CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
50-767

MEDICAL REVIEW

CLEOCIN VAGINAL OVULE
(clindamycin phosphate vaginal suppository)

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MEDICAL OFFICER'S REVIEW OF NDA 50-767

1. General Information

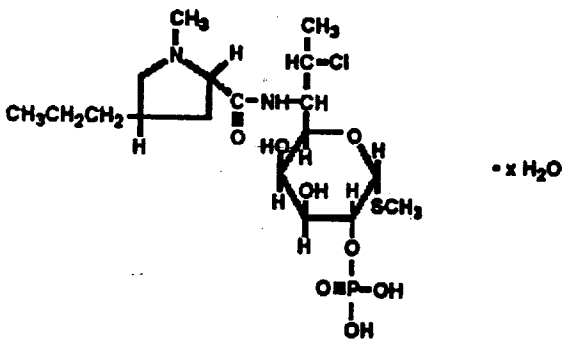
APPLICANT: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

GENERIC NAME: Clindamycin phosphate vaginal suppository

TRADE NAME: CLEOCIN® Vaginal Ovule

CHEMICAL NAME: 7-(S)-chloro-7-deoxylincomycin-2-phosphate

CHEMICAL STRUCTURE:



MOLECULAR FORMULAR: $C_{18}H_{34}ClN_2O_8PS$

MOLECULAR WEIGHT: 504.96

PHARMACOLOGIC CATEGORY : Anti-bacterial

DOSAGE FORM: Vaginal suppository (ovule)

STRENGTH: 100 mg

ROUTE OF ADMINISTRATION: Intravaginal

PROPOSED INDICATION AND USAGE: Cleocin Vaginal Ovule is indicated for the 3-day treatment of bacterial vaginosis.

PROPOSED DOSAGE AND ROUTE OF ADMINISTRATION: The recommended dose is one Cleocin Vaginal Ovule (clindamycin phosphate equivalent to 100 mg clindamycin per 2.5-g suppository) intravaginally, preferably at bedtime, for 3 consecutive days.

RELATED DRUGS: [redacted]
NDAs: 50-200, 50-441, 50-537, 50-600, 50-613, 50-615, 50-639, 50-680
[redacted]

MATERIAL REVIEWED: 117 Volumes

BACKGROUND: Bacterial Vaginosis (BV) is a common disorder seen most often in sexually active women and may be asymptomatic in up to 50% of the cases [1]. Of women seen in gynecologist offices or STD clinics with complaints of vaginal odor or abnormal discharge, BV accounts for approximately 40% of cases. Infections with *Candida albicans* and *Trichomonas vaginalis* account for another 20% to 25% each [2]. Bacterial vaginosis causes significant patient discomfort and has been implicated in several gynecologic diseases and obstetrical disorders, including recurrent urinary tract infections, adnexal tenderness, postpartum endometritis, increased risk of infection after gynecologic surgery, laparoscopically-proven pelvic inflammatory disease and preterm labor. Although generally regarded as a mild, non-life-threatening condition, treatment of bacterial vaginosis is recommended if symptoms are present [2-7].

Bacterial vaginosis (BV) has been recognized as a distinct clinical entity since 1955, when Gardner and Dukes identified *Haemophilus vaginalis* (now *Gardnerella vaginalis*) as the etiologic agent [8]. Historically the variety of terms that have been used to describe BV (nonspecific vaginitis, anaerobic vaginitis, *Haemophilus vaginalis* vaginitis, *Corynebacterium* vaginitis, *Gardnerella vaginalis*) reflect the poor understanding of the pathophysiology and microbiology of this condition. Through the years, investigators have learned that BV is not a simple infection: it is not caused by a single pathogen, and there is no inflammatory response as seen in trichomonal or yeast vaginitis [9]. The etiology of bacterial vaginosis (BV) is thought to be the result of a replacement of the normal, hydrogen peroxide-producing lactobacillus-dominant vaginal flora with several other organisms including *Gardnerella vaginalis, Mobiluncus mulieris, Mobiluncus curtissi, Mycoplasma hominis* and anaerobes (*Peptostreptococcus spp,* and *Bacteroides spp.*)

The clinical criteria used to diagnose BV were standardized by Amsel et al. in 1983. He defined BV as the presence of three or more of the following signs: a white, homogeneous discharge which smoothly coats the vaginal walls; the presence of bacteria-

coated vaginal epithelial cells ("clue cells") on a wet mount or gram-stained preparation of vaginal fluid; a vaginal pH greater than 4.5; and a characteristic amine odor when vaginal secretions are alkalinized [10]. Amsel found that the presence of two or more signs on a swab of vaginal fluid diagnosed BV with 100% sensitivity, 98% specificity, 91% positive predictive value (PPV) and 100% negative predictive value.

Since these criteria were first proposed, the validity of individual signs has been studied extensively by investigators. Eschenbach et al [11], found that the presence of clue cells was more specific for BV when they represented ≥ 20% of epithelial cells. He also found that vaginal pH of 4.7 or greater was the most sensitive sign in patients with at least 20% clue cells. However, pH was the least specific sign. Thomason [12] also found that clue cells were the most sensitive and specific sign of BV, but cautions against using clue cells as the sole diagnostic criterion. Several studies have found that homogeneous discharge was not helpful in diagnosing BV [12,13]. Some women with BV may have slight or no vaginal discharge, and it may be difficult to evaluate discharge in women who have douched or had recent intercourse. [14]. The "whiff" test for volatile amines has been described as a powerful predictor of BV by some, [12,15] but Eschenbach [11] reported a PPV of only 76% for the test compared with a Gram stain diagnosis of BV. Since clinical signs are very difficult to standardize between clinicians, Gram stain has been used to augment the clinical findings. Eschenbach [11] found that the presence of clue cells correlated most highly with Gram stain criteria for BV.

Assuming the presence of a milky homogeneous vaginal discharge, a clinical diagnosis of BV is usually made on the basis of three criteria: 1) an unpleasant, fishy, amine odor, which for diagnostic purposes can be accentuated by the addition of 10% KOH to the vaginal fluid, 2) vaginal fluid pH >4.5, and 3) the presence of clue cells (vaginal epithelial cells heavily coated with bacilli) in the vaginal fluid. The presence of clue cells plus the presence of the amine odor accurately predict BV about 99% of the time [16]. An absence or marked decreased in *Lactobacillus* morphotype (large gram-positive rods) and a predominance of *Gardnerella vaginalis/Bacteroides* spp. morphotypes (small gram-variable/gram-negative rods) observed in vaginal fluid after Gram staining is considered compatible with the diagnosis of BV [2].

Clindamycin is active against the organisms commonly associated with bacterial vaginosis: namely *Bacteroides* spp., Peptococcus spp., *Gardnerella vaginalis*, *Mobiluncus* spp., and *Mycoplasma hominis* [17]. The development of clindamycin as an intravaginal preparation was prompted by an investigator in the early 1980s who was searching for an effective topical therapy for the treatment of BV and treated 10 women with a 1% clindamycin cream administered twice daily. There was marked improvement or cure in all 10 patients.[18] A subsequent study [19] in 1988, reported that oral clindamycin hydrochloride 300 mg twice daily for 7 days was effective in the treatment of bacterial vaginosis. Following these uncontrolled experiences, Pharmacia & Upjohn began clinical development of clindamycin as an intravaginal preparation with Phase II dose-finding studies to determine the most appropriate clindamycin concentration and frequency of administration. Four pivotal Phase III studies [20-23] confirmed that a 2% clindamycin vaginal cream formulation (clindamycinVC), administered once daily at

bedtime for 7 days, is a safe and effective treatment for BV. Subsequent to the approval of the 7-day clindamycin VC regimen, four studies [24-27] were conducted to evaluate the effect of a 3-day regimen of clindamycin VC for the treatment of BV. The results of these studies showed that the efficacy of a 3-day regimen of clindamycin VC is comparable to that seen with the 7-day regimen. Therefore the 3-day regimen was approved for the treatment of BV in the US and several European countries.

The sponsor is of the opinion that solid dosage forms of intravaginal medications are likely to be preferred to creams by many clinicians and patients, due to factors such as the convenience of an exact unit dose and a relatively clean administration procedure not requiring an applicator. Thus, a suppository formulation (ovule) containing 100-mg clindamycin (the recommended dose of clindamycin VC) was developed as an alternative intravaginal dosage form. The safety and efficacy of clindamycin ovule (containing 100 mg of clindamycin) in treating BV will be evaluated in this medical officer's review.

2. Bioavailability of Clindamycin Phosphate Vaginal Ovule

The systemic absorption of clindamycin was evaluated after intravaginal administration of clindamycin phosphate 100-mg ovule and clindamycin phosphate 2% cream to 12 healthy adult female volunteers in a randomized, modified two-way crossover, multiple-dose study [28]. On two separate occasions, each subject received clindamycin phosphate equivalent to 100-mg clindamycin as one ovule or 5 mL of 2% cream once daily in the evening for 3 consecutive days. During the third treatment period, subjects received 100 mg of clindamycin as a 4-minute intravenous infusion of clindamycin phosphate sterile solution (10 mg/mL). A minimum of 14 days intervened between Day 1 of each treatment period. The systemic absorption of clindamycin from the vaginal cream (about 4%) was consistent with results of previous bioavailability studies in healthy females and bacterial vaginosis patients. After intravaginal administration of clindamycin phosphate ovule, systemic absorption averaged 30% (range, 6.5% to 70%), which is about 7-fold greater than that following dosing of the vaginal cream. For the vaginal ovule treatment, no apparent trend toward higher absorption was observed in the 4 subjects reporting vaginal/vulvar pruritus and/or vaginal burning relative to the other subjects. However, results of a preclinical study of intravaginal irritation which utilized the ovariectomized rat model demonstrated mild, reversible vaginal epithelial hyperplasia in rats treated with clindamycin phosphate ovules, and trace to mild vaginal inflammation in both the treated and control (placebo ovule) animals [29]. These findings suggest that the clindamycin phosphate ovule may cause mild vaginal irritation in humans, which may facilitate drug passage into the systemic circulation.

An assessment of the bioavailability of clindamycin phosphate ovule relative to an oral dose of clindamycin hydrochloride, based on comparison of AUC values, demonstrate that systemic absorption from a 100-mg intravaginal dose of clindamycin phosphate ovule is, on average, at least 3-fold lower than that from a 150-mg or 300-mg oral dose [30-32] and at least 5-fold lower that from a 600-mg oral dose [33,34]. See Pharmacology Review dated August 9, 1999 for a complete pharmacology review.

3. Microbiology (Antimicrobial Activity)

The recognition of clindamycin's activity against the pathogens involved in bacterial vaginosis prompted the clinical evaluation of a topical clindamycin formulation for the treatment of this syndrome. Although the precise etiology of BV is not known, clearly the physiology of the vagina is disturbed with a quantitative change in the vaginal flora. In normal women the dominant organism found in the vaginal flora is usually *Lactobacillus* spp, which account for more than 95% of all the organisms present. In contrast, in BV, even though lactobacilli are found in 25%-65% of women, there is a decrease of 100 to 1000-fold in bacterial counts. *Gardnerella vaginalis* is not only more prevalent in BV, but is present at a population level two to three orders of magnitude higher than in normal women. The overgrowth of *Gardnerella vaginalis* is accompanied by similar increases in counts of *Bacteroides* spp, *Peptostreptococcus* spp. *Mycoplasma hominis*, and *Mobiluncus* spp.

Clindamycin demonstrates potent activity with minimum inhibitory concentration values of less than 1µg/mL for nearly all strains of *Mobiluncus* spp, *Mycoplasma hominis* and *Gardnerella vaginalis*. Recent in vitro studies have confirmed the continuing utility of clindamycin against these bacterial species. Clindamycin also demonstrates strong activity against *Bacteroides* spp and *Peptostreptococcus* spp. With the goal of therapy being to reduce the overgrowth of the bacterial associated with BV, the use of clindamycin as a therapeutic modality is supported by the in vitro bacterial susceptibility data, and by the quantitative correlation of antibacterial activity with clinical efficacy in humans [35-37].

4. Scientific Rationale for Suppository Formulation

Bacterial Vaginosis (BV) is a very common disorder seen in sexually active women and account for approximately 40% of all causes of vaginal infections seen by the gynecologist today. Metronidazole administered orally and/or intravaginally are approved and effective treatments for BV but are associated with multiple side effects including gastrointestinal side effects, [redacted] like reactions associated with alcohol intake and mutagenic and carcinogenic effects observed in some pre-clinical studies, These side effects have led to restricted use of metronidazole in treating BV especially in pregnant women. Other oral antibiotics such as ampicillin and cephalosporins are also prescribed for the treatment of BV, but are reported to be less effective than oral metronidazole. In addition, triple sulfa vaginal cream has been used to treat BV, but was shown to be somewhat less effective than orally administered [redacted] (an agent structurally related to metronidazole).

Clindamycin has good antibacterial activity against many of the organisms associated with BV and the 2% clindamycin vaginal cream formulation is approved as once daily treatment for 3 or 7 days. The sponsor is of the opinion that solid dosage forms of intravaginal clindamycin may be preferred to creams by many clinicians and patients, due to factors such as the convenience of an exact unit dose and a relatively clean administration procedure not requiring an applicator. They contend that the ovule

containing 100-mg clindamycin would represent a safe and effective therapy for BV with potentially enhanced patient compliance relative to existing intravaginal therapies.

5. Overview of Clindamycin Ovule Clinical Studies

The sponsor developed and conducted a clinical program to examine the safety and efficacy of clindamycin VO in the treatment of BV. The clinical program consists of three completed studies. They comprise a Phase II placebo-controlled pilot study and two adequate and well-controlled Phase III studies, one using clindamycin VC as the control treatment and one using oral metronidazole. The safety and efficacy studies were multicenter, randomized, blinded trials, using 100-mg clindamycin ovules versus a control (placebo or active comparator); they also used identical criteria for determining the efficacy of the study drugs. Study M/1100/0283 [38] was a placebo controlled, double blind, dose-duration study using a parallel design with sequential analysis: After initial enrollment for a 3-day regimen versus placebo was complete, enrollment for a 5-day regimen versus placebo was begun; 5-day enrollment was to be stopped if analysis of all 3-day efficacy data showed this regimen to be effective. Study M/1114/0001 [39] was an active-controlled, observer-blind study comparing a 3-day clindamycin VO regimen to the approved 7-day regimen of clindamycin VC. Study M/1114/0002 [40] was an active-controlled, double-blind, double-dummy study comparing clindamycin VO to oral metronidazole. Patients received either clindamycin VO for 3 days plus oral placebo for 7 days or oral metronidazole for 7 days plus placebo suppositories for 3 days. Since the three studies share many key design features, they will be discussed as a group and in the subsequent text, the studies will be referred to by the last four digits of the protocol number.

