Study 0027 (Pivotal)

Title: Multicenter Study to Evaluate the Efficacy and Safety of a 3-Day course of Clindamycin Vaginal Cream 2% or a Placebo Cream in the treatment of Bacterial Vaginosis

Investigators: Eleven investigators at various sites in the United Kingdom qualified to treat women with Bacterial Vaginosis enrolled from 2 to 23 patients each.

Objectives: The study objectives were to compare the efficacy, at 7 and 28 days, and the safety of a 3-day course of clindamycin vaginal cream 2% with the effects of placebo cream

Study Design: This was a prospective, multicenter, double blind, placebo controlled, block randomized, parallel group study. Patients were randomized to receive either clindamycin vaginal cream 2% or matching placebo cream (1:1 active:placebo) within each center.

Study Design: This was a prospective, randomized, double-blind, placebo-controlled study. Patients were randomized to receive either clindamycin cream 2% or matching placebo cream for a period of three days. One hundred seven (107) patients were randomized into the clindamycin vaginal cream 2% group and 114 patients into the placebo group. Each patient was instructed to insert 5 grams of 2% clindamycin cream or 5 grams of matching placebo cream high into the vagina at bedtime daily for three consecutive nights, beginning on baseline evaluation night. They were instructed about safe disposal of the used applicators and advised to avoid sexual intercourse or prolonged bathing (more than 5 minutes-showers preferred) until day 7 (return visit 1). Patients were instructed to return unused cream or empty medication tubes on their return visit to the clinic.

The patients were assessed at approximately 7 to 9 days (return visit 1) and 28-35 days (return visit 2) after the start of therapy.

Inclusion Criteria: Patients were included in the study if they were women 18 years of age or older that presented to the clinic complaining of symptoms consistent with Bacterial Vaginosis which was confirmed as defined on page 6.

Exclusion Criteria:

Patients were excluded from the study if they presented with or gave a history of any of the criteria listed under the exclusion criteria on page 6.

Study Population: A total of 221 patients were enrolled and randomized; 107 patients to the clindamycin vaginal cream 2% group and 114 to the placebo cream group. All patients who received any study medication and provided any safety data were analyzed for safety and all evaluable patients were analyzed for efficacy.

The investigators who participated in the study, their geographical locations and the number of evaluable patients for the overall efficacy analyses by the Applicant and the Medical Officer are listed in Table 6 for the clindamycin vaginal cream 2% group and in Table 7 for the placebo group. Tables 8 and 9 list the non-evaluable patients for the respective groups.

All patients enrolled in the study were evaluable for safety.

Table 6

NUMBER OF PATIENTS VALID FOR EFFICACY ANALYSES PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATOR CLINDAMYCIN VAGINAL CREAM 2%

INVESTIGATOR	ENROLLED	EVALUABLE FOR EFFICACY	
		APPLICANT	MED. OFFICER
Ahmed, M.D., IH Nottingham, UK	16	8	11
Arumainayagam, M.D., JT Walsall, UK	10	5	5
Arya, M. D., O Liverpool, UK	15	9	11
Blackwell, M. D., A Swansea, UK	12	9	11
Boakes, M. D., A Stoke Mandeville, UK	10	7	8
Morrison, M. D., GD Plymouth, UK	2	2	2
Shahmanesh, M.D., M Birmingham, UK	23	9	12
Symonds, M. D., MAE Bishops Stortford, UK	2	0	0
Tait, M. D., IB Glasgow, UK	2	0	0
Wilmott, M. D., F Southhampton, UK	5	0	4
Wilson, M. D., J Leeds,UK	10	7	7
Totals	107	56	71
Per Cent		56/107 (52%)	71/107 (66%)

Table 7

NUMBER OF PATIENTS VALID FOR EFFICACY ANALYSES PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATYOR PLACEBO VAGINAL CREAM

