CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-767

STATISTICAL REVIEW(S)

590 Ch1

MAR 26 1999

Statistical Review and Evaluation

NDA:	50-767
Drug Name:	Cleocin® Vaginal Ovule (clindamycin phosphate vaginal ovules 100 mg)
Applicant:	Pharmacia & Upjohn Company
Indications:	Treatment of bacterial vaginosis
Documents Reviewed:	NDA volumes 1.3, 1.75 to 1.107 dated October 13, 1998. Electronic data submitted January 21, 1999.
Medical Officer:	Joseph Winfield, M.D., HFD-590

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1. Introduction

NDA 50-767 for Cleocin® Vaginal Ovule (clindamycin phosphate vaginal ovule 100 mg) was submitted as a new formulation of clindamycin for the treatment of bacterial vaginosis. The old formulation, intravaginal clindamycin cream 2%, administrated for 7 days, was approved for bacterial vaginosis in NDA 50-680. The new formulation, clindamycin phosphate vaginal ovule 100-mg (CVO), administrated for 3 days, is supported by two pivotal, randomized, controlled clinical studies. Study M/1114/0001 (referred to as Study 0001) was an active-controlled, observer-blind study comparing a 3-day clindamycin vaginal ovule regimen to the approved 7-day regimen of clindamycin vaginal cream (CVC). Study M/1114/0002 (referred to as Study 0002) was an active-controlled, double-blind, double-dummy study comparing clindamycin vaginal ovule to oral metronidazole (MET). In Study 0002, patients received either clindamycin vaginal ovule for 3 days plus oral placebo for 7 days or oral metronidazole for 7 days plus placebo suppositories for 3 days.

2. Summary of Designs and the Applicant's Results

2.1 Study 0001 and Study 0002

The objectives of both trials were to demonstrate efficacy and safety of the 3-day Cleocin® Vaginal Ovule 100 mg in the treatment of bacterial vaginosis. The active control was a 7-day Cleocin® Vaginal Cream group (100 mg) in Study 0001 and was a 7-day metronidazole tablet group (2x250-mg capsules daily) in Study 0002.

Subjects must have met the following criteria to be included in the studies: females of age 16 to 60 who have vaginal discharge with (a) positive amine odor on alkalinization of vaginal fluid when mixed with 10% potassium hydroxide solution, (b) presence of clue cells in vaginal discharge, (c) pH of vaginal secretion > 4.5. In addition, a Gram stain of vaginal fluid was required to be compatible with a diagnosis of bacterial vaginosis. Patients were excluded from the studies if they tested positive for *Neisseria gonorrhoeae, Candida albicans, Trichomonas vaginalis, or Chlamydia*

trachomatis.

For Study 0001, two hundred sixty evaluable patients were planned. At the end of this clinical trial, a total of 670 patients were enrolled into the study. Among them, eight patients did not receive the assigned treatment (4 patients in each group). Therefore, three hundred twenty-seven patients were treated with clindamycin vaginal ovule (CVO) and 335 patients were treated by clindamycin vaginal cream (CVC). According to the applicant, 204 patients in the CVO group and 180 patients in the CVC group were evaluable. For Study 0002, 230 evaluable patients were planned and four hundred patients were actually enrolled. Among them, 203 patients received CVO and 197 patients received metronidazole. The applicant determined 113 patients with CVO and 120 patients treated with metronidazole (MET) evaluable. All baseline characteristics between treatment groups were similar in both studies.

The protocols specified that patients would be considered fully evaluable for efficacy if none of the following occurred: failure to meet selection criteria; inadequate dosing (clindamycin VO used for <3 days, clindamycin VC applied for <6 days or > 9 days, or oral metronidazole taken for <6 days or >8 days or fewer than 21 capsules taken); any lapse in dosing of CVO or a lapse of >1 day in dosing of CVC or metronidazole; menses during therapy or at a follow-up visit; non-protocol systemic or vaginal antimicrobial treatment during study participation (unless given after failure assessed at first visit); failure to return for second follow-up visit if visit is required; or development of a concomitant genital infection. In study 0001, douching during protocol therapy or within 2 days prior to a follow-up visit would also make a patient non-evaluable.