6. Inclusion Criteria

For all studies, women were required to be 16 to 60 years old. The required clinical diagnosis of BV was based on three criteria: vaginal fluid with pH>4.5, presence of clue cells in the vaginal discharge, and an amine odor after adding 10% (KOH) to the vaginal discharge. In addition, for studies 0001 and 0002 a Gram stain of vaginal fluid was required to be compatible with a diagnosis of BV.

7. Exclusion Criteria

Patients were excluded for any of the following reasons: known allergy to clindamycin or lincomycin; pregnancy or breast feeding; systemic or vaginal antimicrobial therapy within the previous 2 weeks; previous enrollment in the study; need for non-protocol antibiotic therapy; positive test for *Neisseria gonorrhoea, Candida albicans, Trichomonas vaginalis,* or (for studies 0001 and 0002) *Chlamydia trachomatis;* atrophic vaginitis. Clinical evidence of genital herpes infection; anticipation of menses during treatment or follow-up visit; or any other condition judged by the investigator to be cause for exclusion.

8. Number of Patients

A total of 1177 (Table 1) patients was treated in this clinical program (excluding patient in the 5-day arm of study 0283, which stopped early per protocol): 589 patients were

treated with clindamycin VO, 335 with clindamycin VC, 196 with oral metronidazole, and 57 with placebo suppositories.

Table 1. Distribution of Patients (ITT Population)

STUDY	CVO	CVC	MET	PLACEBO	TOTAL
0283	59	0	0	57	116
0001	203	0	196	0	399
0002	327	335	0	0	662
TOTAL	589	335	196	57	1177

9. Doses and Regimens of Study Medication

Patients were randomized to the following treatment groups:

- Clindamycin VO (all studies): one 100 mg ovule (or placebo in study 0283) inserted intravaginally at bedtime for 3 consecutive days (or 5 days in study 0283); study 0002 patients also took 2 placebo capsules orally twice daily for 7 consecutive days.
- Clindamycin VC (study 0001): 5 g (one applicatorful) of 2% cream equivalent to 100 mg clindamycin) applied intravaginally at bedtime for 7 consecutive days.
- Metronidazole (study 0002): 500 mg (two 250 mg capsules) orally twice daily for 7 consecutive days, plus 1 placebo vaginal ovule inserted intravaginally at bedtime for 3 consecutive days.

10. Data Collection and Evaluation of Clinical Status

Patients were required to return for two follow-up visits in all studies. For study 0283, the scheduled visit windows (per protocol) were 4 to 7 days and 21 to 35 days after completion of treatment (corresponding to 7 to 10 days and 24 to 38 days after the start of treatment for the 3-day regimen); for studies 0001 and 0002, the scheduled windows (per protocol) were 12 to 16 days and 28 to 42 days after the start of treatment. At each of these visits, tests were performed for the three key diagnostic criteria; vaginal pH; amine odor when fluid was mixed with 10% KOH; and clue cells in vaginal fluid.

Clinical status (**cured, failed, or non-assessable**) was determined at each visit based on the number of diagnostic criteria that had resolved, i.e., returned to normal values (vaginal fluid pH<4.5, absence of odor, absence of clue cells). At the first return visit, cure was defined as the return to normal of at least two criteria; at the second return visit, cure was defined as the return to normal of all three criteria. **All other outcomes were defined as failures or were considered non-assessable in the absence of available data.** Patients who did not complete a full course of active drug (i.e., those receiving clindamycin VO for fewer than the assigned 3 or 5 days, or receiving clindamycin VC or metronidazole capsules for fewer than 6 days) because of an adverse event were designated side-effect failures. Patients whose status was failed at the first visit were not required to return for the second visit but were carried forward as failures and were to be treated at the discretion of the investigator.

11. Patient Evaluability

Patients were considered fully evaluable for efficacy unless any 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 and/or fewer than 21 capsules taken);
- any lapse in dosing of clindamycin VO (or placebo ovule in study 0283) or lapse of >1 day in dosing of clindamycin VC 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 was required;
- development of a concomitant genital infection (or discharge of unknown etiology) in studies 0001 and 0002;

12. Evaluation Windows

In all the studies, there were a number of patients who did not return for follow-up visits within the time windows defined in the protocols. The frequent failure to return within protocol-defined windows affected the determination of evaluability. However, in retrospect there is no clinical rationale to exclude patients from the evaluable population if the only reason for exclusion was returning outside the defined window. Therefore, for the purpose of determining evaluability, wider windows were used for the second follow-up visit; The sponsor increased the protocol-specified intervals by 10 days before and after the start of treatment, respectively to 14 to 48 days (study 0283) or 18 to 52 days (studies 0001 and 0002). The Reviewing Medical Officer of the FDA recommended expanding the second return visit window by 10 days: 28 to 52 days after start of treatment for studies 0001 and 0002 and 24 to 48 days for study 0283, with a minimum of 14 days between the first and second follow-up visits. The windows for determination of patient evaluability in this review will be as follows:

Study Report (SR) Window:	**18 to 52 days after start of treatment (±10 days relative to the protocol specified windows).**
Protocol-Defined Window:	**28 to 42 days after the start of treatment.**
FDA requested windows:	**28 to 52 days after the start of treatment, and at least 14 days after the first follow-up visit.**

13. Efficacy Measures

Primary Efficacy

The planned primary efficacy measure was overall clinical outcome (cured, failed, or non-assessable) among patients deemed evaluable. Overall clinical outcome was determined using two methods; the first method, recommended by the sponsor, used the following 3 clinical diagnostic criteria: pH (resolved when ≤4.5, failed when > 4.5), amine odor (resolved when absent, failed when present), and clue cells (resolved when absent, failed when present). Resolution of at least 2 of these 3 criteria at the first follow-up visit and all 3 at the second follow-up visit was to be considered a cure. Resolution of

fewer than 2 criteria at the first follow-up visit or fewer than 3 at the second follow-up visit was to be considered a failure, and the absence of adequate data to categorize an outcome as cured or failed was to be considered non-assessable. See algorithm for overall clinical outcome.

Algorithm for Overall Clinical Outcome

Status of First Follow-up Visit	Status of Second Follow-up Visit	Overall Outcome
Cure (at least 2 of 3 criteria normal)	Cure (3 of 3 criteria normal)	Cure
	Failure (fewer than 3 criteria normal)	Failure
	Non-assessable	Non-assessable
Failure (fewer than 2 criteria normal)	Not applicable (Patients not required to return for visit)	Failure
Side-effect failure		
Non-assessable	Cure	Non-assessable
	Failure	Failure
	Non-Assessable	Non-assessable

The second method used to measure primary efficacy was recommended by the FDA using odor and clue cells as the only criteria for evaluation of clinical status. This recommendation is based on the evidence that the presence of clue cells plus the presence of amine odor alone can more accurately predict BV (with about 99% accuracy) than can these 2 criteria in combination with data on vaginal fluid pH. [38]. This analysis defines cure at either follow-up visit as resolution of both clue cells and odor and failure as resolution of one or fewer of these criteria.

If a patient failed at either visit, regardless of the outcome at the other, overall clinical outcome was considered as failed. In cases where data were only available at one of the two follow-up visits, overall clinical outcome was considered failed if BV symptoms were present, and not evaluable if BV symptoms were resolved. In addition, patients who discontinued treatment due to a medical event are included in the evaluable patient population as failures.

This Medical Officer's review will include the primary efficacy analyses of the overall clinical outcome based on 3 criteria (pH, clue cells and odor) and 2 criteria (clue cells and odor) on the evaluable populations of each study utilizing the widened allowable windows (SR window). However, analyses utilizing the protocol-defined window and the FDA-requested window for the evaluable patient population are also included for comparative purposes when deemed appropriate.

Secondary Efficacy

In this review, clinical outcome of the ITT population is based on the number of assessable ITT patients. This population is defined as all enrolled patients who received any treatment drug and returned for the first follow-up visit or reported sufficient data to be considered as a cure or failure. For each study, planned secondary efficacy measures included analyses of clinical outcome for the assessable intent-to-treat (ITT) population using both the 3 (pH, odor and clue cells) and 2 (clue cells and odor) criteria as defined above.

Gram stain score results defined as (normal, intermediate or compatible with BV) at each follow-up for evaluable patients in studies 0001 and 0002 were determined and compared to the results of the clinical outcome. Gram-stain smears of vaginal fluid collected at entry and both return visits were evaluated by a standardized scoring system. Smears were examined microscopically under oil immersion (x1000 magnification) for the following groups of bacterial morphotypes: lactobacillus (large gram-positive rods), *Gardnerella vaginalis/ Bacteroides* spp (small gram-variable/gram-negative rods), and *Mobiluncus* spp (curved gram-variable rods). A quantity index was derived for each group according to the number of morphotypes in the group seen per oil immersion field:

No Morphotypes	Quantity Index
0	0
<1	1+
1-4	2+
5-30	3+
>30	4+

A Nugent score for each morphotype group was derived according to the quantity index as described below:

MORPHOTYPE	QUANTITY	SCORE
Lactobacillus	4+	0
	3+	1
	2+	2
	1+	3
	0	4
***Gardnerella vaginalis/ Bacteroides* spp**	0	0
	1+	1
	2+	2
	3+	3
	4+	4
***Mobiluncus* spp**	0	0
	1+ or 2+	1
	3+ or 4+	2

An overall score for compatibility with BV (0 to 10) was derived by adding the scores for each morphotype, and the Gram stain outcome was rated as one of the following:

Normal – overall score 0 to 3
Intermediate – overall score 4 to 6
Compatible with BV – overall score 7 to 10

Safety

The only measures of safety were the reporting of medical events. All adverse events that were spontaneously reported by the patient or directly observed by the investigator during the study were to be reported to the sponsor, regardless of whether the events were considered to be related to treatment with the study medication. Also, any event that the investigator judged to be related to treatment with the study medication and that occurred subsequent to the study period were to be reported.

All adverse events were to be followed until they resolved or until the patient's participation in the study ended. All serious adverse events and those non-serious events that were assessed by the investigator as possibly related to treatment with the study medication were to be followed even after the patient's participation in the study had ended, until they resolved, or until the investigator could classify them as "chronic" or "stable".

The original terms used by investigators to identify medical events in the case report forms were translated into COSTART terms by the sponsor and included in the safety report. The medical events were then grouped according to body system and preferred terms. All safety data in this review were listed, categorized and summarized by the sponsor, reviewed by the medical officer and included in the safety analyses of each study.

14. Analysis of Results of Individual Controlled Studies

Study 0283

Title: Clindamycin phosphate suppository treatment of bacterial vaginosis: a placebo controlled, dose-duration study.

Objectives: To determine if clindamycin phosphate vaginal ovules (clindamycin VO), given once daily as a 3-day or 5-day regimen, provide acceptable safety and efficacy in the treatment of bacterial vaginosis (BV). To define acceptable schema for further trials comparing clindamycin VO to conventional therapy for BV.

Investigators: Investigators who participated in the study and their study sites are listed below:

Adams, Jr., Willie, M. D.
Albany, New York

Chatwani, Ashwin, M. D.
Philadelphia, Pennsylvania

Duff, Patrick, M. D.
Gainesville, Florida

Livengood, III, Charles, M. D.
Durham, North Carolina

Maccato, Maurizio, M. D.
Houston, Texas

Martens. Mark, M. D.
Galveston, Texas

O'Sullivan, Mary J., M. D.
Miami, Florida

Study Design: This was a multicenter, prospective, randomized, double-blind study. Patients with a clinical diagnosis of BV were randomized to receive either clindamycin ovule (VO) or placebo. The 3-day regimen was studied first; enrollment for the 5-day regimen began after 3-day enrollment was completed, and was stopped because the 3-day proved effective. Pretreatment visit activities included informed consent, medical history, pelvic examination, diagnostic tests (vaginal fluid, pH, vaginal discharge, clue cells, vaginal fluid odor), test for concomitant pathogens and pregnancy and reporting of

concomitant medication. Follow-up visit activities (7-10 days and 14-48 days after start of treatment) included a vulvovaginal examination, repeat diagnostic tests, tests for concomitant pathogens if symptomatic, and reporting of adverse events and concomitant medications.

Patient Disposition

All enrolled patients were considered as intent-to-treat (ITT) and included in the analysis. The ITT population of the 3-day regimen comprised 116 patients (clindamycin VO, 59 patients; placebo patients, 57 patients). Enrollment for the 5-day arm of Study 0283 was limited to 14 patients (7 clindamycin and 7 placebo); due to the small sample size, efficacy data for these patients were not analyzed.

Demographic Characteristics

Table 2 summarizes demographic data for the 3-day ITT patients. The two 3-day ITT treatment groups were balanced at baseline with regard to age, weight and race with no statistically significant differences between treatment groups.

Table 2 Patient Demographics (3-Day Regimen)

Demographic Variable	CVO N=59	PBO N=57	Total N=116	Treatment P-value
Mean Age, yr ± SD [Range]	29.4 ± 9.7	27.8 ± 8.4	28.6 ± 9.1	0.3608
Mean Wgt, kg ± SD [Range; No. Reporting]	75.0 ±20.1	68.9 ± 13.2	72.1 ±17.3	0.0590
Race: White	10 (16.9%)	11(19.3%)	21 (18.1%)	0.8503
Black	44 (74.6%)	43 (75.4%)	87 (75.0%)	
Hispanic	5 (8.5%)	3 (5.3%)	8 (6.9%)	

Patient Evaluability

Of the 116 ITT 3-day patients, a total of 85 patients were evaluable (42 clindamycin VO; 43 placebo) for efficacy. 31 patients, 28.8% (17/59) of clindamycin VO patients and 24.6% (14/57) of placebo patients were non-evaluable for efficacy. The number of evaluable 3-day patients for each treatment group enrolled by each investigator are given in Tables 4 and 5. A listing of all reasons for non-evaluability of 3-day patients is in Table 3.

Table 3. Primary Reasons for Non-Evaluability (3-Day Regimen)

Reason for Non-Evaluability	Number of Patients (% of Group)		
	CVO N=59	PBO N=57	Total N=116
No information available on study drug administration	2 (3.4)	2 (3.5)	4 (3.4)
Did not have clinical BV	0 (0.0)	1 (1.8)	1 (0.9)
Did not meet inclusion/exclusion criteria	2 (3.4)	1 (1.8)	3 (2.6)
Additional antimicrobial therapy given	4 (6.8)	2 (3.5)	6 (5.2)
Did not comply with dosing regimen	3 (5.1)	3 (5.3)	6 (5.2)
Follow-up not within required window*	5 (8.5)	5 (8.8)	10 (8.6)
Menses during treatment or follow-up visit	1 (1.7)	0 (0.0)	1 (0.9)
Total Nonevaluable	17 (28.8)	14 (24.6)	31 (26.7)

*14 – 48 Days

The most common reason for non-evaluability was failure to return for follow-up visits within required (SR) windows (8.6% of patients). The percentage of patients considered non-evaluable for each primary reason was similar for the two treatment groups.