INVESTIGATOR	ENROLLED	EVALUABLE FOR EFFICACY APPLICANT	EVALUABLE FOR EFFICACY MED. OFFICER
Ahmed, M.D., IH Nottingham, UK	16	7	12
Arumainayagam, M.D., JT Walsall, UK	11	4	9
Arya, M. D., O Liverpool, UK	16	6	13
Blackwell, M. D., A Swansea, UK	13	6	12
Boakes, M. D., A Stoke Mandeville, UK	9	4	8
Morrison, M. D., GD Plymouth, UK	3	1	3
Shahmanesh, M.D., M Birmingham, UK	27	6	16
Symonds, M. D., MAE Bishops Stortford, UK	2	1	2
Tait, M. D., IB Glasgow, UK	0	0	0
Wilmott, M. D., F Southhampton, UK	5	3	4
Wilson, M. D., J Leeds,UK	12	3	9
Totals Per Cent	114	41 41/114 (36%)	88 88/114 (77%)

Table 8

NUMBER OF PATIENTS INVALID FOR EFFICACY ANALYSES PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATYOR CLINDAMYCIN VAGINAL CREAM 2%

INVESTIGATOR	ENROLLED	NON-EVALUABLE FOR EFFICACY APPLICANT	MED. OFFICER
Ahmed, M.D., IH Nottingham, UK	16	8	5
Arumainayagam, M.D., JT Walsall, UK	10	5	5
Arya, M. D., O Liverpool, UK	15	6	4
Blackwell, M. D., A Swansea, UK	12	3	1
Boakes, M. D., A Stoke Mandeville, UK	10	3	2
Morrison, M. D., GD Plymouth, UK	2	0	0
Shahmanesh, M.D., M Birmingham, UK	23	14	11
Symonds, M. D., MAE Bishops Stortford, UK	2	2	2
Tait, M. D., IB Glasgow, UK	2	2	2
Wilmott, M. D., F Southhampton, UK	5	5	1
Wilson, M. D., J Leeds,UK	10	3	3
Totals	107	51	36

Table 9

NUMBER OF PATIENTS INVALID FOR EFFICACY ANALYSES PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATYOR PLACEBO VAGINAL CREAM 2%

INVESTIGATOR	ENROLLED	NON-EVALUABLE FOR EFFICACY APPLICANT	MED. OFFICER
Ahmed, M.D., IH Nottingham, UK	16	9	4
Arumainayagam, M.D., JT Walsall, UK	11	7	2
Arya, M. D., O Liverpool, UK	16	10	3
Blackwell, M. D., A Swansea, UK	13	7	1
Boakes, M. D., A Stoke Mandeville, UK	9	5	1
Morrison, M. D., GD Plymouth, UK	3	2	0
Shahmanesh, M.D., M Birmingham, UK	27	21	11
Symonds, M. D., MAE Bishops Stortford, UK	2	1	0
Tait, M. D., IB Glasgow, UK	0	0	0
Wilmott, M. D., F Southhampton, UK	5	2	1
Wilson, M. D., J Leeds,UK	12	9	3
Totals	114	73	26

The reasons for and the number of patients who were non-evaluable as assessed by the Applicant and the Medical Officer for the Clindamycin and placebo groups are listed in Table 10.

Table 10

Primary Reasons for Invalidity of Patients Excluded from Efficacy Analyses

Protocol 0027

PRIMARY REASON FOR INVALIDITY	# of Pts APPLICANT		# of Pts MED OFF	
	CLIN	PLACEBO	CLIN	PLACEBO
Fail Entry Criteria	0	0	1	0
Did Not Meet Eval Criteria at RV-2*	36	48	0	0
Lost to Follow-up	14	23	27	26
Protocol Violation	0	2	7	0
Did not Complete Evaluation	1	2	0	0
Took Other Med for BV	0	0	1	0
Total	51	73	36	26

*Patients who were failures at return visit one were not carried forward to return visit two and were classified as not evaluable at visit two by the Applicant but were carried forward by the Medical Officer and counted as failures. All patients who qualified to enter the study were allowed by the Medical Officer to remain in the study through the second follow-up visit.

Demographics: The two treatment groups were generally comparable at admission to the study. Table 11 lists the demographic and baseline data of patients enrolled in the study.

