the CVC-treated group, 5.6% experienced genital warts, 5.6% vulvar pruritus, 4.7% candida infection, 3.7% vulva disorders, 2.8% chlamydial infection, 2.8% candidiasis, 1.9% vaginal disorders NEC/NOS, and 1.9% vaginal discharge. Other types of medical events included menstrual cycle abnormal or irregular (5.6%), macular rash (1.9%), abdominal pain, diarrhea, and loose stools (1.9% each), and cystitis and urinary tract infection (1.9% each).

MEDICAL EVENT SUMMARY

	CVC (N=107)	PLACEBO (N=114)
Patients (%) with ME's		
All ME's	54 (50.5)	42 (36.8)
Drug-related ME's	24 (22.4)	12 (10.5)
Total # of ME reports		
All ME's	75	52
Drug-related ME's	30	13
Patients w/ serious ME's	0	0
Patient dropouts due to ME	4	2
Deaths	0	0

Comments

The sponsor developed an additional variable, called "overall outcome", in an attempt to compare the results of this study with those of study 0020. This reviewer believes that any attempt to compare results of studies 0020 and 0027 is inappropriate, due to the design of the studies. In study 0020, the patients were given treatment and then assessed approximately a month after treatment. Since there was only one follow-up visit, there is no chance to examine recurrence rates. One can only examine cure/improved/failure rates a month after treatment. In study 0027, the patients were given treatment and then assessed at approximately one week and approximately one month after treatment. Thus,

in study 0027 one can examine recurrence rates. One can also examine cure/improved/failure rates at one week and cure/improved/failure/recurrence rates at one month after treatment. The only way to compare the two studies would be to ignore the information about what happens a week after treatment in study 0027, which would be inappropriate. There is also the problem that outcome (cure, improvement, etc.) was defined differently in the two studies. In study 0020, only clinical signs are assessed to determine outcome (clue cells, pH, and KOH odor test). In study 0027, these 3 signs plus an additional 3 (being symptomatic/asymptomatic for BV, normal/abnormal gram stain, and normal/abnormal vaginal discharge) are used to determine outcome.

C. Pilot Study 0021

Methods

This was a single-center (U.K.), randomized, double-blind, placebo-controlled clinical trial. The objective was to determine whether 5 grams of 2% CVC administered intravaginally at bedtime for 3 consecutive days is a safe and effective treatment for bacterial vaginosis. The placebo group administered 5 grams of vehicle intravaginally at bedtime for 3 days.

Premenopausal women at least 18 years old were included in the study if they had a clinical diagnosis of BV (increased thin, homogeneous, malodorous, vaginal discharge; vaginal fluid pH>4.5; clue cells; and an amine odor after adding 10% KOH to vaginal discharge), a gram stain of vaginal fluid smear consistent with diagnosis of BV (significant reduction in the number of normally occurring *Lactobacillus* morphotypes concurrent with an increase in the *Gardnerella vaginalis/Bacteroides* and *Mobiluncus* morphotypes), were not menstruating nor expected to menstruate in the next 4 days, and signed a written informed consent statement. Patients were excluded for: known allergy to clindamycin; pregnant or breast feeding; presence of IUD; of child-bearing potential not taking adequate contraceptive measures; systemic or vaginal antimicrobial therapy within the previous 2 weeks; previous enrollment in this study; history of antibiotic-associated colitis, inflammatory bowel disease, or frequent periodic diarrhea; atrophic vaginitis; clinical evidence of genital herpes, cervical or vaginal vault warts, or symptoms suggestive of pelvic inflammatory disease; current participation in any other clinical trials, or any other investigational medication within the previous 3 months; previously had a hysterectomy; any other serious or uncontrolled disease.

At visit 1, patients were randomized to receive either CVC or placebo. Follow-up visits were conducted 7-9 and 28-35 days after treatment commenced (visits 2 and 3, respectively).