Efficacy Results

Primary Efficacy (Overall clinical Outcome for Evaluable Patients)

1) Primary analysis (Three Diagnostic Criteria)

A summary of the treatment outcome by investigator for evaluable 3-day patients, as determined from tests of pH, clue cells and odor, is shown in Table 4 for the clindamycin treatment group and in Table 5 for the Placebo treatment group.

TABLE 4
OVERALL CLINICAL OUTCOME FOR EVALUABLE 3-DAY PATIENTS BY 3 DIAGNOSTIC CRITERIA
CLEOCIN (PROTOCOL 283)

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ADAMS	16	11	4	7	9	2	7	11	4	7
CHATWANI	10	6	5	1	4	3	1	5	4	1
DUFF	3	2	1	1	2	1	1	2	1	1
LIVENGOOD	16	13	5	8	13	5	8	13	5	8
MARTENS	10	7	4	3	6	3	3	6	3	3
O"SULLIVAN	4	3	3	0	3	3	0	3	3	0
TOTAL	59	42	22	20	37	17	20	40	20	20

TABLE 5
OVERALL CLINICAL OUTCOME FOR EVALUABLE 3-DAY PATIENTS BY 3 DIAGNOSTIC CRITERIA
PLACEBO (PROTOCOL 283)

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ADAMS	16	10	1	9	9	0	9	10	1	9
CHATWANI	10	9	1	8	9	1	8	9	1	8
DUFF	2	1	1	0	1	1	0	1	1	0
LIVENGOOD	15	13	1	12	13	1	12	13	1	12
MACCATO	1	0	0	0	0	0	0	0	0	0
MARTENS	9	7	2	5	7	2	5	7	2	5
O"SULLIVAN	4	3	0	3	3	0	3	3	0	3
TOTAL	57	43	6	37	42	5	37	43	6	37

A summary of the overall clinical outcome for evaluable patients based on the three diagnostic criteria is shown in Table 5a. Utilizing the SR windows, the primary analysis of the evaluable 3-day patient population, reveals that 52.4% (22/42) of patients in the clindamycin VO group were cured compared with 14.0% (6/43) of the patients in the placebo group. This difference was statistically significant (CI = 20.1,56.7). Similar cure rates were found for each treatment group when the protocol-defined and FDA-requested windows were considered.

TABLE 5a
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS
BY 3 DIAGNOSTIC CRITERIA
(SR, PROTOCOL-DEFINED, FDA-REQUESTED WINDOWS)

EVALUABLE PATIENTS	OUTCOME	No of Patients (% of Group)		95% CI
		CVO	PBO	
SR WINDOW (18 – 52 DAYS) N = 42 CVO; 43 PBO	CURE	22 (52.4)	6 (14.0)	20.1, 56.7
	FAILURE	20 (47.6)	37 (86.0)	
PROTOCOL-DEF. WINDOW (28 – 42 DAYS) N = 37 CVO; 42 PBO	CURE	17 (45.9)	5 (11.9)	15.2, 52.9
	FAILURE	20 (54.1)	37 (88.1)	
FDA REQ. WINDOW (28 – 52 DAYS) N = 40 CVO; 43 PBO	CURE	20 (50.0)	6 (14.0)	17.4, 54.9
	FAILURE	20 (50.0)	37 (86.0)	

CVO – Clindamycin vaginal ovule, 3-day treatment
PBO – Placebo vaginal ovule, 3-day treatment
DEF – Defined; REQ –Requested

2) Secondary Analysis (Two Diagnostic Criteria)

A summary of the 3-day treatment outcome by investigator as determined from tests of clue cells and odor is shown in Table 6 for the clindamycin group and Table 7 for the placebo treatment group.

TABLE 6
OVERALL CLINICAL OUTCOME FOR EVALUABLE 3-DAY PATIENTS BY 2 DIAGNOSTIC CRITERIA
CLEOCIN (PROTOCOL 283)

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ADAMS	16	11	4	7	9	2	7	11	4	7
CHATWANI	10	6	5	1	4	3	1	5	4	1
DUFF	3	2	1	1	2	1	1	2	1	1
LIVENGOOD	16	13	9	4	13	9	4	13	9	4
MARTENS	10	7	4	3	6	3	3	6	3	3
O"SULLIVAN	4	3	3	0	3	3	0	3	3	0
TOTAL	59	42	26	16	37	21	16	40	24	16

TABLE 7
OVERALL CLINICAL OUTCOME FOR EVALUABLE 3-DAY PATIENTS BY 2 DIAGNOSTIC CRITERIA
PLACEBO (PROTOCOL 283)

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ADAMS	16	10	3	7	9	2	7	10	3	7
CHATWANI	10	9	1	8	9	1	8	9	1	8
DUFF	2	1	1	0	1	1	0	1	1	0
LIVENGOOD	15	13	1	12	13	1	12	13	1	12
MACCATO	1	0	0	0	0	0	0	0	0	0
MARTENS	9	7	2	5	7	2	5	7	2	5
O"SULLIVAN	4	3	0	3	3	0	3	3	0	3
TOTAL	57	43	8	35	42	7	35	43	8	35

Based on the secondary analysis of the evaluable 3-day patient population, 61.9% (26/42) of the patients in the clindamycin VO group were cured compared with 18.6% (8/43) of the patients in the placebo group (SR window). The difference was statistically significant. Cure rates for Protocol–defined and FDA-requested windows were comparable and are included in Table 8 for comparison. Since improvement was only required in two rather than three diagnostic criteria, these cure rates are consistently greater than those obtained by analysis of three diagnostic criteria, by definition.

SUMMARY TABLE 8 OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY 2 DIAGNOSTIC CRITERIA (SR, PROTOCOL-DEFINED, FDA-REQUESTED WINDOWS)

EVALUABLE PATIENTS	OUTCOME	No of Patients (% of Group)		95% CI
		CVO	PBO	
SR WINDOW (18 – 52 DAYS) N = 42 CVO; 43 PBO	CURE	26 (61.9)	8 (18.6)	24.6, 62.3
	FAILURE	16 (38.1)	35 (81.4)	
PROTOCOL-DEF. WINDOW (28 – 42 DAYS) N = 37 CVO; 42 PBO	CURE	21 (56.8)	7 (16.7)	20.6, 59.6
	FAILURE	16 (43.2)	35 (83.3)	
FDA REQ. WINDOW (28 – 52 DAYS N = 40 CVO; 43 PBO	CURE	24 (60.0)	8 (18.6)	22.3, 60.5
	FAILURE	16 (40.0)	35 (81.4)	

CVO – Clindamycin vaginal ovule, 3-day treatment
PBO – Placebo vaginal ovule, 3-day treatment
DEF – Defined; REQ –Requested

Secondary Efficacy

1) Overall Clinical Outcome for Assessable ITT Patients

Primary analysis: A summary of the treatment outcome as determined from tests of pH, clue cells, and odor for all patients who received any drug and were assessable , (ITT) population, is shown in Table 9.

TABLE 9 Overall Clinical Outcome for 3-Day ITT Patients by Three Diagnostic Criteria (Primary Analysis)

OUTCOME	NUMBER OF PATIENTS (% OF GROUP*)		95% CI
	CVO (N = 59; 49 ASSESSABLE)	PBO (N = 57; 49 ASSESSABLE)	
CURE	27 (55.1%)	7 (14.3%)	23.8, 57.8
FAILURE	22 (44.9%)	42 (85.7%)	

CVO – clindamycin vaginal ovule
PBO – Placebo
* Percentage based on number of patients assessable

Based on the primary analysis of the 3-day ITT patient population, 55.1% (27/49) of the assessable patients in the clindamycin VO group were cured compared with 14.3% (7/49) of the assessable patients in the placebo group. Assessable patients were defined as those patients who had data reported for both follow-up visits or those who had sufficient data from visit one to be deemed a failure. This difference was statistically significant (95%CI 23.8, 57.8). The ITT cure rates for the clindamycin VO group are comparable to those observed in evaluable patients.

Secondary analysis. The summary of the treatment outcome as determined from tests of clue cells and odor only is shown in Table 10.

TABLE 10 Overall Clinical Outcome for 3-Day ITT Patients by Two Diagnostic Criteria (Secondary Analysis)

OUTCOME	NUMBER OF PATIENTS (% OF GROUP*)		95% CI
	CVO (N = 59; 49 ASSESSABLE)	PBO (N = 57; 49 ASSESSABLE)	
CURE	31 (63.3%)	9 (18.0%)	27.6, 62.2
FAILURE	18 (36.7%)	41 (82.0%)	

CVO – clindamycin vaginal ovule
PBO – Placebo
* Percentage based on number of patients assessable

Based on the secondary analysis of the ITT patient population, 63.3% (31/49) of the assessable patients in the clindamycin VO group were cured compared to 18.0% (9/50) of the assessable patients in the placebo group. The difference was statistically significant (95% CI= 27.6, 62.2). Since improvement was only required in two rather than three diagnostic criteria, these cure rates are consistently greater than those obtained by analysis of three diagnostic criteria, by definition. The ITT cure rates for the clindamycin VO group are comparable to those observed in evaluable patients.

SAFETY RESULTS

Overall Summary of Medical Events

Similar numbers of patients in each treatment group reported at least one medical event for both the 3-day regimen (clindamycin VO patients 27.1% [16/59]; placebo patients 28.1% [16/57]) and the 5-day regimen (clindamycin VO patients 42.9% [3/7]; placebo patients 33.3% [2/6]) (Table 11). The distribution of reported medical events by body system was similar in both treatment groups within both regimens; events were most frequently reported in the body (as a whole) and urogenital systems. Frequencies of events were generally low; only headache, moniliasis, trauma, upper respiratory infection, diarrhea, vulvovaginal disorder, urinary tract infection and unintended pregnancy were reported by more than one patient in either treatment group. There did not appear to be meaningful differences in event frequencies between treatment groups;

however, the total number of events reported for the 3-day regimen was greater for the clindamycin VO group (32) than for the placebo group (17). There were only three events reported in each treatment group for the 5-day regimen.

Table 11
Medical Events By Body System and COSTART Description
ITT Patients (3-Day and 5-Day Regimens) All Causality

Body System	COSTART Description	Cleocin Ovule 3-Day		Placebo 3-Day		Cleocin Ovule 5-Day		Placebo 5-Day	
		N	%	N	%	N	%	N	%
Patient with No Medical Events		43	72.9	41	71.9	4	57.1	4	66.7
Patients with at Least One Medical Event		16	27.1	16	28.1	3	42.9	2	33.3
Body	Abdominal Cramp	1	1.7						
	Fever	1	1.7						
	Generalized Pain	1	1.7						
	Headache	4	6.8	5	8.8	1	14.3		
	Infection Fungal Nos	1	1.7						
	Infection Parasitic Nos			1	1.8				
	Localized Pain	1	1.7						
	Moniliasis	2	3.4						
	Pelvic Pain	1	1.7						
	Trauma	2	3.4						
	Upper Resp Infection	2	3.4	2	3.5			1	16.7
Digestive	Diarrhea	3	5.1	1	1.8				
	Gastritis			1	1.8				
	Nausea	1	1.7					1	16.7
	Vomiting	1	1.7						
Nervous	Dizziness			1	1.8				
Respiratory	Congestion Chest	1	1.7						
Skin	Dermatitis Fungal	1	1.7						
	Herpes Simplex Derm			1	1.8			1	16.7
	Rash	1	1.7						
Urogenital	Disorder Vulvovaginal	2	3.4						
	Dysmenorrhea	1	1.7						
	Hemorrhage Uterine					1	14.3		
	Infection Urinary Tract	2	3.4	1	1.8	1	14.3		
	Pap Smear Abnormal	1	1.7						
	Pregnancy Unintended			2	3.5				
	Salpingitis	1	1.7						
	Vaginal Pain			1	1.8				
	Vaginitis Trichomonal			1	1.8				
	Vaginitis/Vag Inf	1	1.7						
Total Number of Medical Events		32		17		3		3	
Number of Patients on Which % is Based		59		57		7		6	

Medical Event Frequencies by Maximum Intensity

Of the 55 total events reported for both the 3-day and 5-day regimens, one event (an unintended pregnancy reported in a 3-day placebo patient) was rated as severe. There was no apparent difference between the two treatment groups with regard to the distribution of event intensity, with the majority of events in either group rated as mild.

Drug Related Medical Events

The investigators assessed the relatedness of the medical events to the use of study drug. The 3-day clindamycin VO patients (total 59) reported 6 events judged to be drug-

related: abdominal cramp, fungal infection, diarrhea, rash, and vulvovaginal disorder (2 reports). Fifty-seven 3-day placebo patients reported 2 events (diarrhea and vaginal pain) judged to be drug related. All the drug-related events reported for the 3-day regimen were mild or moderate in intensity. No drug-related events were reported for the 5-day regimen.

Dropouts Due to Medical Events

A listing of patients who dropped out of the study due to medical events is in Table 12. Seven patients dropped out due to nonserious medical events, comprising five 3-day patients (2 clindamycin VO, 3 placebo) and two 5-day patients (1 clindamycin VO, 1 placebo). A detailed narrative summary for each patient who dropped out follows the table.

TABLE 12 MEDICAL EVENTS FOR PATIENTS WHO DROPPED OUT DUE TO MEDICAL EVENTS

Patient Number	INVESTIGATOR	INVESTIGATORS DESCRIPTION (EVENT)	INTENSITY	STUDY DAY	DRUG-RELATED*
CLINDAMYCIN VO (3-DAY)					
52	ADAMS	URI	MILD	+25†	NO
		UTI	MILD	3	NO
141	LIVENGOOD	RED RASH ON STO-MACH AND FOREARMS	MODERATE	+1†	YES
		VAGINAL ITCHING	MODERATE	+1†	YES
		YEAST INFECTION	MILD	+1†	YES
PLACEBO (3-DAY)					
60	ADAMS	UTI	MILD	+4†	NO
62	ADAMS	HSV II flare-up	MILD	+5†	NO
137	LIVENGOOD	*TRICHOMONAS*	MILD	+8†	NO
CLINDAMYCIN VO (5-DAY)					
1013	ADAMS	UTI	MILD	+3†	NO
PLACEBO (5-DAY)					
1011	ADAMS	HSV II flare-up	MILD	+3†	NO

*Investigators opinion
†Days after treatment discontinued

Narrative for Patient #52[redacted]
Investigator: Adams
Medical Events: Upper respiratory tract infection, urinary tract infection
This 19-year-old, 54-kg black woman was enrolled in the study (3-day clindamycin VO group) on 5/28/93. The patient developed a urinary tract infection on 5/30/93 for which she received Macrobid. At the time of the second follow-up visit, the patient was found to have an upper respiratory tract infection and vaginal monilia, for which she received Zithromax and vagistat. The patient was dropped from the study because of the receipt of the urinary tract antimicrobial as well as the systemic antibiotic and vaginal antifungal.

Narrative for Patient # 60
Investigator: Adams
Medical Event: Urinary Tract Infection
This 27-year-old, 75-kg white woman was enrolled in the study (3-day placebo group) on 6/25/93. At the first follow-up visit, the patient was found to have a urinary tract infection and received Macrobid as treatment. The patient was dropped from the study because of the receipt of Macrobid.