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Table 11

Demographics and Baseline Data

	Clindamycin	Placebo
Total Number of Patients	107	114
Age		
Minimum		
Maximum		
Mean	27.5	26.2
Weight (KG)		
Minimum		
Maxium		
Mean	60.3	60.9
Race		
White	88	95
Black	18	17
Oriental/Asian	1	1
West Indian	0	1
Contraceptive Use		
Oral	64	66
Condom	20	19
Abstinence	10	11
IUD	2	1
Other	11	17
Previous BV Infection		
None	39	39
1-2	30	31
3-5	11	13
>5	5	10
Unknown	22	21

Results

The Applicant assessed efficacy return visits one and two as: Success, Improved, Failure, Medical Event Failure (visit one only) and Recurrence. The definitions are the same as those for Study 0021 on pages 10 an 11.

Overall Outcome: An efficacy parameter called "overall outcome" was determined by the Applicant for all evaluable patients and takes into consideration the results from both the first and second follow-up visits. Overall outcome definitions by the Applicant are shown in the following table.

Determination of Overall Outcome

First Follow-up Visit	Second Follow-up Visit*	Overall Outcome
Cure	Cure Improvement Failure***	Cure Improvement Failure
Improvement	Cure Improvement Failure***	Cure Improvement Failure
Failure or ME Failure	Cure Improvement Failure***	Failure Failure Failure
Missing/DNA**	Cure Improvement Failure***	Cure Improvement Failure

*Patients who were cured or improved at the first visit and were then listed as missing/DNA at the second visit were not included in assessment of overall outcome
**DNA = Did Not Attend
*** Includes relapse or reinfection

Patients were included in the overall evaluation if they were cured or improved at return visit 1 and remained cured at return visit 2 or received alternative treatment for BV (e.g., treatment failures who were otherwise evaluable at return visit 1). The overall outcome is considered the "test of cure" and is based on the number of evaluable patients found at return visit 2.

The Applicant determined that the overall cure rate at return visit 2 (Day 28) for the clindamycin cream 2% was 53.6 % compared to 2.4% for the placebo group, while the failure rate was 19.6% and 90.2% for the clindamycin and placebo groups, respectively (Table 12).

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Table 12

Overall Evaluation of Therapy (By Applicant)

	2% CLINDAMYCIN (N=56)	PLACEBO (N=41)
CURE n (%)	30 (53.6)	1 (2.4)
FAILURE n (%)	11 (19.6)	37 (90.2)
RELAPSE n (%)	15 (26.8)	3 (7.3)

In the Medical Officer's analyses, patients who were cured or improved at return visit 1 were assessed as cures or failures at return visit 2 (overall). All failures at return visit 1 were carried forward as failures to return visit 2 (overall). Cure rates of 54% for the clindamycin group and 5% for the placebo group were obtained by the medical officer, Table 13.

Table 13

Overall Evaluation of Therapy (By Medical Officer)

	2% CLINDAMYCIN (N=71)	PLACEBO (N=88)
CURE n (%)	38 (54)	4 (4.5)
FAILURE n (%)	33 (46)	84 (95.5)

Safety

Medical events data including information on all medical events, drug-related medical events, serious medical events, and dropouts due to medical events are summarized in the Table 14. Medical events that occurred in 1% or more of the treated patients in either group are summarized in Table 15. Genital tract medical events were the most commonly reported in both treatment groups.

Table 14

Medical Events Summary

Treatment	CLINDAMYCIN	PLACEBO
Total Number of Patients*	107	114
Patients (%) with no MEs	53 (49.5%)	72 (63.2%)
Patients (%) with MEs		
All MEs	54 (50.5%)	42 (36.8%)
"Drug"-related MEs	24 (22.4%)	12 (10.5%)
Total Number of ME Reports		
All MEs	75	52
"Drug"-Related MEs	30	13
Patients with serious MEs	0	0
Patient dropouts due to MEs	4	2