The primary endpoint was the rate of cure/improvement. Other endpoints included the rate of recurrence and the changes in pH. **Success** was defined to be the absence of all BV symptoms, gram stain negative for BV, no clue cells, normal vaginal fluid, pH≤4.5, and negative amine odor test with KOH. **Improved** was defined to be the same as success except that ≤2 of the last 3 criteria for success were met. **Failed** was BV present based on conditions under the inclusion criteria. **Medical event failure** was inability to complete treatment due to a medical event. **Recurrence** was BV at second follow-up after either success or improvement at first follow-up.

The analysis of efficacy was conducted for 5 population groups: (1) the ITT group (patients with missing data had their last observation carried forward); (2) "population 1" -- defined as all subjects who attended the follow-up visit being analyzed and who completed protocol medication; (3) "population 2" -- all subjects who attended the follow-up visit, except those who menstruated during the first 7 days, or who received other antimicrobial medication before the visit being analyzed; (4) "population E" -- all subjects who attended the follow-up visit, except those who menstruated during the first 7 days, or who received other antimicrobial therapy before the visit being analyzed, or who had sexual intercourse before the day 7 visit; and (5) "population 3" -- all subjects who attended the follow-up visit, except those who menstruated during the first 7 days, received other antimicrobial therapy before the visit being analyzed, had sexual intercourse before the day 7 visit, or in whom other non-BV pathogens were cultured from the vaginal fluid. Populations 1, 2, and 3 (minus the exclusion of patients who had sexual intercourse before day 7) were specified in the protocol for efficacy analyses. After the study, when it was determined that there was a subgroup of patients who failed to comply with the specific instructions to avoid sexual intercourse before the first follow-up visit, population E was added and such patients were excluded from population 3. An ITT group was also added.

Results

Fifty-five patients were enrolled (27 on CVC and 28 on placebo). There were no differences at baseline in demographics between the two groups.

At both the 7- and 28-day follow-up visits, CVC was more effective than placebo in all patient groups. These results are summarized in the table below. Of the 22 CVC patients in population 1 who were either a success or improved at visit 2, 2 (9.1%) had a recurrence of BV at visit 3.

"SUCCESS" OR "IMPROVED" BY TREATMENT GROUP, POPULATION, AND VISIT

POPULATION	VISIT 2		VISIT 3	
	CVC % (n/N)	PLACEBO % (n/N)	CVC % (n/N)	PLACEBO % (n/N)
ITT	82 (22/27)*	4 (1/28)	56 (15/27)*	7 (2/28)
1	96 (22/23)*	5 (1/21)	83 (15/18)*	22 (2/9)
2	95 (20/21)*	5 (1/20)	77 (10/13)#	0 (0/2)
E	94 (17/18)*	5 (1/19)	80 (8/10)	0 (0/2)
3	92 (12/13)*	8 (1/13)	78 (7/9)	0 (0/2)

*$p < 0.001$ compared to placebo (chi-square test)
#$p < 0.05$ compared to placebo (chi-square test)

Safety is summarized in the table below. Eight patients (5 CVC, 3 placebo) reported 12 medical events throughout the study. In the CVC group, there were 2 reports of vaginitis/cervicitis, and 1 report each of diarrhea, candidal vulvovaginitis, vulvar warts, and

acute tonsillitis. In the placebo group, there were 2 reports of vaginitis/cervicitis and 1 report each of diarrhea, lightheadedness, dizziness, and nausea. The cases of diarrhea and vaginitis were considered drug related in both the CVC and placebo groups. Overall, there were 5 patients who developed candidiasis following treatment with CVC, compared to 4 in the placebo group (note that some of these cases were not reported as ME's).