Patients were required to return for two follow-up visits in all studies. The scheduled windows (per protocol) were 12 to 16 days and 28 to 42 days after the start of treatment. At the end of the studies, many patients were found to be non-evaluable because they did not return for follow-up visits within the time windows defined by the protocols. The applicant believed that there is no clinical rationale to exclude patients from the evaluable population if the only reason for exclusion was returning outside the defined window. The applicant used a wider window for the second follow-up visit: 18 to 52 days after start of treatment, an increase of 10 days before and after the protocol-specific intervals. The wider window for evaluability was used in the submitted NDA. The primary reasons for nonevaluability were also given by the applicant in Table 1. Based on the applicant's determination, the primary reasons for nonevaluability in both studies are "failure to meet inclusion/exclusion criteria", and "follow-up not within required window". "Failure to comply with dosing regimen" is also a major reason of nonevaluability in Study 0001.

Table 1. Primary Reasons for Nonevaluability Given by Applicant

Primary Reason For Nonevaluability	No. Patients (% of Group)			
	Study 0001		Study 0002	
	CVO N=327	CVC N=335	CVO N=203	MET N=196*
Did not have clinical BV	6 (1.8)	7 (2.1)	2 (1.0)	1 (0.5)
Did not meet inclusion/exclusion criteria	41 (12.5)	51 (15.2)	38 (18.7)	37 (18.9)
Additional antimicrobial therapy	14 (4.3)	8 (2.4)	13 (6.4)	10 (5.1)
Did not comply with dosing regimen	35 (10.7)	52 (15.5)	2 (1.0)	3 (1.5)
Follow-up not within required window:				
Outside of the wider window	18 (5.5)	28 (8.4)	29 (14.3)	24 (12.2)
Outside of the window per protocol	28 (8.6)	36 (10.7)	37 (18.2)	34 (17.3)
Menses during treatment or follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Douche during treatment or within 2 days of follow-up	0 (0.0)	1 (0.3)	Not applicable	
Had symptomatic concomitant vaginal infection	8 (2.4)	4 (1.2)	6 (3.0)	0 (0.0)
No information available on study drug administration	1 (0.3)	4 (1.2)	0 (0.0)	1 (0.5)
Total nonevaluable				
Wider window	123 (37.6)	155 (46.3)	90 (44.3)	76 (38.8)
Protocol-specified window	133 (40.7)	163 (48.7)	98 (48.3)	86 (43.7)

*One patient whose data were reported by the applicant as unavailable for efficacy analysis has been excluded from this table and from the following tables in this review.

Short Statistical Comments: Patients could be considered nonevaluable due to multiple reasons. The applicant did not explain in the NDA why one reason rather than another was chosen as the primary reason and presented in the table. Furthermore, this statistical reviewer found that the results of Table 1 could not be duplicated from the SAS data sets. More discussion will be given later on.

The primary efficacy endpoints in the original protocol were clinical status (cured, failed or non-evaluable) measured at 12-16 days (follow-up visit 1) and 28-42 days (follow-up visit 2) after the start of treatment. A wider window (18-52 days) was also used by the applicant as the second follow-up visit. Clinical status was determined based on the number of diagnostic criteria that had resolved, (i.e., return to pH of vaginal discharge ≤ 4.5, absence of a "fishy" amine odor when mixed with 10% KOH solution, an absence of clue cells). At the first visit (day 12-16), cure was defined as the return to normal of at least two criteria. At the second visit, cure was defined as the return to normal of all three criteria. Overall cures were patients cured at both visits. The applicant also performed an analysis of cure based on 2 diagnostic criteria (resolution of amine odor and clue cells for both visits). Two-sided 95% confidence intervals for the difference in cure rates, test drug minus control, were to be used and are presented in Table 2. Equivalence was to be concluded if the lower bound of this confidence interval excluded –20%.