*Evaluable Patients by Applicant

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Table 15

Medical Events That Occurred in 1% or More of Patients

BODY SYSTEM & EVENT	2% CLINDAMYCIN (N=107) N	%	PLACEBO (N=114) N	%
DERMATOLOGICAL				
macular rash	2	1.9	-	-
ENDOCRINE				
menstrual cycle abnormal or irregular	6	5.6	4	3.5
GASTROINTESTINAL				
abdominal pain	2	1.9	2	1.8
diarrhea	2	1.9	1	0.9
loose stools	2	1.9	-	-
GENITAL TRACT				
chlamydial infection	3	2.8	5	4.4
candidiasis	3	2.8	4	3.5
fungal infection vagina	5	4.7	4	3.5
genital warts	6	5.6	3	2.6
vaginal disorders	2	1.9	2	1.8
vaginal discharge	2	1.9	-	-
vulva disorders	4	3.7	1	0.9
vulvar pruritus	6	5.6	2	1.8
URINARY TRACT				
cystitis	2	1.9	1	0.9
urinary tract inf	2	1.9	1	0.9

SUMMARY

The results of this study indicate that a 3-day course of clindamycin cream 2% is an effective treatment for bacterial vaginosis when compared to placebo cream. The overall cure rates obtained by the Applicant was 54% for patients using the clindamycin cream and 2% in the placebo patients. Simularily the Medical Officer found a cure rate of 54% in the clindamycin cream group and 5% in the placebo group. These results appear to confirm the findings of the pilot study presented earlier in this review.

No serious drug-related medical events were reported in this study. There was a trend of a higher proportion of patients reporting vulvo-vaginal irritation or soreness following the active preparation. The incidence of candidiasis in the two groups was similar. The incidence of systemic side effects (abdominal pain, vomiting) was similar in both groups although there was a slight excess of reports of diarrhea/loose stools in the clindamycin cream 2% group.

Conclusion: From those data, it may be concluded that 5 grams of clindamycin cream 2% daily for 3 days is more effective than placebo cream in the treatment of patients with bacterial vaginosis.

Study 0020 (Pivotal)

Title: Comparison of Two Dosing Regimens of 2% Clindamycin Vaginal Cream for the Treatment of Bacterial Vaginosis: 3 Days vs 7 Days

Investigators: Ten investigators (nine in U. S., one in Canada) who were physicians well qualified to diagnose and treat bacterial (BV) participated in this study.

Objective: To compare the efficacy and safety between two dosing regimens of 2% clindamycin vaginal cream in the treatment of bacterial vaginosis - a 3-day regimen vs the standard 7-day regimen.

Study Design: This was a multicenter, prospective, randomized, observer-blind, parallel group study. Patients with BV were randomly assigned to one of the following treatment regimens on a 1:1 ratio:

1) Clindamycin phosphate vaginal cream 2% (Cleocin Vaginal Cream) 5 grams intravaginally at bedtime for 3 consecutive nights.

2) Clindamycin phosphate vaginal cream 2% (Cleocin Vaginal Cream) 5 grams intravaginally at bedtime for 7 consecutive nights.

Patients were seen for follow-up evaluation at 21-35 days following completion of therapy.

Inclusion Criteria: Patients were included in the study if they:

- were between the ages
- had signed a written informed consent statement.
- had a clinical diagnosis of BV as defined by the presence of a vaginal discharge that (a) had a pH greater than 4.5; (b) gave off a "fishy" amine odor when mixed with 10% KOH solution; and © contained clue cells on microscopic examination.
- had a Gram stain of the vaginal fluid consistent with a diagnosis of BV (a score of 7-10).

Exclusion Criteria: The specific exclusion criteria were the following:

- Pregnancy or breast feeding.
- Allergy to clindamycin.
- Systemic or vaginal antimicrobial therapy within 2 weeks prior to the study.

- Previous enrollment in this study or current enrollment in another investigational protocol.
- A history of antibiotic associated colitis or of frequent periodic diarrhea.
- Necessity to use non-protocol antibiotics.
- A positive culture for *Neisseria gonorrhea*.
- A positive KOH for *Candida albicans*.
- A positive wet mount for *Trichomonas vaginalis*.
- A positive rapid diagnostic test for *Chlamydia trachomatis*.
- Clinical evidence of active genital herpes viral infection.
- Atrophic vaginitis.
- Suspected menstruation during the treatment period or at follow-up visit.
- Women unwilling to stop douching during therapy.