Narrative for Patient #62
Investigator: Adams
Medical Event: HSV_2 infection
This 21-year-old, 64-kg black woman was enrolled in the study (3-day placebo group) on 6/29/93. At the first follow-up visit, the patient was found to have HSV_2 infection for which she received Zovirax; also, the patient had symptoms of bacterial vaginosis and/or monilia and therefore received both Flagyl and Terazol therapy. The patient was dropped because of the antibiotic and antiviral therapies.

Narrative for Patient #137
Investigator: Livengood
Medical Event: *Trichomonas vaginalis* infection
This 25-year-old, 45-kg black woman was enrolled in the study (3-day placebo group) on 10/7/93. On the second examination on 10/18/93, the patient was found to have a positive vaginal smear for *Trichomonas vaginalis*. The patient received treatment for the infection and was dropped from the study because of this finding.

Narrative for Patient #141
Investigator: Livengood
Medical Events: Red rash on stomach and forearms, vaginal itching, yeast infection.
This 30-year-old, 150-kg white woman was enrolled in the study (3-day clindamycin VO group) on 11/15/93. On 11/17/93 the patient developed vaginal itching and a rash on the stomach; she was found to have no clue cells, but yeast was found on the screening examination. The investigator believed that the red rash on the stomach might have been an allergic reaction to the study drug, of which the patient took only one dose. The patient was dropped from the study because of the adverse events.

Narrative for Patient #1011
Investigator: Adams
Medical Event: Herpetic flare-up
This 19-year-old, 54-kg black woman was enrolled in the study (5-day placebo group) on10/26/93. At the first follow-up visit on 11/9/93, the patient was found to have continuing symptoms of bacterial vaginosis, as well as a herpetic eruption on the labia majora. The patient received Flagyl and Zovirax as treatment for these conditions. The patient was dropped from the study secondarily to the herpetic flare-up.

Narrative for Patient #1013
Investigator: Adams
Medical Event: Urinary tract infection
This 21-year-old, 91-kg black woman was enrolled in the study (5-day clindamycin VO group) on 11/5/93. At the first follow-up visit on 11/12/93, the patient was found to have a urinary tract infection for which she received treatment with Keflex. The patient was dropped from the study secondarily to the use of the systemic antibiotic. The patient continued to have urinary tract infection symptoms and on 11/29/93 received ciprofloxacin.

Study 0283 Summary

This study indicates that a 3-day course of clindamycin vaginal ovules (clindamycin VO) is significantly more effective than placebo in the treatment of bacterial vaginosis (BV). The overall cure rate by the primary efficacy analysis for the evaluable population was 52.4% in the clindamycin VO patients, compared to 14.0% in the placebo patients (95% CI = 20.1, 56.7). Similar results were observed in the intent-to-treat population (55.1% versus 14.3% , respectively (95% CI = 23.8, 57.8). In accordance with the study protocol, the efficacy observed for the 3-day regimen was sufficient to justify discontinuing the planned 5-day regimen, for which only 14 patients were enrolled and 13 followed. Therefore efficacy analysis of data from the 5-day patients was not done.

The secondary efficacy analysis (based on clue cells and odor only) of the 3-day regimen showed higher overall cure rates than the primary analysis for both the evaluable population (clindamycin VO 61.9 %, placebo 18.6%), and the ITT population (clindamycin VO 63.3%, placebo 18.0%) with statistically significant differences between treatment groups. The cure rate difference at the second visit may reflect the influence of the vaginal fluid pH data on the primary analysis. The rates of improvement in pH at each visit were consistently lower than those observed for clue cells or odor; thus improvement in pH appears to be a limiting factor for cure rate at the second visit by the primary analysis, which requires improvement in all three criteria. The higher cure rates by the secondary analysis may reflect the absence of this limiting factor, since pH was not considered.

The predominant reason for non-evaluability was failure to return for follow-up, or follow-up visits occurring outside the desired windows. The distribution of reasons for non-evaluability was similar between treatment groups.

Clindamycin ovules were well tolerated in this study. Reported frequencies of medical events were generally low; few events were reported by more than one patient in either treatment group. There did not appear to be meaningful differences in event frequencies between treatment groups; however; the total number of events reported for the 3-day regimen was greater for the clindamycin VO group (32) than for the placebo group (17). Clindamycin VO patients reported 6 events judged to be drug-related and placebo patients reported 2 such events, all of which were of mild to moderate intensity. No deaths or serious medical events were reported during this study. Seven patients (3 clindamycin VO, 4 placebo) dropped out due to non-serious medical events (mainly concurrent infections) of mild to moderate intensity; events in one of these patients (in the 3-day clindamycin VO regimen) were considered drug related.

Conclusion

Clindamycin 100 mg vaginal ovules given once nightly for 3 consecutive nights appear to be safe and effective therapy for bacterial vaginosis, with a cure rate superior to placebo.

Study 0001

Title: Efficacy of Clindamycin Ovule (3-Day Treatment) Vs Clindamycin Vaginal Cream (7-Day Treatment) in Bacterial Vaginosis.

Objectives: To compare the efficacy and safety of clindamycin vaginal ovule given as a 3-day regimen with clindamycin vaginal cream given as a 7-day regimen in the treatment of bacterial vaginosis (BV).

Investigators: Eighteen domestic and two foreign well-qualified investigators participated in the study. Their names and investigative sites are listed below:

Arrendondo, Jose L., M.D.
Lomas Virreyes, Mexico

Benrubi, Guy, M.D.
Jacksonville, Florida

Chatwani, Ashwin, M. D.
Philadelphia, Pennsylvania

Gall, Stanley, M. D.
Louisville, Kentucky

Gordon, Stephen F., M. D.
Atlanta, Georgia

Jackson, Raymond, M. D.
Southfield, Michigan

Lesser, Robert D., M. D.
New Orleans, Louisiana

Livengood, Charles, M. D.
Durham, North Carolina

McCarty, James L., M. D.
Fresno, California

McGregor, James, MDCM
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Pastorek II, Joseph, M. D.
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Peipert, Jeffery, M. D.
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Stone, Judy, M. D.
Cumberland, Maryland

Trottier, Sylvie, M. D.
Quebec, Canada

Watson, Heather Jean, M. D.
El Paso, Texas

Wendel, George D., M. D.
Dallas, Texas

Study Design

This was a multicenter, prospective, randomized, observer-blind study. Patients with a clinical diagnosis of BV were randomized within each center to treatment with either clindamycin vaginal ovules or clindamycin vaginal cream. Pretreatment visit activities included informed consent, medical history, pelvic examination, diagnostic tests (vaginal fluid pH, vaginal discharge, clue cells, vaginal fluid odor, Gram stain score), and tests for concomitant pathogens. First and second follow-up visits (12 to 16 days ~~and 18~~ to 52 days after start of treatment, respectively) included vulvovaginal examination, repeat

diagnostic tests, tests for concomitant pathogens if symptomatic, efficacy evaluation, reporting of adverse events and concomitant medications.

Patient Enrollment

A total of 670 patients were enrolled. Of these, 662 patients received study drug and were included in the ITT patient population and evaluated for safety (327 in the ovule group and 335 in the cream group). Three hundred thirty–one (331) patients were considered evaluable for efficacy (203 in the ovule group and 178 in the cream group).

Demographic Characteristics

Table 13 below summarizes demographic data for the ITT patients. There were no statistically significant differences in the pretreatment demographics (age, weight, and race) for ITT patients between treatment groups. Demographic profile was likewise similar for evaluable patients.

Table 13 Patient Demographics (ITT Population)

Demographic Variable	CVO N=327	CVC N=335	Total N=662	Treatment P-value
Mean Age, yr ± SD [Range]	29.5 ± 8.3	29.5 ± 8.0	29.5 ± 8.2	0.8961
Mean Wgt, kg ± SD [Range; No. Reporting]	69.0 ±19.4	69.3 ± 17.5	69.2 ±18.4	0.8340
Race: White	113 (34.6%)	112(34.4%)	225 (34.0%)	0.8340
Black	148 (45.3%)	149 (44.5%)	297 (44.9%)	
Oriental/Asian	3 (0.9%)	2(0.6%)	5 (0.8%)	
Hispanic	61 (18.7%)	68(20..3%)	129(19.5%)	
Other	2(0.6%)	4(1.2%)	6(0.9%)	

Patient Evaluability

All enrolled 3-day patients were included in the ITT population except 8 patients (4 from each group) reported to have taken no study medication. Patients were not considered fully evaluable for efficacy if any of the following occurred: failure to meet patient selection criteria; <3 days of treatment with clindamycin vaginal ovules or less than 6 days or more that 8 days (with an allowable lapse of 1 day) of treatment with clindamycin vaginal cream; menses during therapy or at a follow-up visit; non-protocol systemic or vaginal antimicrobial treatment during the study; failure to return for follow-up visit (18 to 52 days after start of treatment [SR-Window], 18 to 42 days [Protocol-defined window], 28 to 52 days [FDA-requested window]; douching during therapy or within 2 days prior to follow-up visit; development of a symptomatic concomitant genital infection or discharge of unknown etiology; or any other reason that in the opinion of the investigator and monitor made the case non-evaluable. An exception was imposed for clinical and side-effect failures for all evaluable criteria except for those relating to data derived prior to initiation of treatment. The reasons for non-evaluability for each treatment group are listed in Table 14.

Of the total of 662 ITT patients, 381 (57.6%) patients were considered evaluable; (203 [62.1%] ovule group, 178 [53.1%] cream group, respectively. The most common primary reasons for non-evaluability were failure to meet inclusion/exclusion criteria post enrollment (reported for 13.9% of patients); many of these patients were non-evaluable due to a Gram stain score at baseline which was incompatible to BV and not complying with the dosing regimen (reported as 13.1%). The percentage of patients considered non-evaluable for each primary reason was similar for the two treatment groups.

Table 14 . Primary Reasons for Non-Evaluability (ITT Patients-SR WINDOW)

Reason for Non-Evaluability	Number of Patients (% of Group)		
	CVO N=327	CVC N=335	Total N=662
No information available on study drug administration	1 (0.3)	4 (1.2)	5 (0.8)
Did not have clinical BV	6 (1.8)	7 (2.1)	13 (2.0)
Did not meet inclusion/exclusion criteria	41 (12.5)	51 (15.2)	92 (13.9)
Additional antimicrobial therapy given (except failures)	14 (4.3)	8 (2.4)	22 (3.3)
Did not comply with dosing regimen	35 (10.7)	52 (15.5)	87 (13.1)
Follow-up not within required window*	18 (5.5)	28 (8.4)	46 (6.9)
Douche during treatment or within 2 days of follow-up	0 (0)	1 (0.3)	1 (0.2)
Had symptomatic concomitant vaginal infection	8.(2.4)	4 (1.2)	12 (1.8)
Not assessable due to incomplete data	1 (0.3)	2 (0.6)	3 (0.5)
Total Nonevaluable	124 (37.9)	157 (46.9)	281(42.4)
Total Evaluable	203 (62.1)	178 (53.1)	381 (57.6)

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
*14 – 48 Days

The number of evaluable patients by investigator and treatment windows is listed in Table 15 for the clindamycin vaginal ovule (VO) group and in Table 16 for the clindamycin cream CVC group.

Efficacy Results

Efficacy of the clindamycin ovule was based on primary and secondary measures. The primary measure determined the overall clinical outcome of evaluable patients using both the 3 diagnostic criteria (pH, clue cells and odor) and the 2 diagnostic criteria (clue cells and odor only). The secondary measure determined the overall clinical outcome for ITT patients (based on 3 and 2 criteria), and on Gram stain scores for evaluable patients. Tables 15 and 16 present clinical outcome based on the 3 diagnostic criteria as determined by each investigator for the VO and CVC groups, respectively. The data presented is based on the amended protocol window (SR window) defined as the second follow-up visit occurring 18 and 52 days after the start of treatment. Additional analyses are included for comparison purposes based on the original protocol-defined window (28 and 42 days after the start of treatment), and the FDA-requested window (28 and 52 days after start of treatment, and at least 14 days after the first follow-up visit.

TABLE 15
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
3 DIAGNOSTIC CRITERIA (ALL WINDOWS) CLEOCIN OVULE TREATMENT GROUP
PROTOCOL 0001

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ARREDONDO,J	27	26	21	5	25	20	5	25	20	5
BENRUBI, G	9	4	3	1	4	3	1	4	3	1
CHATWANI, A	24	20	15	5	13	8	5	19	14	5
GALL, S	30	13	4	9	13	4	9	13	4	9
GORDON, S	19	11	1	10	11	1	10	11	1	10
JACKSON, R	12	9	6	3	9	6	3	8	5	3
LESSER, R	12	9	7	2	9	7	2	9	7	2
LIVENGOOD, I	33	24	17	7	24	17	7	24	17	7
MARTEL, A	9	6	1	5	6	1	5	6	1	5
McCARTY, J	3	2	0	2	2	0	2	2	0	2
McGREGOR, J	33	21	8	13	19	6	13	21	8	13
PASTOREK, J	5	0	0	0	0	0	0	0	0	0
PEIPERT, J	51	28	10	18	28	10	18	28	10	18
PIPER, J	3	2	2	0	2	2	0	2	2	0
REED, B	10	7	6	1	7	6	1	7	6	1
ROY, S	22	9	3	6	9	3	6	8	2	6
SOBEL, J	20	11	5	6	11	5	6	11	5	6
STONE, J	0	0	0	0	0	0	0	0	0	0
WATSON, H	4	1	0	1	1	0	1	1	0	1
WENDEL, G	1	0	0	0	0	0	0	0	0	0
TOTAL	327	203	109	94	193	99	94	199	105	94

TABLE 16
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
3 DIAGNOSTIC CRITERIA (ALL WINDOWS) CLEOCIN CREAM TREATMENT GROUP
PROTOCOL 0001

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ARREDONDO,J	28	21	16	5	20	15	5	20	15	5
BENRUBI, G	12	6	5	1	6	5	1	6	5	1
CHATWANI, A	24	13	10	3	11	8	3	13	10	3
GALL, S	30	12	2	10	11	1	10	11	1	10
GORDON, S	20	9	0	9	9	0	9	9	0	9
JACKSON, R	12	6	6	0	6	6	0	6	6	0
LESSER, R	10	7	4	3	7	4	3	7	4	3
LIVENGOOD, I	33	20	5	15	18	3	15	19	4	15
MARTEL, A	10	7	3	4	7	3	4	7	3	4
McCARTY, J	2	2	1	1	2	1	1	2	1	1
McGREGOR, J	35	17	9	8	16	8	8	15	7	8
PASTOREK, J	3	0	0	0	0	0	0	0	0	0
PEIPERT, J	52	25	10	15	24	9	15	23	8	15
PIPER, J	4	3	0	3	3	0	3	3	0	3
REED, B	11	9	5	4	9	5	4	9	5	4
ROY, S	22	7	1	6	7	1	6	7	1	6
SOBEL, J	20	13	8	5	13	8	5	13	8	5
STONE, J	1	1	0	1	1	0	1	1	0	1
WATSON, H	4	0	0	0	0	0	0	0	0	0
WENDEL, G	2	0	0	0	0	0	0	0	0	0
TOTAL	335	178	85	93	170	77	93	171	78	93

A summary of the overall clinical outcome as determined by 3 diagnostic criteria (resolution of pH, clue cells and odor) is given in Table 17. The overall clinical outcome for evaluable patients by 3 diagnostic criteria (SR window) showed that 53.7% (109/203) of patients in the ovule group were cured compared with 47.8% (85/178) of patients in the cream group. This difference was not statistically significant, (95% CI = -4.1 to 16.0). Comparable cure rates were determined using the protocol-defined window (51.3% for the VO group versus 45.3% for the CVC group) and (52.% VO versus 45.6% CVC) when the FDA-requested window was used.