Table 2. Overall Clinical Outcome- Evaluable Patients Assessed by the Wider Window

Analysis	Outcome	No. of Patients (% of Assessable Patients)			
		Study 0001		Study 0002	
		CVO (N=204)	CVC (N=180)	CVO (N=113)	MET N=120)
3 criteria	Cure	109 (53.7)	85 (47.8)	57 (50.4)	70 (58.3)
	Failure	94 (46.3)	93 (52.2)	56 (49.6)	50 (41.7)
	Non-assessable*	1	2	0	0
	95% CI for difference	(-4.1, 16.0)		(-20.7, 4.9)	
2 criteria	Cure	134 (66.0)	106 (59.6)	77 (68.1)	80 (66.7)
	Failure	69 (34.0)	72 (40.4)	36 (31.9)	40 (33.3)
	Non-assessable*	1	2	0	0
	95% CI for difference	(-3.4, 15.2)		(-10.6, 13.4)	

* If a patient did not have available data, she was considered non-assessable.

Short Statistical Comment: It is unusual to have non-assessable patients in the evaluable population. But here, this problem is negligible since the number of such patients is very small. The applicant also conducted an analysis based on the protocol-specified time window. The results are very similar to the ones shown in the above table, and therefore are not presented here.

The applicant also did an analysis in the ITT population and the results are summarized in Table 3. The rates of cure and failure, as well as the confidence intervals, were calculated in the population of patients who were assessable. Those who do not have data were excluded from analysis.

Table 3. Overall Clinical Outcome- ITT Patients (Those who were Assessable)

Analysis	Outcome	No. of Patients (% of Assessable Patients)*			
		Study 0001		Study 0002	
		CVO (N=327)	CVC (N=335)	CVO (N=203)	MET (N=196)
3 criteria	Cure	134 (56.3)	113 (50.4)	90 (57.7)	93 (60.0)
	Failure	104 (43.7)	111 (49.6)	66 (42.3)	62 (40.0)
	Non-assessable	89	111	47	41
	95% CI for difference	(-3.2, 14.9)		(-13.2, 8.6)	
2 criteria	Cure	164 (68.3)	142 (62.3)	114 (73.1)	107 (68.6)
	Failure	76 (31.7)	86 (37.7)	42 (26.9)	49 (31.4)
	Non-assessable	87	107	47	40
	95% CI for difference	(-2.6, 14.7)		(-5.6, 14.6)	

* Rates and comparisons are among patients who are assessable. If a patient did not have available data, she was considered non-assessable.

Short Statistical Comment: If those patients who had missing data are included in the analysis and treated as failures, the cure rates of all treatment groups will be lower than what has been shown in Table 3. But the rates of all treatment groups will still be comparable and the confidence intervals of the difference in rates will be in favor of clindamycin VO in Study 0001 because more patients in the clindamycin VC group than in the clindamycin VO group would be considered failures. Much less effect in terms of the cure rates and the confidence interval of the difference will be seen in Study 0002. For this reason, this analysis is not presented here. If we consider an extreme case in which non-assessables in the CVO groups are treated as failures and non-assessables in the control groups are treated as cures, then in Study 0001, the 95% confidence intervals will be (-33.5%, -18.2%) using 3 criteria and (-31.6%, -16.7%) using 2 criteria; in Study 0002, the confidence interval will be (-34.0%, -14.1%) using 3 criteria and (-28.5%, -9.2%) using 2 criteria.

3. Reviewer's Comments

3.1 Evaluability

As discussed in the previous section, the primary reason of nonevaluability can not be validated by the data submitted by the applicant. To study the role each criterion played in determining evaluability, the number of unevaluable patients by reason is summarized in Table 4. A patient could be counted more than once if she had multiple violations of evaluability.

Table 4. Number of Unevaluable patients by Reason

Reason For Nonevaluability	No. of Patients(%)*			
	Study 0001		Study 0002	
	CVO N=327	CVC N=335	CVO N=203	MET N=196
Did not have clinical BV	6 (1.8)	7 (2.1)	2 (1.0)	1 (0.5)
Did not meet inclusion/exclusion criteria	46 (14.1)	53 (15.8)	40 (19.7)	38 (19.4)
Additional antimicrobial therapy(except for failure)	16 (4.9)	14 (4.2)	16 (7.9)	12 (6.1)
Did not comply with dosing regimen	54 (16.5)	67 (20.0)	2 (1.0)	3 (1.5)
Follow-up not within required window: Outside of the wider window	89 (27.2)	111 (33.1)	51 (25.1)	49 (25.0)
Douche during treatment or 2 days prior to follow-up	0 (0.0)	4 (1.2)	1 (0.5)	0 (0.0)
Menses during treatment or follow-up	1 (0.0)	11 (3.3)	3 (1.5)	0 (0.0)
Lost to follow-up	87 (26.6)	105 (31.3)	46 (22.7)	42 (21.4)
Had symptomatic concomitant vaginal infection	19 (5.8)	22 (6.6)	13 (6.4)	7 (3.6)
No information available on study drug administration	39 (11.9)	43 (12.8)	12 (5.9)	17 (8.7)
Total nonevaluable records Wider window	357	437	186	169