MEDICAL EVENT SUMMARY

	CVC (N = 27)	PLACEBO (N = 28)
Patients (%) with ME's		
All ME's	5 (18.5)	3 (10.7)
Drug-related ME's	3 (11.1)	2 (7.1)
Total # of ME reports		
All ME's	6	6
Drug-related ME's	3	3
Patients w/ serious ME's	0	0
Patient dropouts due to ME	0	0
Deaths	0	0

Comments

In the table describing clinical outcome on the previous page, the sponsor uses the chi-square test to test for treatment differences in the rate of patients classified as success or improved for CVC versus placebo. Due to the small number of successes in the placebo group in each patient population considered, it would have been more appropriate to use Fisher's exact test. However, it does seem clear that CVC is more effective than placebo, thus the conclusions would remain the same.

In this (placebo-controlled) study, the definition of the primary efficacy variable is the same as in study 0027 (the placebo-controlled pivotal trial). Both definitions are different from that given in study 0020 (the active-controlled pivotal trial, which compares 3-day treatment with CVC to 7- day treatment with CVC). In this study and in study 0027, the presence of clue cells requires the patient to be considered a failure. In study 0020, the patient may have clue cells present and still be considered improved. Recall that in study 0020, significantly more patients treated for 3 days had clue cells present than those treated for 7 days (p = 0.004; 26% versus 12%).

III. CONCLUSIONS (Which May be Conveyed to the Sponsor)

1. Safety is acceptable on the 3-day course of treatment with clindamycin phosphate 2% for bacterial vaginosis. Study 0020 suggests that safety is slightly improved (i.e., side effects are somewhat reduced) by shortening the course of treatment with clindamycin from 7 to 3 days.

2. It is obvious from studies 0027 and 0021 that the 3-day course of treatment with clindamycin phosphate 2% for bacterial vaginosis is more effective than treatment with a placebo. However, after looking at the data from study 0020, it is unclear whether the 3-day course of treatment with clindamycin phosphate 2% is as effective as the currently approved 7-day course of treatment. Depending on the clinical definition of bacterial vaginosis that is used (and this definition varies among the three studies), in many of the cases examined, the 3-day course of treatment is statistically inferior to the 7-day course of treatment. Whether these differences are clinically significant will have to be determined by the reviewing medical officers. If there is not enough evidence presented in this application to enable the medical officers to make a determination about approvability, perhaps an additional study of 3- versus 7-day treatment should be conducted. I note that the Division of Anti-Infective Drug Products' "Points to Consider" document states that in order to consider approving a drug for the treatment of bacterial vaginosis, "two statistically adequate and well-controlled multicenter trials establishing equivalence or superiority to an approved product are suggested".

RECOMMENDED REGULATORY ACTION:

While safety appears acceptable for the 3-day course of treatment with clindamycin phosphate 2% for bacterial vaginosis, and this 3-day course of treatment is statistically superior to treatment with placebo, it remains unclear whether the 3-day course of treatment with clindamycin is as effective as the currently approved 7-day course of treatment with clindamycin. If the evidence presented in this application is not enough to enable the reviewing and supervisory medical officers to make a determination about approvability, perhaps an additional study of 3- versus 7-day treatment with clindamycin phosphate 2% for bacterial vaginosis should be required.

/S/

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/S/

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APPEARS THIS WAY
ON ORIGINAL

/S/ 11/30/95

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Chron.
This review contains 23 pages and 27 tables (15 in the text, and 12 in Appendix 1).

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APPENDIX 1

TABLE 1: CLUE CELLS -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Absent	97 (74.1)	113 (88.3)
Present	34 (26.0)	15 (11.7)

Chi-square p = 0.003.

TABLE 2: pH -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Normal (≤4.5)	91 (69.5)	88 (68.8)
High (>4.5)	40 (30.5)	40 (31.3)

Chi-square p = 0.90.

TABLE 3: ODOR -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Absent	114 (87.0)	117 (91.4)
Present	17 (13.0)	11 (8.6)

Chi-square p = 0.26.

TABLE 4: DISCHARGE -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Absent	112 (85.5)	117 (91.4)
Present	19 (14.5)	11 (8.6)

Chi-square p = 0.14.