TABLE 17 OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY 3 DIAGNOSTIC CRITERIA (SR, PROTOCOL-DEFINED, FDA-REQUESTED WINDOWS)

EVALUABLE PATIENTS	OUTCOME	No of Patients (% of Group)		95% CI
		CVO	CVC	
SR WINDOW (18 – 52 DAYS) N = 203 CVO; 178 CVC	CURE	109 (53.7)	85 (47.8)	-4.1, 16.0
	FAILURE	94 (46.3)	93 (52.2)	
PROTOCOL-DEF. WINDOW (28 – 42 DAYS) N = 193 CVO; 170 CVC	CURE	99 (51.3)	77 (45.3)	-4.3, 16.3
	FAILURE	94 (48.7)	93 (54.7)	
FDA REQ. WINDOW (28 – 52 DAYS N = 199 CVO; 171 CVC	CURE	105 (52.8)	78 (45.6)	-3.0, 17.3
	FAILURE	94 (47.2)	93 (54.4)	

CVO – Clindamycin vaginal ovule, 3-day treatment
CVC – Clindamycin vaginal cream, 7-day treatment
DEF – Defined; REQ –Requested
* Cured at both follow-up visits

Secondary Analysis (Two Diagnostic Criteria)

Supplementary analyses for the overall clinical outcome based on 2 diagnostic criteria for each defined treatment window are shown in Table 18 for clindamycin ovule and Table 19 for clindamycin cream.

TABLE 18
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
2 DIAGNOSTIC CRITERIA (ALL WINDOWS) CLEOCIN OVULE TREATMENT GROUP
PROTOCOL 0001

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ARREDONDO,J	27	26	23	3	25	22	3	25	22	3
BENRUBI, G	9	4	2	2	4	2	2	4	2	2
CHATWANI, A	24	20	15	5	13	8	5	19	14	5
GALL, S	30	13	7	6	13	7	6	13	7	6
GORDON, S	19	11	7	4	11	7	4	11	7	4
JACKSON, R	12	9	4	5	9	4	5	8	4	4
LESSER. R	12	9	7	2	9	7	2	9	7	2
LIVENGOOD, I	33	24	19	5	24	19	5	24	19	5
MARTEL, A	9	6	2	4	6	2	4	6	2	4
.McCARTY, J	3	2	1	1	2	1	1	2	1	1
McGREGOR, J	33	21	14	7	19	12	7	21	14	7
PASTOREK, J	5	0	0	0	0	0	0	0	0	0
PEIPERT, J	51	28	12	16	28	12	16	28	12	16
PIPER, J	3	2	2	0	2	2	0	2	2	0
REED, B	10	7	6	1	7	6	1	7	6	1
ROY, S	22	9	8	1	9	8	1	8	7	1
SOBEL, J	20	11	5	6	11	5	6	11	5	6
STONE, J	0	0	0	0	0	0	0	0	0	0
WATSON, H	4	1	0	1	1	1	1	1	0	1
WENDEL, G	1	0	0	0	0	0	0	0	0	0
TOTAL	327	203	134	69	193	124	69	199	131	68

TABLE 19
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
2 DIAGNOSTIC CRITERIA (ALL WINDOWS) CLEOCIN CREAM TREATMENT GROUP
PROTOCOL 0001

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
ARREDONDO,J	28	21	17	4	20	16	4	20	16	4
BENRUBI, G	12	6	4	2	6	4	2	6	4	2
CHATWANI, A	24	13	10	3	11	8	3	13	10	3
GALL, S	30	12	4	8	11	3	8	11	3	8
GORDON, S	20	9	5	4	9	5	4	9	5	4
JACKSON, R	12	6	5	1	6	5	1	6	5	1
LESSER. R	10	7	4	3	7	4	3	7	4	3
LIVENGOOD, I	33	20	7	13	18	5	13	19	6	13
MARTEL, A	10	7	3	4	7	3	4	7	3	4
McCARTY, J	2	2	1	1	2	1	1	2	1	1
McGREGOR, J	35	17	13	4	16	12	4	15	11	4
PASTOREK, J	3	0	0	0	0	0	0	0	0	0
PEIPERT, J	52	25	14	11	24	13	11	23	12	11
PIPER, J	4	3	0	3	3	0	3	3	0	3
REED, B	11	9	5	4	9	5	4	9	5	4
ROY, S	22	7	4	3	7	4	3	7	4	3
SOBEL, J	20	13	10	3	13	10	3	13	10	3
STONE, J	1	1	0	1	1	0	1	1	0	1
WATSON, H	4	0	0	0	0	0	0	0	0	0
WENDEL, G	2	0	0	0	0	0	0	0	0	0
TOTAL	335	178	106	72	170	98	72	171	99	72

The overall clinical outcome obtained for evaluable patients by 2 diagnostic criteria using the SR window was 66% (134/203) of patients in the ovule group compared with 59.6% (106/178) of patients in the cream group. Again, this difference was not statistically significant (95% CI = -3.4 to 15.2). Since resolution of pH was not one of the criteria used to define cure, these cure rates were higher than those based on 3 diagnostic criteria and may reflect the influence of pH in artificially lowering the cure rates. The cure rates obtained using the protocol-defined and/or the FDA-requested window did not differ significantly from those obtained in the SR window. A summary of the clinical outcome as determined by the 2 diagnostic criteria for each defined treatment window is given in Table 20.

TABLE 20 OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY 2 DIAGNOSTIC CRITERIA (SR, PROTOCOL-DEFINED, FDA-REQUESTED WINDOWS)

EVALUABLE PATIENTS	OUTCOME	No of Patients (% of Group)		95% CI
		CVO	CVC	
SR WINDOW (18 – 52 DAYS) N = 203 CVO; 178 CVC	CURE	134 (66.0)	106 (59.6)	-3.4, 15.2
	FAILURE	69 (34.0)	72 (40.4)	
PROTOCOL-DEF. WINDOW (28 – 42 DAYS) N = 193 CVO; 170 CVC	CURE	124 (64.2)	98 (57.6)	-2.9, 16.2
	FAILURE	69 (35.8)	72 (42.4)	
FDA REQ. WINDOW (28 – 52 DAYS N = 199 CVO; 171 CVC	CURE	131 (65.8)	99 (57.9)	-2.0, 17.0
	FAILURE	68 (34.2	72 (42.1)	

CVO – Clindamycin vaginal ovule, 3-day treatment
CVC – Clindamycin vaginal cream, 7-day treatment
DEF – Defined; REQ –Requested

Secondary Efficacy Measures

1) Overall Clinical Outcome for ITT Patients

A summary of the overall clinical outcome for the assessable patients of the ITT population as determined from 3 diagnostic criteria (resolution of pH, clue cells, and odor) and 2 diagnostic criteria (resolution of clue cells and odor) is shown in Table 21. Assessable patients were defined as those patients who had data reported for both follow-up visits or those who had sufficient data from one visit to be deemed a failure.

The overall clinical outcome by 3 diagnostic criteria demonstrated that among the ITT patient population, 134 (56.3%) of the 238 assessable patients in the ovule group were cured compared with 113 (50.4%) of the 224 assessable patients in the cream group. This difference was not statistically significant, (95% CI = -3.2% to 14.9%).

The overall clinical outcome by 2 diagnostic criteria demonstrated that among the ITT patient population, 164 (68.3%) of the 240 assessable patients in the ovule group were cured compared with 142 (62.3%) of the 228 assessable patients in the cream group. This difference was not statistically significant (95% CI = -2.6% to 14.7%). Since improvement was only required in 2 rather than 3 diagnostic criteria, these cure rates were higher than those based on analysis of 3 diagnostic criteria, reflecting the influence of pH in artificially lowering the cure rates. The cure rates for the ITT patients are comparable to those observed in evaluable patients by 3 and 2 diagnostic criteria.

Table 21. Overall Clinical Outcome by 3 and 2 Diagnostic Criteria (ITT Patients)

Outcome	By 3 Diagnostic Criteria			By 2 Diagnostic Criteria		
	No. of Patients (% of Group*)		95% CI	No. of Patients (% of Group*)		95% CI
	CVO (N=327; 238 Ass)	CVC (N=335; 224 Ass)		CVO (N=327; 240 Ass)	CVC (N=335; 228 Ass)	
Cure	134 (56.3)	113 (50.4)	-3.2 to 14.9	164 (68.3)	142 (62.3)	-2.6 to 14.7
Failure	104 (43.7)	111 (49.6)		76 (31.7)	86 (37.7)	
Nonassessable	89	111		87	107	

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
Ass – Assessable; * Percentage based on number of patients assessable.

2) Gram Stain Scores

Gram stains scores at the first and second follow-up visits for evaluable patients who reported Gram stain are shown below in Table 22.

Based on the evaluable patient population who reported Gram stain, there was no statistically significant difference between treatments groups regarding the distribution among Gram stain score categories at either follow-up visit. At the first follow-up visit, a majority of patients in both treatment groups had normal or intermediate Gram stain score (ovule group, 55.8% or 32.0%; cream group, 43.8% or 42.6%). At the second follow-up visit, a majority of patients had normal Gram stain scores (ovule group, 57.8%; cream group, 58.9%).

Table 22. Gram Stain Scores at Both Follow-up Visits (Evaluable Patients)

Gram Stain Score	No. of Patients (% of Group*)			
	First Follow-up Visit		Second Follow-up Visit	
	CVO N=197	CVC N=169	CVO N=187	CVC N=151
Normal (0-3)	110 (55.8)	74 (43.8)	108 (57.8)	89 (58.9)
Intermediate (4-6)	63 (32.0)	72 (42.6)	41 (21.9)	33 (21.9)
Compatible with BV (7-10)	24 (12.2)	23 (13.6)	38 (20.3)	29 (19.2)

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
N – Number of valuable patients who reported Gram stain
* Percentages are based on the number of patients reporting results.

Efficacy Conclusions

The results of all efficacy analyses for overall clinical outcome demonstrate that a 3-day course of clindamycin vaginal ovules is equally effective as a 7-day course of clindamycin vaginal cream in the treatment of bacterial vaginosis (BV). The overall cure rate, using 3 diagnostic criteria (clue cells, odor, and pH) and the SR window, for the evaluable patient population was 53.7% and 47.8% for the ovule and cream groups, respectively; (95% CI = -4.1% to 16.0%). The overall cure rates were similar in the ITT patient population (ovule group, 56.3%, cream group, 50.4%; 95% CI = -3.2% to 14.9%). The cure rates based on 2 diagnostic criteria (clue cells and odor) were higher than those obtained by 3 diagnostic criteria for both the evaluable population (ovule group, 66%; cream group, 59.6%; 95% CI = -3.4% to 15.2%) and for the ITT patient population (ovule group, 68.3%; cream group, 62.3%; 95% CI = -2.6% to 14.7%), with no statistically significant difference between treatment groups. Additional analyses of overall clinical outcome were performed based on windows for patient evaluability designated by the study protocol and as requested by the FDA Medical Officer Reviewer.. The overall cure rates were similar for the treatment groups irrespective of the window applied.

The predominant primary reasons for classification of patients as non-evaluable were not meeting inclusion/exclusion criteria and dosing noncompliance and similar in each treatment group. There was no difference in the number of patients who reported normal or intermediate Gram stain results at the second follow-up visits between the two treatment groups.

SAFETY EVALUATION

All patients enrolled in the study and who received any study drug were included in the safety analyses. Evaluation for safety was based on all reported medical event data. Table 23 summarizes the number of patients who reported medical events by investigator. There is no significant difference between groups for the percentage of patients reporting al least one medical event (ovule group 33% [109/327]; cream group, 32% [107/335].

TABLE 23
Number of patients who Reported Medical Events by Investigator – ITT Patients
Protocol 0001

	Medical Events – Intent-To-Treat (ITT) Patients					
	Cleocin Ovule			Cleocin Cream		
INVESTIGATOR	ITT	ME	%	ITT	ME	%
ARREDONDO,J	27	6	22	28	12	43
BENRUBI, G	9	3	33	12	4	33
CHATWANI, A	24	1	4	24	3	13
GALL, S	30	16	53	30	8	27
GORDON, S	19	6	32	20	5	25
JACKSON, R	12	2	17	12	2	17
LESSER. R	12	1	8	10	2	20
LIVENGOOD, I	33	11	33	33	10	30
MARTEL, A	9	6	67	10	3	30
McCARTY, J	3	2	67	2	2	100
McGREGOR, J	33	11	33	35	12	34
PASTOREK, J	5	2	40	3	2	67
PEIPERT, J	51	22	43	52	18	35
PIPER, J	3	2	67	4	2	50
REED, B	10	5	50	11	6	55
ROY, S	22	0	0	22	3	14
SOBEL, J	20	12	60	20	11	55
STONE, J	0	0	0	1	1	100
WATSON, H	4	1	25	4	1	25
WENDEL, G	1	0	0	2	0	0
Total	327	109	33	335	107	32

The percentages of patients reporting medical events by body system were similar for both treatment groups (Table 24), with most events reported in the categories "body as a whole" (ovule group, 17.4% [57/327]; cream group, 16.7% [56/335]) and "urogenital" (ovule group, 16.8% [55/327]; cream group, 17.6% [59/335]).

TABLE 24
PATIENTS REPORTING MEDICAL EVENTS BY BODY SYSTEM ITT PATIENTS
PROTOCOL 0001

BODY SYSTEM	CLEOCIN OVULE		CLEOCIN CREAM		TOTAL	
	Number	%	Number	%	Number	%
Body as Whole	57	17.4	56	16.7	113	17.1
Cardiovascular	2	0.6	1	0.3	3	0.5
Digestive	18	5.5	10	3.0	28	4.2
Endocrine	1	0.3	0	0	1	0.2
Hemic and Lymphatic	1	0.3	1	0.3	2	0.3
Metabolic & Nutritional	1	0.3	0	0	1	0.2
Musculo-Skeletal	0	0	1	0.3	1	0.2
Nervous	3	0.9	3	0.9	6	0.9
Respiratory	10	3.1	10	3.0	20	3.0
Skin	11	3.4	4	1.2	15	2.3
Special Senses	2	0.6	0	0	2	0.3
Urogenital	55	16.8	59	17.6	114	17.2
No of Patients % is Based	327		335		662	

Table 25 below summarizes medical events reported by at least 1% of patients in either the ovule or the cream treatment group, and shows for each event the number of patients for whom the investigators considered the event to be related to the study drug.