* Percentages do not necessarily add to 100 because patients could be counted more than once for multiple violations of evaluability. Multiple records of the same reason for a patient were counted only once.

"Follow-up not within required window" is the number-one reason for nonevaluability. Patients who were "lost to follow up" and patients whose "follow up visits were not within required window" are basically the same group of patients; therefore, the category of "Lost to follow up" was eliminated by the applicant. It would perhaps be more appropriate to eliminate the "follow-up not within required window" category. Patients in these categories constitute one third of the patients in Study 0001 and one fourth of the patients in Study 0002. Most patients in "No information available on study drug administration" and in "Did not comply with dosing regimen" did not have follow-up visits either. Therefore, missing data make it impossible to assess the impact of evaluability criteria on clinical outcome. As detailed in Table 5, most of the patients in each violation of evaluability do not have the required data for clinical assessment of drug effect. On the other hand, the available data in non-evaluable patients do not seem to predict that one treatment might be more efficacious than the other. The worst scenario that most of non-evaluable patients in the clindamycin VO group were unsuccessfully treated and most of non-evaluable patients in the other two groups had unsatisfactory results is not indicated by the data, but could not be ruled out either. The conclusion could only be that the attempt to assess efficacy including every single patient in the analysis is impossible due to the amount of missing data in the NDA. The regulatory decision has to be made based upon the facts that clindamycin VO and its comparators are similar in cure rate, failure rate, as well as in similarly sizeable rates of patients with missing data.

Table 5. Clinical Outcome by Reason of Nonevaluability

Reason For Nonevaluability	(Cure, Failure, Missing Data) / No. of Patients due to each Reason			
	Study 0001		Study 0002	
	CVO	CVC	CVO	MET
Did not have clinical BV	(1, 0, 5)/6	(5,1,1) / 7	(2,0,0)/2	(0,0,1)/1
Did not meet inclusion/exclusion criteria	(10, 6, 30)/46	(15, 7, 31)/53	(17,7,16)/40	(12,5,21)/38
Additional antimicrobial therapy(except for failure)	(8, 1, 7)/16	(8, 1, 5)/14	(13,0,3)/16	(11,0,1)/12
Did not comply with dosing regimen	(4, 1, 49)/54	(9, 1, 57)/67	(1,0,1)/2	(1,0,2)/3
Follow-up not within required window: Outside of the wider window	(2, 1, 86)/89	(6, 4, 101)/111	(5, 0, 46)/51	(7, 1, 41)/49
Douche during treatment or 2 days prior to follow-up	0	(0, 0, 4)/4	(0,0,1)/1	0
Menses during treatment or follow-up	(0,0,1)/1	(2, 1, 8)/11	(1,0,2)/3	0
Lost to follow-up	(0,1,86)/87	(0, 4, 101)/105	(0,0,46)/46	(0,1,41)/42
Had symptomatic concomitant vaginal infection	(13, 1, 5)/19	(8, 2, 12)/22	(11,0,2)/13	(4,0,3)/7
No information available on study drug administration	(3, 1, 35)/39	(9, 3, 31)/43	(0,0,12)/12	(0,1,16)/17

It was also noticed by this statistical reviewer that all of the patients in "Did not meet inclusion/exclusion criteria" are due to violation of exclusion criteria. These patients were tested positive for *Neisseria gonorrhoeae, Candida albicans, Trichomonas vaginalis, or Chlamydia trachomatis.*

3.2 Efficacy Based on Existing Data

The statistical reviewer confirmed the applicant's efficacy analysis (Table 2 and Table 3) using the submitted SAS data sets. Table 6 demonstrates clinical assessment of each component in overall clinical outcome and represents the actual data that were collected.