Study Population: The ten investigators enrolled a total of 411 patients (207 3-day, 204 7-day). Four hundred nine (409) patients were evaluable for safety (2 patients in the three day group did not receive any drug); 259 patients were evaluable for efficacy (131 3-day; 128 7-day). In the medical officer's analyses, the number of evaluable patients for efficacy differed from those of the investigators. There were 167 in the 3-day regimen and 161 in the 7-day group.

The principal investigators, their locations and the number of patients enrolled and evaluable for efficacy, as determined by the investigators and the Medical Officer, at each center are listed in Tables 16 and 17 for clindamycin 3 day and clindamycin 7 day, respectively. Tables 18 and 19 lists the non-evaluable patients for the two treatment groups.

Table 16
NUMBER OF PATIENTS VALID FOR EFFICACY ANALYSES
PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATOR
CLINDAMYCIN VAGINAL CREAM 2% 3-DAY

INVESTIGATOR	# ENROLLED	EVALUABLE APPLICANT	EVALUABLE MEDICAL OFFICER
Benrubi, Guy Jacksonville, Fl.	20	7	11
Carey, J. Chris Oklahoma City, OK	7	3	3
Duff, Patrick Gainesville, Fl.	24	16	19
Eschenbach, David Seattle WA.	50	36	46
Gall, Stanley Louisville, KY	11	6	7
Livengood, Charles Durham, NC	19	11	16
Martel, Alain Sainte Foy, Quebec	24	18	23
McGregor, James Denver, Colo.	30	18	23
Newton, Edward San Antonio, TX	11	8	11
Soper, David Richmond, VA	9	8	8
Total	205	131	167
Per Cent		131/205 (64%)	167/205 (81%)

Table 17
NUMBER OF PATIENTS VALID FOR EFFICACY ANALYSES
PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATOR
CLINDAMYCIN VAGINAL CREAM 2% 7-DAY

INVESTIGATOR	# ENROLLED	EVALUABLE APPLICANT	EVALUABLE MEDICAL OFFICER
Benrubi, Guy Jacksonville, Fl.	21	10	14
Carey, J. Chris Oklahoma City, OK	7	1	2
Duff, Patrick Gainesville, Fl.	23	14	19
Eschenbach, David Seattle WA.	48	33	41
Gall, Stanley Louisville, KY	7	5	6
Livengood, Charles Durham, NC	21	15	17
Martel, Alain Sainte Foy, Quebec	26	20	23
McGregor, James Denver, Colo.	32	19	25
Newton, Edward San Antonio, TX	11	5	6
Soper, David Richmond, VA	8	6	8
Total	204	128	161
Per Cent		128/204 (63%)	161/204 (79%)

Table 18

NUMBER OF PATIENTS INVALID FOR EFFICACY ANALYSES
PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATOR
CLINDAMYCIN VAGINAL CREAM 2% 3-DAY

INVESTIGATOR	# ENROLLED	INVALID APPLICANT	INVALID MEDICAL OFFICER
Benrubi, Guy Jacksonville, Fl.	20	13	9
Carey, J. Chris Oklahoma City, OK	7	4	4
Duff, Patrick Gainesville, Fl.	24	8	5
Eschenbach, David Seattle WA.	50	14	4
Gall, Stanley Louisville, KY	11	5	4
Livengood, Charles Durham, NC	19	8	3
Martel, Alain Sainte Foy, Quebec	24	6	1
McGregor, James Denver, Colo.	30	12	7
Newton, Edward San Antonio, TX	11	3	0
Soper, David Richmond, VA	9	1	1
Total	205	74	38

Table 19

NUMBER OF PATIENTS INVALID FOR EFFICACY ANALYSES
PER APPLICANT AND MEDICAL OFFICER BY INVESTIGATOR
CLINDAMYCIN VAGINAL CREAM 2% 7-DAY

INVESTIGATOR	# ENROLLED	INVALID APPLICANT	INVALID MEDICAL OFFICER
Benrubi, Guy Jacksonville, Fl.	21	11	7
Carey, J. Chris Oklahoma City, OK	7	6	5
Duff, Patrick Gainesville, Fl.	23	9	4
Eschenbach, David Seattle WA.	48	15	7
Gall, Stanley Louisville, KY	7	2	1
Livengood, Charles Durham, NC	21	6	4
Martel, Alain Sainte Foy, Quebec	26	6	3
McGregor, James Denver, Colo.	32	13	7
Newton, Edward San Antonio, TX	11	6	5
Soper, David Richmond, VA	8	2	0
Total	204	76	43

The reasons for and the number of patients excluded from the efficacy analyses by the Applicant and the Medical Officer are listed in Table 20.