Table 25. Medical Events Reported by ≥1% of Patients in the Clindamycin Vaginal Ovule or Cream Groups

Body System	Event (COSTART Description)	No. Patients (% of Group) [No. Drug-Related*]	
		CVO N=327	CVC N=335
Body as a Whole	Abdominal cramp	4 (1.2) [1]	6 (1.8) [3]
	Generalized abdominal pain	2 (0.6)	6 (1.8) [1]
	Localized abdominal pain	5 (1.5) [1]	2 (0.6)
	Flu syndrome	3 (0.9)	9 (2.7)
	Headache	21 (6.4) [2]	12 (3.6) [1]
	Infection fungal NOS	5 (1.5) [5]	4 (1.2) [2]
	Trauma	4 (1.2)	1 (0.3)
	Upper respiratory infection	6 (1.8)	3 (0.9)
Digestive	Diarrhea	4 (1.2) [2]	3 (0.9) [2]
	Nausea	5 (1.5) [1]	4 (1.2) [3]
Respiratory	Sinusitis	4 (1.2)	5 (1.5)
Skin	Pruritus (non-application site)	5 (1.5) [3]	1 (0.3) [1]
Urogenital	Vulvovaginal disorder	24 (7.3) [14]	28 (8.4) [16]
	Dysmenorrhea	5 (1.5)	4 (1.2)
	Dysuria	4 (1.2) [1]	3 (0.9) [2]
	Urinary tract infection	9 (2.8)	8 (2.4)
	Metrorrhagia	1 (0.3)	5 (1.5) [1]
	Vaginal moniliasis	5 (1.5) [3]	3 (0.9) [2]
	Vaginal pain	11 (3.4) [11]	3 (0.9)[2]
	Unintended pregnancy	2 (0.6)	4 (1.2)

CVO - clindamycin vaginal ovule, 3-day treatment
CVC - clindamycin vaginal cream, 7-day treatment
NOS - not otherwise specified
* Number of patients reporting events judged by investigator to be related to study drug

The percentages of patients reporting medical events were similar for both treatment groups except for vaginal pain (ovule group, 3.4%; cream group, 0.9%), flu syndrome (ovule group, 0.9%; cream group, 2.7%), and headaches (ovule group, 6.4%; cream group, 3.6%). All terms listed by the investigators which coded to the COSTART term "vaginal pain" were described as vaginal burning. The investigator terms which coded to the COSTART terms of "flu syndrome" and "headache" are typical medical terms to describe these medical events.

Fungal infections affecting either the skin or the urogenital system occurred in a similar percentage of patients in the two treatment groups. Since no patient in either treatment group had a concomitant diagnosis of a fungal infection which was coded to "urogenital" and/or "skin" and/or "body as a whole", COSTART terms describing fungal (monilial or otherwise not specified) infections can be combined to estimate the worst-case frequency of fungal infections. Combining the terms seen in this study (infection fungal NOS, moniliasis vaginal, and moniliasis), the incidences were: ovule group, 3.0%; cream group, 2.4%.

The most frequently reported medical event was termed "vulvovaginal disorder" (ovule group, 7.3%; cream group, 8.4%). Most of the investigator descriptions for these events describe vulvar or vaginal itching.

Medical Event Frequency by Maximum Intensity

Table 26 displays the counts of medical events tabulated by maximum intensity (mild, moderate, or severe). Most events had a maximum intensity of mild to moderate (95.2% [177/186] in the ovule group; 87.1% [149/171] in the cream group), while 9 (4.8%) events in the ovule group and 19 (11.1%) in the cream group were rated as severe.

Table 26 Medical Events by Body System, COSTART Description Term and Maximum Intensity –ITT Patients (Protocol 0001) All Causality

BODY SYSTEM	COSTART DESCRIPTION	CLEOCIN OVULE				CLEOCIN CREAM				TOTAL			
		Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot
BODY	Abdominal Cramp	2	2		4	2	2	2	6	4	4	2	10
	Abdominal Distention					1		1	2	1		1	2
	Abdominal Pain Gen	2			2	2	4		6	6	4	4	8
	Abdominal Pain Loc	4	1		5	2			2	6	1		7
	Allergic Reaction	1			1					1			1
	Asthenia					1			1	1			1
	Back Pain	1			1	1		1	2	2		1	3
	Cellulitus							1	1			1	1
	Chest Pain	1			1			1	1	1		1	2
	Fatigue	1			1					1			1
	Fever	1	1		2		1		1	1	2		3
	Flank Pain			1	1							1	1
	Flu Syndrome	2		1	3	1	7	1	9	3	7	2	12
	Generalized Pain	1			1			1	1	1		1	2
	Headache	14	6	1	21	9	2	1	12	23	8	2	33
	Infection Bacterial Nos		1		1	1			1	1	1		2
	Infection Fungal Nos	5			5	3	1		4	8	1		9
	Infection Nec		1		1								1
	Infection Viral Nos					1			1	1			1
	Localized Edema	1			1					1			1
	Localized Pain	1	1		2	1	2		3	2	3		5
	Micro Test Abnormal					1			1	1			1
	Moniliasis					1			1	1			1
	Overdose						1		1		1		1
	Pelvic Pain	1	1		2	2			2	3	1		4
	Reaction Unevaluable						2		2		2		2
	Sebaceous Cyst					1			1	1			1
	Trauma	1	2	1	4	1			1	2	2	1	5
	Upper Resp Infection	3	3		6	1	1	1	3	4	4	1	9
CARDIO-VASCULAR	Hemorrhage	1			1					1			1
	Migraine		1		1	1			1	1	1		2
DIGESTIVE	Bloody Stool					1			1	1			1
	Constipation	1	1		2					1	1		2
	Diarrhea	3	1		4	1	1	1	3	4	2	1	7
	Gastritis		1		1	1		1	2	1	1	1	3
	Gastroenteritis	1		1	2		1		1	1	1	1	3
	Nausea	2	3		5	1	2	1	4	3	5	1	9
	Tooth Abscess	1	1		2					1	1		2
	Toothache	1			1	1			1	2			2
	Vomiting	2	1		3		1		1	2	2		4

Table 26 Continued Medical Events by Body System, COSTART Description Term and Maximum Intensity –ITT Patients (Protocol 0001)

BODY SYSTEM	COSTART DESCRIPTION	CLEOCIN OVULE				CLEOCIN CREAM				TOTAL			
		Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot
ENDOCRINE	Disorder Thyroid	1			1					1			1
HEMIC and LYMPHATIC	Adenopathy		1		1		1		1	1	1		2
METABOLIC / ENDOCRINE	Hypoglycemia		1		1						1		1
MUSCULO-SKELETAL	Arthralgia Single and Multiple Joints					1			1	1			1
NERVOUS	Depressive symptoms					2			2	2			2
	Insominia		2		2	1			1	1	2		3
	Neuritis			1	1							1	1
RESPIRA-TORY	Asthma					1			1	1			1
	Bronchitis					1	1		2	1	1		2
	Cough	1	1		2	2			2	3	1	4	
	Dyspnea							1	1			1	1
	Pharyngitis	1			1		1		1	1	1		2
	Rhinitis	2			2	1			1	3			3
	Sinusitis	1	3		4	3	2		5	4	5		9
	Wheezing	1			1					1			1
SKIN	Diaphoretic	1			1					1			1
	Erythema	1			1					1			1
	Folliculitis		1		1						1		1
	Hair Loss	1			1					1			1
	Herpes Simplex Derm						1		1		1		1
	Pruritus Non-Appl Site	3	1	1	5		1		1	3	2	1	6
	Rash	2			2	1	1		2	3	1		4
	Wart	1			1					1			
SPECIAL SENSES	Otitis Externa	1			1					1			1
	Otitis Media		1		1						1		1
UROGENITAL	Bleeding Anovulatory	1			1					1			1
	Breast Pain						1		1		1		1
	Disorder Cervix							1	1			1	1
	Disorder Vulvovaginal	13	10	1	24	21	5	2	28	34	15	3	52
	Dysmenorrhea	4	1		5	3	1		4	7	2		9
	Dyspareunia					1			1	1			1
	Dysuria	2	2		4	1	1	1	3	3	3	1	7
	Frequency Urinary		1		1	1			1	1	1		2
	Hemorrhage Uterine					1			1	1			1
	Hemorrhage Vaginal					1	1		2	1	1		2
	Infection Urinary Tract	4	5		9	3	4	1	8	7	9	1	17
	Mastitis		1		1					1			1
	Metrorrhagia	1			1	5			5	6			6
	Moniliasis Vaginal	3	2		5	2	1		3	5	3		8
	Pregnancy Unintended*	1	1		2	1			4*	2	1		6*
	Pylonephritis			1	1							1	1
	Salpingitis		1		1	1	2		3	1	3		4
	Vaginal Discharge Nos	1	1		2	2			2	3	1		4
	Vaginal Pain	5	6		11	2	1		3	7	7		14
	Vaginitis/Vaginal Inf	1			1					1			1
Total Number of Medical Events		107	70	9	186	96	53	19	171	203	123	28	357

*3 Additional Pregnancies reported but not Intensity

Drug-Related Medical Events

The investigators assessed the relatedness (Yes/No) of the medical events to the use of the study drug. The percentage of patients reporting at least one drug-related medical event was similar between treatment groups (ovule group, 11.3% [37/327]; cream group, 9.3% [31/335]) with no statistically significant difference observed. Patients in the ovule treatment group reported more drug-related events (54) than those in the cream group (43) [Table 27].

Table 27
Drug-Related Medical Events by Body System ITT Patients
Protocol 0001

BODY SYSTEM	CLEOCIN OVULE		CLEOCIN CREAM		TOTAL	
	Number	%	Number	%	Number	%
Patients with no Medical Event	290	88.7	304	90.7	594	89.7
Patients with at Least One Medical Event	37	11.3	31	9.3	68	10.3
Body as Whole	13	4.0	14	4.2	27	4.0
Digestive	4	1.2	5	1.5	9	1.3
Skin	5	1.5	1	0.3	6	0.9
Urogenital	32	9.8	23	6.9	55	8.3
Total No of Med Event	54	16.5	43	12.8	97	14.7
No of Patients % is Based	327		335		662	

Intensity of Drug-Related Medical Events

Most drug-related events had a maximum intensity of mild or moderate with only 3 medical events in the ovule group and 8 medical events in the cream group described as severe. Only 3 events determined by the investigator to be drug-related were reported in more than 3 patients in either treatment group; infection fungal NOS (ovule group, 5 [1.5%]; cream group 2 [0.6%]), vulvovaginal disorder (ovule group, 14 (4.3%); cream group 16 [4.8%]), and vaginal pain (ovule group, 11 [3.4%]; cream group, 2 [0.6%]) [Table 28].

Table 28
Drug-Related Medical Events by Body System, COSTART Description, and Maximum Intensity – ITT Patients

BODY SYSTEM	COSTART DESCRIPTION	CLEOCIN OVULE				CLEOCIN CREAM				TOTAL			
		Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot	Mild	Mod	Sev	Tot
BODY	Abdominal Cramp	1			1		1	2	3	1	1	2	4
	Abdominal Distention							1	1			1	1
	Abdominal Pain Gen						1		1		1		1
	Abdominal Pain Loc	1			1					1			1
	Back Pain							1	1			1	1
	Fever	1			1					1			1
	Flank Pain			1	1							1	1
	Generalized Pain	1			1			1	1	1		1	2
	Headache	1	1		2		1		1	1	2		3
	Infection Fungal Nos	5			5	1	1		2	6	1		7
	Localized Edema	1			1					1			1
	Moniliasis					1			1	1			1
	Pelvic Pain					2			2	2			2
	Reaction Unevaluable						1		1		1		1
DIGESTIVE	Diarrhea	2			2		1	1	2	2	1	1	4
	Nausea	1			1	1	1	1	3	2	1	1	4
	Vomiting	1			1					1			1
SKIN	Pruritus non-applic site	2	1		3		1		1	2	2		4
	Rash	2			2					2			2
UROGENITAL	Disorder Vulvovaginal	7	6	1	14	11	5		16	18	11	1	30
	Dysuria		1		1	1		1	2	1	1	1	3
	Metrorhagia					1			1	1			1
	Moniliasis Vaginal	2	1		3	2			2	4	1		5
	Pylonephritis			1	1							1	1
	Vaginal Discharge Nos	1			1					1			1
	Vaginal Pain	5	6		11	1	1		2	6	7		13
	Vaginitis/Vag Infection	1			1					1			1
Total Number of Med Events		35	16	3	54	21	14	8	43	56	30	11	97

Discontinuations Due to Medical Events

The patients considered as having discontinued treatment due to medical events are those who stopped taking study drug (those who took ovules for less than 3 consecutive days or cream for less than 6 days, and had a Medical Event Form indicating that the medical event occurred during the dosing period and that the action taken was discontinued or interrupted). One patient (#1313) of 327 patients in the ovule group and 6 of 335 patients in the cream group discontinued study medication due to medical events. Details of medical events for these 7 patients can be found in narratives below.

Narratives of Discontinuations due to Medical Events

Clindamycin Vaginal Ovule

Patient # 1313 (Investigator McGregor)
Medical Event: pelvic cramping and slight bleeding
This 22-year-old woman with BV began a 3-day course of clindamycin vaginal ovules on January 15, 1996. On January 17, 1996 the investigator received a phone call from the patient who reported pelvic cramping and slight bleeding, both mild, occurring on January 15 and 16, 1996. Only one dose of medication is reported to have been taken, and this patient did not return for follow-up visit. The investigator considered the events to be unrelated to the study medication.

Clindamycin Vaginal Cream

Patient # 2663 (Investigator Gall)
Medical Event: diarrhea, external vaginal irritation, nausea
This 33-year-old woman with BV began a 7-day course of clindamycin vaginal cream on August 7, 1997. On the second day of treatment (August 8, 1997), she began experiencing nausea, diarrhea, and external vaginal irritation, all of moderate intensity. After 4 doses, medication was discontinued on August 10, 1997. The following day the nausea and diarrhea had resolved without treatment. However, the vaginal irritation continued. The patient was unable to be contacted to obtain a date of resolution for the external vaginal irritation. The investigator noted that there was a reasonable possibility that these events were related to the study medication.

Patient # 164 (Investigator Lesser)
Medical Event: burning and itching affecting labia
This 28-year-old woman with BV began a 7-day course of clindamycin vaginal cream on February 2, 1995. On the second day of treatment (February 3, 1995), she complained of mild labial burning and itching. After continuing treatment for another 2 days, the study medication was discontinued on February 5, 1995. The medical event resolved the following day without any treatment (as reported). This event was considered by the investigator to be related to the study medication.