Table 6. Percentage of Patients with Clinical Outcome by Visit and Criteria - ITT Patients

Criteria	Visit	% of Patients (Present/ Absent/ Missing data)			
		Study 0001		Study 0002	
		CVO (N=327)	CVC (N=335)	CVO (N=203)	MET (N=196)
Fishy Odor	Baseline	99.3, 0.7, 0.0	99.7, 0.3, 0.0	99.0, 1.0, 0.0	100.0, 0.0, 0.0
	Follow-up 1	7.3, 74.6, 18.1	10.1, 67.2, 22.7	5.9, 82.8, 11.3	6.6, 79.6, 13.8
	Follow-up 2	8.9, 60.2, 30.9	9.0, 50.7, 40.3	7.9, 65.5, 26.6	11.2, 63.3, 25.5
Clue Cell	Baseline	100.0, 0.0, 0.0	100.0, 0.0, 0.0	100.0, 0.0, 0.0	100.0, 0.0, 0.0
	Follow-up 1	10.4, 71.6, 18.0	14.3, 62.7, 22.6	6.9, 81.8, 11.3	7.7, 78.6, 13.7
	Follow-up 2	10.4, 58.4, 31.2	10.1, 49.6, 40.3	11.3, 62.1, 26.6	13.3, 61.2, 25.5
pH Mean (S.D.)*	Baseline	5.66 (0.85)	5.67 (0.94)	5.63 (0.65)	5.51 (0.72)
	Follow-up 1	4.66 (0.80)	4.77 (0.79)	4.46 (0.52)	4.31 (0.55)
	Follow-up 2	4.49 (0.62)	4.61 (0.78)	4.44 (0.63)	4.41 (0.64)

* Mean and standard deviation were calculated based on data available. The subset of patients who did not have pH data most likely did not have "clue cell" data and "Fishy Odor" test, either.

In Study 0001, the successful rates of clindamycin VO at both follow-up visits are better than the comparator given the existence of missing data. In Study 0002, the cure rates in the treatment groups are almost the same and the extent of missing data is relatively lower than what we see in Study 0001, especially at follow-up visit 1. The failure rates in Table

6 are lower than those in Table 3 because failures in Table 3 could be presence of "fishy odor", "clue cell" or "pH>4.5" in either one of visits, i.e., any failures in Table 6. Some patients who had failed in visit 1 did not return for visit 2. They were considered failures in Table 3, but were considered missing in Table 6. Given the fact that in study 0001 and in the 2-criteria analysis of Study 0002, the lower bounds of the 95% confidence intervals for the difference in cure rates are well above the tolerated limit (-0.15 and –0.20 are sometimes used by the FDA), Clindamycin VO 3 days might still have been able to demonstrate therapeutically equivalent to Clindamycin VC 7 days or metronidazole 7 days if all of the patients with missing data had had their data collected by a more diligent retention plan.

3.3 Safety

Because the applicant reports very lower adverse events, no sophisticated statistical comparison is needed for this NDA. The summarized safety review will be deferred to the Medical Officer.

4. Statistical Reviewer's Overall Assessment and Conclusion

Based on the applicant's analysis, the treatment of Clindamycin VO 3 days is demonstrated to be equivalent to treatment with Clindamycin VC 7 days in Study 0001 or metronidazole 7 days in Study 0002. However, both studies also consist of one third to one fourth of the total patients who can not be assessed due to missing data (Table 2 and 3). The implication of these patients is investigated in Table 5 but the conclusion still remains open. After considering the results of existing data and the manner of missing data, this statistical reviewer suggests that given the fact that in study 0001 and in the 2-criteria analysis of Study 0002, the lower bounds of the 95% confidence interval for the difference in cure rates are well above the tolerated limit (-0.15 and –0.20 are sometimes used by the FDA), Clindamycin VO 3 days might still be able to demonstrate therapeutical equivalence to Clindamycin VC 7 days or metronidazole 7 days if all of the patients with missing data had had their data collected by a more diligent retention plan.

/S/

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