TABLE 5: GRAM STAIN -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 128) n (%)	7-DAY (N = 127) n (%)
Normal	71 (55.5)	71 (55.9)
Intermediate	28 (21.9)	37 (29.1)
Bacterial Vaginosis	29 (22.7)	19 (15.0)

Chi-square p = 0.19 (general association)
Mantel-Haenszel p = 0.41 (monotonicity)

TABLE 6: PATIENT'S ASSESSMENT -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Cure	95 (72.5)	103 (80.5)
Improvement	26 (19.9)	16 (12.5)
Failure	10 (7.6)	9 (7.0)

Chi-square p = 0.26 (general association).
Mantel-Haenszel p = 0.25 (monotonicity).

TABLE 7: OUTCOME* -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Cure	54 (41.2)	57 (44.5)
Improvement	13 (9.9)	12 (9.4)
Failure	64 (48.9)	59 (46.1)

*Defined as in studies 0027 and 0021.
Chi-square p = 0.87 (general association).
Mantel-Haenszel p = 0.61 (monotonicity).
95% confidence interval for difference in cure rates, 3- minus 7-day: (-0.16, 0.10).

TABLE 8: OUTCOME* -- ALL PATIENTS

OUTCOME	3-DAY (N = 205) n (%)	7-DAY (N = 204) n (%)
Cure	60 (29.3)	66 (32.4)
Improvement	14 (6.8)	15 (7.4)
Failure	131 (63.9)	123 (60.3)

*Defined as in studies 0027 and 0021.
Chi-square p = 0.75 (general association).
Mantel-Haenszel p = 0.46 (monotonicity).
95% confidence interval for difference in cure rates, 3- minus 7-day: (-0.13, 0.06).

TABLE 9: OUTCOME* -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Cure	77 (58.8)	80 (62.5)
Improvement	18 (13.7)	31 (24.2)
Failure	36 (27.5)	17 (13.3)

*Defined as per the medical officer's first request (i.e., success = clue cells, pH, and odor normal; improvement = clue cells and pH or clue cells and odor normal; failure = everyone else (including patients with clue cells)).
Chi-square p = 0.006 (general association).
Mantel-Haenszel p = 0.07 (monotonicity).
95% confidence interval for difference in cure rates, 3- minus 7-day: (-0.16, 0.09).

TABLE 10: OUTCOME* -- ALL PATIENTS

OUTCOME	3-DAY (N = 205) n (%)	7-DAY (N = 204) n (%)
Cure	85 (41.5)	90 (44.1)
Improvement	21 (10.2)	35 (17.2)
Failure	99 (48.3)	79 (38.7)

*Defined as per the medical officer's first request (i.e., success = clue cells, pH, and odor normal; improvement = clue cells and pH or clue cells and odor normal; failure = everyone else (including patients with clue cells)).
Chi-square p = 0.053 (general association).
Mantel-Haenszel p = 0.18 (monotonicity).
95% confidence interval for difference in cure rates, 3- minus 7-day: (-0.13, 0.07).

TABLE 11: OUTCOME* -- EVALUABLE PATIENTS

OUTCOME	3-DAY (N = 131) n (%)	7-DAY (N = 128) n (%)
Cure	94 (71.8)	110 (85.9)
Failure	37 (28.2)	18 (14.1)

*Defined as per the medical officer's second request (i.e., success = clue cells and odor normal; failure = everyone else).

Chi-square p = 0.005.

95% confidence interval for difference in cure rates, 3- minus 7-day: (-0.25, -0.04).

TABLE 12: OUTCOME* -- ALL PATIENTS

OUTCOME	3-DAY (N = 205) n (%)	7-DAY (N = 204) n (%)
Cure	104 (50.7)	123 (60.3)
Failure	101 (49.3)	81 (39.7)

*Defined as per the medical officer's second request (i.e., success = clue cells and odor normal; failure = everyone else).

Chi-square p = 0.052.

95% confidence interval for difference in cure rates, 3- minus 7-day: (-0.20, 0.01).