Patient # 71 (Investigator Livengood)
Medical Event: abdominal pain
This 23-year-old woman with BV began a 7-day course of clindamycin vaginal cream on January 6, 1995. She complained of moderate abdominal pain each time she applied the cream. The last day she used study medication was January 8, 1995. At follow-up, she tested negative for BV and reported no further pain. The investigator noted that the abdominal pain was possibly related to the study medication.

Patient # 1150 (Investigator Peipert)
Medical Event: urinary tract infection
This 25-year-old woman with BV began a 7-day course of clindamycin vaginal cream on September 29, 1995. At the first follow-up visit (October 4, 1995), an antibiotic was prescribed for an urinary tract infection that was reported to have started on September 30, 1995. A stop date for the study medication was not provided, but it is reported that the medication was discontinued due to the medical event. The investigator did not believe that the study medication caused the medical event.

Patient # 2604 (Investigator Peipert)
Medical Event: burning on urination
This 25-year-old woman with BV began a 7-day course of clindamycin vaginal cream on July 8, 1997. She reported that she noticed mild intermittent burning on urination after the first dose and so did not take the medication as directed, using it irregularly over a span of 11 days. The investigator reported that the burning on urination was related to the study medication.

Patient # 1161 (Investigator Reed)
Medical Events: abdominal pain/cramping, back pain, pain with urination
This 23-year-old woman with BV was randomized to reeeive a 7-day course of clindamycin vaginal cream on August 16, 1995. The patient reported moderate abdominal pain/cramping, severe back pain, and severe pain with urination after the second day of treatment. The medication was discontinued a day later (August 18, 1995). The medical events resolved the following day without treatment. The investigator could not rule out the study medication as the cause of the medical events.

Deaths, Other Serious Medical Events and Other Significant Medical Events

There were no deaths reported in either treatment group. One patient in the ovule group and 4 patients in the cream group had serious medical events during the study. All of these medical events except one were considered not related to study drug, but mostly related to previous medical history. The medical event of pyelonephritis that the investigator judged to be related to study drug occurred in Patient # 2605 in the ovule treatment group. None of the events that occurred in the cream group were related to study drug.

Patient Narratives

Serious Medical Events

Clindamycin Vaginal Ovule
Patient # 2605 (Investigator Peipert),
Serious Medical Event: pyelonephritis
This 21-year-old woman with BV and a pretreatment history of pyelonephritis and urinary tract infections was randomized to receive a 3-day treatment with ovule beginning on July 14, 1997. Three days after treatment completion, she was diagnosed with severe pyelonephritis accompanied by right flank pain, dysuria, nausea, vomiting, abdominal cramps, and fever. Treatment consisted of intramuscular gentamicin, acetaminophen, codeine, and hydroxyzine pamoate. She recovered 5 days later without residual effects. The investigator considered the pyelonephritis related to the investigational medication. However, the P&U monitor noted that although theoretically possible, the study medication was an unlikely cause.

Clindamycin Vaginal Cream
Patient # 2665 (Investigator Gall)
Serious Medical Events: fever, heavy vaginal bleeding, lower abdominal cramping, viral episode (flu)
This 22-year-old woman with BV was randomized to receive a 7-day treatment with cream beginning on September 3, 1997. Subsequent to study entry, she was found to be ineligible based on a positive Chlamydia test and a Gram stain score of "3" at pretreatment. Relevant history includes a therapeutic abortion 3 weeks prior to treatment and a Depo-Provera injection on the day prior to treatment. On treatment Day 2, she reported episodic lower abdominal cramping of moderate intensity. Four days after treatment she was hospitalized with a viral episode, heavy vaginal bleeding, and abdominal pain. She developed a fever the next day, was treated with IV antibiotics, and recovered on September 16, 1997 without residual effects. The investigator considered these medical events to be unrelated to the study medication.

Patient # 1145 (Investigator Peipert)
Serious Medical Event: overdose of acetaminophen
This 23-year-old woman with BV was randomized to receive a 7-day treatment of cream beginning on July 14, 1995. Five days after treatment was completed, she took an overdose of acetaminophen, went to a local hospital, had her stomach pumped, and received a referral for counseling. She recovered without residual effects. The investigator considered the medical event to be unrelated to the study medication.

Patient # 1199 (Investigator Sobel)
Serious Medical Event: chest pain, shortness of breath
This 47-year-old woman with BV was randomized to receive a 7-day treatment of cream beginning on October 13, 1995. Fourteen days after treatment completion, she was hospitalized with chest pain and shortness of breath, both of severe intensity. EKG and stress tests were normal. She was diagnosed with esophageal reflux/gastritis, treated with [redacted] and omeprazole, and recovered 8 days later without residual effects. The investigator considered these medical events to be unrelated to the study medication.

Patient # 1249 (Investigator Watson)
Serious Medical Event: bronchitis/asthma
This 26-year-old woman with BV and history of asthma was randomized to receive a 7-day treatment of cream beginning on September 14, 1995. Five days after completion of treatment she was diagnosed with bronchitis/asthma. Although the entry in the MEF indicated that the study medication was interrupted, however, the days of use recorded on the Study Medication Use Record indicated that the treatment was completed 5 days prior to the onset of the medical event. She was treated with erythromycin, triamcinolone [redacted] and albuterol, and recovered 4 days later without residual effects. The investigator considered the medical event to be unrelated to the study medication.

Exposure In Utero

Six pregnancies were reported during the study, 2 in the ovule group and 4 in the cream group. Four pregnancies (Patients # 1504 and # 2696, ovule group; Patients # 91 and #1159, cream group) ended in live births with no abnormalities. Two pregnancies in the cream group ended in abortions. One of these patients (#66) elected to have an induced abortion, the other (Patient # 281) had a spontaneous (missed) abortion on April 4, 1995, approximately 7 weeks after the last dose of medication (February 12, 1995). This patient underwent a D&C with evacuation of a 7 week fetus. This spontaneous abortion was not regarded by the investigator to be related to study medication.

Safety Conclusions

An overall summary of medical events is provided in Table 29. The percentage of patients reporting at least one medical event was similar for both treatment groups (ovule group, 33%; cream group, 32%). No deaths were reported in this study. A total of only 5 serious medical events were reported, one in the ovule group and 4 in the cream group. The serious medical event, which occurred in the ovule group (pyelonephritis), was deemed by the investigator to be related to study drug. None of the serious medical events in the cream group were considered by the investigators to be related to study drug. The percentage of patients reporting medical events was similar for the two treatment groups, with the exception of vaginal pain, headaches, and flu syndrome. While flu syndrome and headaches probably occurred by chance, "vaginal burning" was the inciting event reported by a higher percentage of patients in the ovule group. However, no patient discontinued for "vaginal burning". The incidence of fungal infections affecting either skin or urogenital system was reported by a similar percentage

of patients for the two treatment groups (ovule group, 3.0%; cream group, 2.4%) as was the incidence of events described as "vulvovaginal disorder" (mainly vulvar or vaginal itching [ovule group, 7.3%; cream group, 8.4%]).

The percentage of patients reporting at least one drug-related medical event was similar for the two treatment groups.

Very few patients discontinued treatment due to medical events (1/327 in the ovule group, and 6/335 in the cream group). There was no one particular drug-related event that led to treatment discontinuation.

This study does not demonstrate a significant safety problem with the clindamycin vaginal ovule. The comparison of ovule and cream indicates a similar safety profile for both treatment groups. While the ovule caused more vaginal burning than the cream, the incidence rate was acceptable.

Table 29. Overall Summary of Medical Events

Parameter	CVO 3-Day N = 327	CVC 7-Day N = 335	Total N = 662
	n (%)	n (%)	n (%)
All Medical Events			
Patients with no Mes	218 (66.7)	228 (68.1)	446 (67.4)
Patients with ≥1 ME	109 (33.3)	107 (31.9)	216 (32.6)
ME episodes*	186	171	357
Drug-Related Medical Events			
Patients with no drug-related Mes	290 (88.7)	304 (90.7)	594 (89.7)
Patients with ≥1 drug-related Mes	37 (11.3)	31 (9.3)	68 (10.3)
Drug-related ME Episodes*	54	43	97
Discontinuations Due to Medical Events			
Patients discontinuing dosing due to Mes	1	6 (1.8)	6 (0.9)
ME episodes leading to discontinuation of dosing	2	10	10
Serious Medical Events			
Patients with no serious Mes	326 (99.7)	331 (98.8)	657 (99.2)
Patients with ≥1 serious ME	1 (0.3)	4 (1.2)	5 (0.8)
Serious ME episodes*	1	8	9
Deaths	0	0	0

ME = medical event
CVO = clindamycin vaginal ovule, 3-day treatment
CVC = clindamycin vaginal cream, 7-day treatment
* Each patient is counted once per COSTART description

Discussion and Overall Conclusions

This study indicates that a 3-day course of clindamycin vaginal ovules (100 mg [one ovule], inserted intravaginally at bedtime for 3 consecutive days) is equally effective as a 7-day course of clindamycin vaginal cream (5 g [one applicatorful, equal to 100 mg clindamycin] applied intravaginally at bedtime for 7 consecutive days) in the treatment of bacterial vaginosis (BV). The overall cure rates by 2 diagnostic criteria (clue cells and odor) or 3 criteria (pH, clue cells, and odor) for both the evaluable and the ITT patient population consistently demonstrate that treatment with clindamycin vaginal ovules is as effective as clindamycin vaginal cream.

The incidence of medical events was similar for both treatment groups, with the majority being of mild to moderate intensity. The incidence of fungal infections and "vulvovaginal disorder" were similar for the two treatment groups. Very few patients discontinued treatment due to medical events. This study does not demonstrate a significant safety problem with the clindamycin vaginal ovule. The comparison of safety between clindamycin vaginal ovule and clindamycin vaginal cream indicates a similar safety profile for the two treatment groups. While the clindamycin vaginal ovule caused more vaginal burning relative to the clindamycin vaginal cream, the incidence rate was acceptable.

This short-term regimen of 3 days with clindamycin vaginal ovules as shown in this study is effective, well tolerated, and offers women a shortened regimen with an alternative dosage form for the treatment of bacterial vaginosis.

Study 0002

Title: Efficacy of clindamycin vaginal ovule (3-day treatment) versus oral metronidazole (7-day treatment) in bacterial vaginosis.

Objectives: To compare the efficacy and safety of clindamycin phosphate vaginal ovule (CVO), given as a 3-day regimen, with oral metronidazole (MET) given twice daily for 7-days for the treatment of bacterial (BV).

Investigators: Twenty-three well-qualified foreign investigators participated in the study. There names and investigative sites are listed below:

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Catania, Italy

Creatsas, George, M. D.
Athens, Greece

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Schiltigheim Cedex, France

Dhont, Marc, M. D.
Gent, Belgium

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Kolben, Martin, M. D.
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Study Design
This was a multi-center, prospective, randomized, double-blind study. Patients with a clinical diagnosis of BV were randomized within each center to treatment with either clindamycin VO, one ovule (100 mg) daily for 3 days or metronidazole 500 mg (two 250 mg capsules) orally twice daily for 7 days. Pretreatment visit activities included informed consent, medical history, pelvic examination, diagnostic tests (vaginal fluid pH, vaginal discharge, clue cells, vaginal fluid odor, Gram stain), and tests for concomitant pathogens. Follow-up visit activities (12 to 16 days and 18 to 52 days after start of treatment [SR window] included a vulvovaginal examination, repeat diagnostic tests, tests for concomitant pathogens if symptomatic, efficacy evaluations, and reporting of drug compliance (Days 12-16 only), adverse events, and concomitant medications.

Patient enrollment
Four hundred (203 clindamycin VO, 197 metronidazole) enrolled in the study, however one patient (#1401) in the metronidazole received medication but did not return for any follow-up and was not considered in the intent-to treat (ITT) population. A total of 233 patients (113 clindamycin VO, 120 metronidazole) were considered evaluable for efficacy based on the Study Report (SR) window as defined on page 8.

Demographic Characteristics
Table 30 below summarizes demographic data for the ITT patients. There were no statistically significant differences in the pretreatment demographics (age, weight, and race) for ITT patients between treatment groups. Demographic profile was likewise similar for evaluable patients.

Table 30. Patient Demographics (ITT Population)

Demographic Variable	CVO N=203	MET N=196	Total N=399	Treatment P-value
Mean Age, yr ± SD [Range]	33.0 ± 10.4	33.7 ± 10.7	33.3 ± 10.6	0.5007
Mean Wgt, kg ± SD [Range; No. Reporting]	63.3 ±11.4	61.8 ± 9.6	62.6 ±10.6	0.1678
Race: White	185 (91.1%)	178(90.8%)	363 (91.0%)	0.7216
Black	16 (7.9%)	14 (7.1%)	30 (7.5%)	
Oriental/Asian	2 (1.0%)	1 (0.5%)	3 (0.8%)	
Other		3(1.5%)	3 (0.8%)	

CVO – Clindamycin vaginal ovule, 3-day treatment
MET – metronidazole, 7-day treatment

Patient Evaluability
All patients (except one in the metronidazole group) were included in the safety and the intent-to-treat efficacy analyses. The criteria for evaluability in this study were identical to those in Study 001 as defined on page 22. Of the 399 ITT patients, a total of 166 patients (42.6%) were considered non-evaluable; 44.3% (90/203) of clindamycin VO patients and 38.8% (76/196) of the metronidazole patients. Table 31 summarizes the primary reasons for non-evaluability. The number of evaluable patients enrolled by each

investigator is given in Tables 32 and 33 for clindamycin and metronidazole, respectively.

Table 31. Primary Reasons for Non-Evaluability (ITT Patients-SR WINDOW)

Reason for Non-Evaluability	Number of Patients (% of Group)		
	CVO N=203	MET N=196	Total N=399
No information available on study drug administration	0 (0)	1 (0.5)	1 (0.3)
Did not have clinical BV	2 (1.0)	1 (0.5)	3 (0.8)
Did not meet inclusion/exclusion criteria	38 (18.7)	37 (18.9)	75 (18.8)
Additional antimicrobial therapy given (except failures)	13 (6.4)	10 (5.1)	23 (5.8)
Did not comply with dosing regimen	2 (1.0)	3 (1.5)	5 (1.3)
Follow-up not within required window*	29 (14.3)	24 (12.2)	53 (13.3)
Had symptomatic concomitant vaginal infection	6 (3.0)	0 (0.0)	6 (1.5)
Total Non-Evaluable	90 (44.3)	76 (38.8)	166 (41.6)
Total Evaluable	113 (55.7)	120 (61.2)	233 (58.4)

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
*14 – 48 Days

The most common primary reasons for non-evaluability were failure to meet inclusion/exclusion criteria post-enrollment (reported for 18.8% of ITT patients) and not returning for follow-up visits within the required windows (reported for 13.3% of ITT patients. The proportion of patients considered non-evaluable for each primary reason was similar for the two treatment groups, except that all the patients considered non-evaluable due to concomitant vaginal infection were in the clindamycin VO group.