Table 20

Primary Reasons for Invalidity of Patients Excluded from Efficacy Analyses

Protocol 0020

PRIMARY REASON FOR INVALIDITY	# of Pts APPLICANT CLIN-3	APPLICANT CLIN-7	# of Pts MED OFF CLIN-3	MED OFF CLIN-7
Did not Use Study Medication	0	0	1	0
Failed Entry Criteria*	21	13	9	6
Protocol Violation	16	19	12	17
Took Other Antibiotics	8	8	7	8
Had Other Vaginal Infection	9	10	2	5
Lost to Follow-up	4	9	7	2
Follow-up not 21-35 days**	16	17	-	-
Total	74	76	38	43

*Patients with non-confirmatory Gram stains excluded by the Applicant were included by the Medical Officer

** Patients were not excluded by the Medical Officer for failure to return within the 21-35 days window. Window used by Medical Officer was 21-35 ± 7 days.

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Demographics: The two treatment groups were generally comparable at admission to the study. There were no significant differences between treatments with respect to the patient population demographics. Patients ranged in age from
Approximately 56% of the patients were white and 33% were black. Table 21 summarizes the demographic variables submitted by Applicant.

Table 21
Demographics and Baseline Data
Study 0020

	Clinda-3day	Clinda-7day
Total Number of Patients*	131	128
Age		
Minimum		
Maximum		
Mean	28.0	28.6
Weight (lb)		
Minimum		
Maximum		
Mean	145.9	142.5
Race		
White	71	75
Black	44	41
Oriental/Asian	5	5
Hispanic	10	6
Other	1	1
Contraceptive Use		
Oral	46	51
Condom	31	26
Abstinence	29	17
IUD	1	2
Surgically Sterile	22	24
Other	2	8
Previous BV Infection		
yes	55	63
no	64	54
Unknown	12	11

*Evaluable Patients by Applicant

Results

The Applicant assessed efficacy of the two treatment groups based on clinical findings. The primary efficacy was based on the overall clinical outcome at the return visit and defined as clinical cure, improvement, clinical failure or side effect failure.

Clinical Cure - Patients in whom all three diagnostic criteria (pH, odor, and clue cells) were normal at the follow-up visit.

IMPROVEMENT - Patients who had a return to normal for any two of the three diagnostic entry criteria.

Failure - Patients with a return to normal of one or none of the three diagnostic criteria.

Side Effect Failure - Patients unable to complete protocol therapy due to adverse effects related to protocol medication.

The Applicant analyses reveal that in the 3 day treatment group, 59% of the patients were cured, 22% improved and 19% were failures. In the 7 day treatment group, 63% were cured, 28% improved and 9% were failures, Table 22.

Table 22

Treatment Outcome - Evaluable Patients By Applicant

Outcome	Clindamycin-3	Clindamycin-7	95% CI
Cure	77/131 (58.8%)	80/128 (62.5%)	(-16.4, 8.9)
Improvement	29/131 (22.1%)	36/128 (28.1%)	(-17.3, 5.3)
Failure	25/131 (19.1%)	12/128 (9.4%)	

In the Medical Officer's analyses, clinical outcome differed from the analyses done by the Applicant in that there was no improvement category in the final outcome. Patients were considered either a cure or a failure based on the clinical findings at the return visit. Therefore, all patients that were considered as improved by the Applicant were assessed as a cure or a failure by the Medical Officer. Additionally to be considered a cure, all patients must have had a discharge that was negative for clue cells and negative for ("fishy") amine odor with or without the pH returning to 4.5 or less.

In the 3 day treatment group 74% of the patients were cured and 26% were failures. In the 7 day treatment group, 86% were cured and 14% were failures.