Efficacy Results:

As in Study 0001, efficacy of the clindamycin ovule was based on primary and secondary measures. The primary measure determined the overall clinical outcome of evaluable patients using both the 3 diagnostic criteria (pH, clue cells and odor) and the 2 diagnostic criteria (clue cells and odor only). The secondary measure determined the overall clinical outcome for ITT patients (based on 3 and 2 criteria), and on Gram stain scores for evaluable patients. Tables 32 and 33 present clinical outcome based on the 3 diagnostic criteria as determined by each investigator for the clindamycin VO and metronidazole groups, respectively. The data presented is based on the amended protocol window (SR window) defined as the second follow-up visit occurring 18 and 52 days after the start of treatment. Additional analyses are included for comparison purposes based on the original protocol-defined window (28 to 42 days after the start of treatment), and the FDA-requested window (between 28 and 52 days after start of treatment), and at least 14 days after the first follow-up visit.

TABLE 32
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
3 DIAGNOSTIC CRITERIA (ALL WINDOWS) CLEOCIN OVULE TREATMENT GROUP
PROTOCOL 0002

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
Ahmed	24	9	5	4	7	3	4	9	5	4
Arya	7	6	3	3	5	2	3	6	3	3
Capetta	4	2	0	2	2	0	2	2	0	2
Christoffersen	8	2	2	0	1	1	0	1	1	0
Cianci	1	0	0	0	0	0	0	0	0	0
Creatsas	8	3	2	1	3	2	1	3	2	1
Dellenbach	2	2	1	1	2	1	1	2	1	1
Dhont	4	2	0	2	2	0	2	2	0	2
Judlin	2	1	1	0	0	0	0	1	1	0
Kolben	7	4	1	3	4	1	3	4	1	3
Mangioni	3	3	3	0	3	3	0	3	3	0
Moi	5	4	2	2	4	2	2	4	2	2
Neuer	6	2	2	0	2	2	0	2	2	0
Paavonen	31	21	10	11	18	7	11	21	10	11
Peterek	8	7	6	1	7	6	1	7	6	1
Radcliffe	17	6	3	3	6	3	3	6	3	3
Schmidt	13	11	4	7	11	4	7	11	4	7
Schnittger	15	10	6	4	10	6	4	8	4	4
Szczurowicz	8	0	0	0	0	0	0	0	0	0
Thoren	10	6	3	3	6	3	3	6	3	3
Ungar	8	7	0	7	7	0	7	7	0	7
Wilson	11	5	3	2	5	3	2	5	3	2
Xercavins	1	0	0	0	0	0	0	0	0	0
Total	203	113	57	56	105	49	56	110	54	56

TABLE 33
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
3 DIAGNOSTIC CRITERIA (ALL WINDOWS) METRONIDAZOLE TREATMENT GROUP
PROTOCOL 0002

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
Ahmed	23	12	6	6	10	4	6	12	6	6
Arya	6	5	2	3	5	2	3	5	2	3
Capetta	5	3	2	1	3	2	1	3	2	1
Christoffersen	6	2	2	0	1	1	0	1	1	0
Cianci	0	0	0	0	0	0	0	0	0	0
Creatsas	8	5	3	2	5	3	2	5	3	2
Dellenbach	1	0	0	0	0	0	0	0	0	0
Dhont	4	2	0	2	2	0	2	2	0	2
Judlin	4	1	1	0	1	1	0	1	1	0
Kolben	6	3	1	2	2	0	2	3	1	2
Mangioni	2	2	2	0	2	2	0	2	2	0
Moi	6	3	1	2	2	0	2	3	1	2
Neuer	6	5	3	2	4	2	2	4	2	2
Paavonen	31	18	12	6	17	11	6	17	11	6
Peterek	8	8	8	0	8	8	0	8	8	0
Radcliffe	18	5	0	5	5	0	5	5	0	5
Schmidt	10	8	6	2	8	6	2	8	6	2
Schnittger	16	15	9	6	14	8	6	15	9	6
Szczurowicz	7	2	1	1	1	0	1	2	1	1
Thoren	10	8	5	3	8	5	3	8	5	3
Ungar	8	8	1	7	8	1	7	8	1	7
Wilson	11	5	5	0	5	5	0	5	5	0
Xercavins	0	0	0	0	0	0	0	0	0	0
Total	196	120	70	50	111	61	50	117	67	50

A summary of the overall clinical outcome for evaluable patients who received clindamycin VO and metronidazole as determined by 3 diagnostic criteria (resolution of pH, clue, cells and odor) is given in Table 34 below.

TABLE 34 OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY 3 DIAGNOSTIC CRITERIA (SR, PROTOCOL-DEFINED, FDA-REQUESTED WINDOWS)

EVALUABLE PATIENTS	OUTCOME	No of Patients (% of Group)		95% CI
		CVO	MET	
SR WINDOW (18 – 52 DAYS) N = 113 CVO; 120 MET	CURE	57 (50.4)	70 (58.3)	-20.7, 4.9
	FAILURE	56 (49.6)	50 (41.7)	
PROTOCOL-DEF. WINDOW (28 – 42 DAYS) N = 105 CVO; 111 MET	CURE	49 (46.7)	61 (55)	-21.6, 5.0
	FAILURE	56 (53.3)	50 (45)	
FDA REQ. WINDOW (28 – 52 DAYS N = 110 CVO; 117 MET	CURE	54 (49.1)	67 (57.3)	-21.1, 4.8
	FAILURE	56 (50.9)	50 (42.7)	

CVO – Clindamycin vaginal ovule, 3-day treatment
MET – Metronidazole Capsules 500 mg , 7-day treatment
DEF – Defined; REQ –Requested

The overall clinical outcome for evaluable patients by 3 diagnostic criteria (SR window) showed that 50.4% (57/113) of patients in the ovule group were cured compared with 58.3% (70/120) of patients in the metronidazole group. This difference was not statistically significant (95% CI = -20.7, 4.9). For the protocol defined window 46.7% (49/105) of the clindamycin VO group and 55% (61/111) of the metronidazole group were cured. In the FDA-requested window, similar results were obtained for each treatment group with 49.1% (54/110) in the clindamycin VO group and 57.3% (67/117) of the metronidazole group reported as cures. There was no significant difference among treatment groups in either of the treatment windows. Statistical equivalence was not demonstrated in any of the analysis populations.

Secondary Analysis (Two Diagnostic Criteria)

Supplementary analyses for the overall clinical outcome based on 2 diagnostic criteria (resolution of clue cells and odor) was performed for each treatment group using the three treatment windows a defined on page 8. Tables 34 and 35 summarize the cure rates by investigator for the clindamycin VO and metronidazole treatments groups, respectively.

TABLE 34
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
2 DIAGNOSTIC CRITERIA (ALL WINDOWS) CLEOCIN OVULE TREATMENT GROUP
PROTOCOL 0002

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
Ahmed	24	9	5	4	7	3	4	9	5	4
Arya	7	6	6	0	5	5	0	6	6	0
Capetta	4	2	0	2	2	0	2	2	0	2
Christoffersen	8	2	1	1	1	1	0	1	1	0
Cianci	1	0	0	0	0	0	0	0	0	0
Creatsas	8	3	2	1	3	2	1	3	2	1
Dellenbach	2	2	1	1	2	1	1	2	1	1
Dhont	4	2	0	2	2	0	2	2	0	2
Judlin	2	1	1	0	0	0	0	1	1	0
Kolben	7	4	1	3	4	1	3	4	1	3
Mangioni	3	3	3	0	3	3	0	3	3	0
Moi	5	4	2	2	4	2	2	4	2	2
Neuer	6	2	2	0	2	2	0	2	2	0
Paavonen	31	21	12	9	18	9	9	21	12	9
Peterek	8	7	7	0	7	7	0	7	7	0
Radcliffe	17	6	3	3	6	3	3	6	3	3
Schmidt	13	11	8	3	11	8	3	11	8	3
Schnittger	15	10	8	2	10	8	2	8	6	2
Szczurowicz	8	0	0	0	0	0	0	0	0	0
Thoren	10	6	5	1	6	5	1	6	5	1
Ungar	8	7	6	1	7	6	1	7	6	1
Wilson	11	5	4	1	5	4	1	5	4	1
Xercavins	1	0	0	0	0	0	0	0	0	0
Total	203	113	77	36	105	70	35	110	75	35

TABLE 35
OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY INVESTIGATOR
2 DIAGNOSTIC CRITERIA (ALL WINDOWS) METRONIDAZOLE TREATMENT GROUP
PROTOCOL 0002

INVESTIGATOR	ITT	REPORT WINDOW			PROTOCOL WINDOW			FDA WINDOW		
		Eval	Cure	Fail	Eval	Cure	Fail	Eval	Cure	Fail
Ahmed	23	12	6	6	10	4	6	12	6	6
Arya	6	5	3	2	5	3	2	5	3	2
Capetta	5	3	2	1	3	2	1	3	2	1
Christoffersen	6	2	2	0	1	1	0	1	1	0
Cianci	0	0	0	0	0	0	0	0	0	0
Creatsas	8	5	3	2	5	3	2	5	3	2
Dellenbach	1	0	0	0	0	0	0	0	0	0
Dhont	4	2	0	2	2	0	2	2	0	2
Judlin	4	1	1	0	1	1	0	1	1	0
Kolben	6	3	1	2	2	0	2	3	1	2
Mangioni	2	2	2	0	2	2	0	2	2	0
Moi	6	3	2	1	2	1	1	3	2	1
Neuer	6	5	4	1	4	3	1	4	3	1
Paavonen	31	18	13	5	17	12	5	17	12	5
Peterek	8	8	8	0	8	8	0	8	8	0
Radcliffe	18	5	1	4	5	1	4	5	1	4
Schmidt	10	8	6	2	8	6	2	8	6	2
Schnittger	16	15	9	6	14	8	6	15	9	6
Szczurowicz	7	2	1	1	1	0	1	2	1	1
Thoren	10	8	5	3	8	5	3	8	5	3
Ungar	8	8	6	2	8	6	2	8	6	2
Wilson	11	5	5	0	5	5	0	5	5	0
Xercavins	0	0	0	0	0	0	0	0	0	0
Total	196	120	80	40	111	71	40	117	77	40

A summary of the overall clinical outcome for each treatment group (ovule and metronidazole) as determined by 2 diagnostic criteria (resolution of clue cells and odor) is given in Table 36.

TABLE 36 OVERALL CLINICAL OUTCOME FOR EVALUABLE PATIENTS BY 2 DIAGNOSTIC CRITERIA (SR, PROTOCOL-DEFINED, FDA-REQUESTED WINDOWS)

EVALUABLE PATIENTS	OUTCOME	No of Patients (% of Group)		95% CI
		CVO	MET	
SR WINDOW (18 – 52 DAYS) N = 113 CVO; 120 MET	CURE	77 (68.1)	80 (66.7)	-10.6, 13.5
	FAILURE	36 (31.9)	40 (33.3)	
PROTOCOL-DEF. WINDOW (28 – 42 DAYS) N = 105 CVO; 111 MET	CURE	70 (66.7)	71 (64.0)	-10.0, 15.4
	FAILURE	35 (33.3)	40 (36.0)	
FDA REQ. WINDOW (28 – 52 DAYS N = 110 CVO; 117 MET	CURE	75 (68.2)	77 (65.8)	-9.9, 14.6
	FAILURE	35 (31.8)	40 (34.2)	

CVO – Clindamycin vaginal ovule, 3-day treatment
MET – Metronidazole Capsules 500 mg , 7-day treatment
DEF – Defined; REQ –Requested

The results of the overall clinical outcome for evaluable patients by 2 diagnostic criteria were better compared to those obtained for the 3 diagnostic criteria. Since resolution of pH was not one of the criteria used to defined cure, these results were generally higher than those based on 3 diagnostic criteria and probably reflect the influence of pH in lowering the cure rates of the 3 criteria is used. The overall cure rate was 68.1% in the ovule treat group and 66.7% in the metronidazole treated group. Statistical equivalence was demonstrated in all three analysis populations.

Secondary Efficacy Measures

1) Overall Clinical Outcome for Assessable ITT Patients

A summary of the overall clinical outcome for the ITT patient population as determined from 3 diagnostic criteria (resolution of pH, clue cells, and odor) and 2 diagnostic criteria (resolution of clue cells and odor) is shown in Table 37.

Table 37. Overall Clinical Outcome by 3 and 2 Diagnostic Criteria (ITT Patients)

Outcome	By 3 Diagnostic Criteria			By 2 Diagnostic Criteria		
	No. of Patients (% of Group*)		95% CI	No. of Patients (% of Group*)		95% CI
	CVO (N=203; 156 Ass)	MET (N=196; 155 Ass)		CVO (N=203; 156 Ass)	MET (N=196; 156 Ass)	
Cure	90 (57.7)	93 (60.0)	-13.2 , 8.6	114 (73.1)	107 (68.6)	-5.6, 14.6
Failure	66 (42.3)	62 (40.0)		42 (26.9)	49 (31.4)	
Nonassessable	47	41		47	40	

CVO – clindamycin vaginal ovule, 3-day treatment
MET– metronidazole capsules, 7-day treatment
Ass – Assessable; * Percentage based on number of patients assessable;

Based on the primary analysis of the ITT patient population, 90 (57.7%) of the 156 assessable patients in the clindamycin VO group were cured compared with 93 (60.0%) of the 155 assessable patients in the metronidazole group. This difference was not significant (95% CI = -13.2, 8.6). Based on 2 diagnostic criteria of the ITT population, a cure rate of 73.1% (114/156) was obtained for the clindamycin VO group compared with 68.6% (107/156) in the metronidazole group (95% CI = -5.6, 14.6). Cure rates in both treatment groups were based on assessable patients. The ITT cure rates are comparable to those observed in evaluable patients and are not statistically significantly different among treatment groups.

2) Gram Stain Scores

Gram stain scores at the first and second follow-up visits for evaluable patients who reported Gram stains are shown below in Table 38.

Table 38. Gram Stain Scores at Both Follow-up Visits (Evaluable Patients)

Gram Stain Score	No. of Patients (% of Group*)			
	First Follow-up Visit		Second Follow-up Visit	
	CVO N=108 (%)	MET N=113 (%)	CVO N=102 (%)	MET N=111 (%)
Normal (0-3)	79 (73.1)	86 (76.1)	61 (59.8)	80 (72.1)
Intermediate (4-6)	19 (17.6)	2 (1.8)	15 (14.7)	5 (4.5)
Compatible with BV (7-10)	10 (9.3)	25 (22.1)	26 (25.5)	26 (23.4)
P-value†	<0.0001		0.0274	

CVO – clindamycin vaginal ovule, 3-day treatment
CVC – clindamycin vaginal cream, 7-day treatment
N – Number of valuable patients who reported Gram stain
*Percentages are based on the number of patients reporting results
†P-values were calculated using the chi-square test, comparing the overall distributions between treatment groups.