Table 23

Treatment Outcome - Evaluable Patients
By Medical Officer

Outcome	Clindamycin-3	Clindamycin-7	95% CI
Cure	124/167(74%)	139/161(86%)	(-21.2, -3.00)
Failure	43/167(26%)	22/161(14%)	

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ON ORIGINAL

Safety: A total of 409 of the 411 enrolled patients received some protocol drug in this study and are evaluated for safety. Two patients in the clindamycin 3 day group did not receive any drug and were not evaluable for safety. All safety data are taken from the reports of the Applicant. Safety information was obtained in two ways: 1) by asking patients if they had developed symptoms of vaginitis post treatment and 2) by reporting of medical events occurring during the treatment period.

Of the 409 patients evaluable for safety in this study who received clindamycin 2% vaginal cream, 117 (29%) reported a total of 163 medical events. There were 58 patients in the 3-day treatment group and 59 patients on the 7 day regimen that reported at least one medical event.

Table 25

All Reported Events

	Clindamycin-3	Clindamycin-7
# of pts in which % is based	205	204
# of pts without any ME	147	145
# of pts with at least one ME	58	59
# of Events by Body System		
Allergy	0	1
Dermatology	5	1
Endocrine	2	2
Gastrointestinal	11	11
Genital tract	44	52
Miscellaneous	3	5
Musculoskeletal	4	0
Neurologic	2	4
Respiratory	0	1
Special senses	0	1
Surgical Procedure	1	0
Urinary tract	6	7
Total	78	85

Among 205 patients on the 3-day regimen, 35 reported 40 medical events that were thought to be treatment related. Of the 204 patients on the 7-day treatment, 46 reported 58 events.

Table 25
All Drug Related Events

	Clindamycin-3	Clindamycin-7
# of pts in which % is based	205	204
# of pts without any ME	170	158
# of pts with at least one ME	35	46
# of Events by Body System		
Allergy	0	1
Endocrine	1	1
Gastrointestinal	4	6
Genital tract	35	48
Special Senses	0	1
Urinary Tract	0	1
Total	40	58

Symptomatic vaginitis or cervicitis following treatment was reported in 19.7% of the patients in the 3-day treatment group compared to 21.2% in the 7-day treatment group. Ten (10) of these patients (7 3-day, 3 7-day) with these vaginal symptoms continued to have BV that failed to respond to protocol therapy.

Table 26
Symptomatic for Vaginitis/Cervicitis

	Clindamycin-3	Clindamycin-7
# of pts in which % is based	188	179
# of pts with no symptoms	151	141
# of pts with symptoms	37	38
# of pts who did not report	17	25

The following Table lists all medical events occurring with a frequency of >1% in either treatment group.

TABLE 27

ADVERSE MEDICAL EVENT FREQUENCIES OF >1% - ALL PATIENTS				
Event	Clindamycin 3 day		Clindamycin 7 day	
	Number	%	Number	%
Vaginitis*	32	15.6	39	19.1
Yeast infection**	1	0.5	5	2.5
Nausea	1	0.5	5	2.5
Abdominal pain	4	2.0	2	1.0
Vulvovaginal itching***	5	2.4	4	2.0
Headache	2	1.0	3	1.5

* includes vaginitis and vulvovaginitis
** includes "yeast infection vagina" and "fungal infection vagina"
*** includes vaginal itching and vulvar pruritus

A total of five patients dropped out of the study due to a medical event. In two of the five cases, the medical event causing the patient to discontinue participation in the study was judged by the investigator to be related to the protocol medication. Below are brief summaries of the five patients.

Patient # 131 (Investigator, Martel) - A 39-year-old white female with bacterial vaginosis was treated with clindamycin vaginal cream for 7 days. Fifteen days after completing therapy, patient developed a urinary tract infection which was treated with norfloxacin, and therefore the patient was dropped from the study. Medical event was judged unrelated to protocol drug.

Patient #136 (Investigator, Martel) - A 30-year-old white female discontinued treatment with clindamycin vaginal cream after 2 days because of abdominal cramping which she thought was due to the study drug. The abdominal cramps started 2 days before the study drug was begun and subsided one day after stopping study drug. Investigator judged the event not related to protocol medication and she was dropped from the study.

Patient #163 Investigator, Martel) - A 43-year-old white female administered clindamycin vaginal cream for 7 days. Six days post-treatment she developed vulvar itching, redness and edema for which Terazol vaginal cream was prescribed. Although the bacterial vaginosis was cured, she was discontinued from the study. Investigator

judged the medical event to be possibly-related to study drug.

Patient #269 (Investigator, Gall) - A 32-year-old black female received 3 days of clindamycin vaginal cream treatment. At a follow-up visit 4 days after completing therapy, she had developed yeast vaginitis and was treated with Terazol 3 vaginally. Although the bacterial vaginosis had cleared at this early follow-up visit, the patient was dropped from the study. Investigator judged medical event as related to study drug.

Patient #758 (Investigator, Livengood) - A 36-year-old black female completed 7 days of study medication. Sixteen days after treatment, patient developed a strep throat for which she was hospitalized and treated with IV cefuroxime for 5 days. Therefore, the patient was taken off the study. Investigator judged medical event unrelated to protocol drug.

Summary

This was a multicenter, prospective, randomized, observer-blind study conducted to evaluate the efficacy of a 3 day treatment regimen of clindamycin vaginal cream compared to the standard 7 day treatment. In the Medical Officer's analyses, there was a statistically-significant difference between the cure rates indicating the 3-day regimen is inferior to the 7 day regimen.

Conclusion:

The treatment of bacterial vaginosis with a 3 day regimen of clindamycin vaginal cream does not appear to be equivalent to the 7 day regimen based on this study.

Summary of NDA Supplement-002

The Applicant, The Upjohn Company, submitted this supplement to NDA 50-680 for the purpose of obtaining approval for the use of clindamycin vaginal cream 2% once daily for three days. The Applicant feels that treating bacterial vaginosis with a once-a-day, three day treatment of 2% clindamycin vaginal cream will potentially improve patient compliance and decrease the adverse events associated with the current once-a-day seven day treatment.

To obtain approval for this indication, the Applicant submitted the results of three clinical studies that were conducted to

demonstrate that clindamycin 3-day is equivalent to clindamycin 7-day in treating bacterial vaginosis. Two of the studies were placebo-controlled and administered 5 grams of clindamycin vaginal cream 2% daily for three consecutive days compared to 5 grams of placebo daily for three consecutive days in women with BV.

In Study 0021, the overall cure rate obtained by the Applicant was 72% for the patients who used clindamycin vaginal cream 2% compared to a 22% cure rate for those who used the placebo compared to a cure rate of 67% for clindamycin and 0% obtained by the Medical Officer. In Study 0027, the Applicant reported a cure rate of 54% in the clindamycin group and 2% in the placebo group compared to 54% and 5% for the clindamycin and placebo groups, respectively reported by the Medical Officer.

These cure rates are similar to those obtained in the original seven day studies against placebo and demonstrate that a three day treatment of BV with clindamycin is superior to placebo however, they do not support the theory that the three day regimen of clindamycin is equivalent to the seven day regimen in the treatment of BV.

Essential in determining if the 3-day treatment of BV with clindamycin vaginal cream 2% is equivalent to the 7-day treatment with clindamycin vaginal cream 2% was Study 0020 conducted by 10 investigators (9 in the US and 1 in Canada) which compared the two regimens in a multicenter, observer-blind, randomized clinical trial.

The Applicant assessed efficacy of the two treatment groups based on the clinical findings at the final return visit and defined efficacy as a cure, improvement or failure. The study results obtained by the Applicant are summarized below.

Treatment Outcome - Evaluable Patients
By Applicant

Outcome	Clindamycin-3	Clindamycin-7	95% CI
Cure	77/131 (58.8%)	80/128 (62.5%)	(-16.4, 8.9)
Improvement	29/131 (22.1%)	36/128 (28.1%)	(-17.3, 5.3)
Failure	25/131 (19.1%)	12/128 (9.4%)	

In the Medical Officer's analyses, the efficacy was also based on the clinical findings at the final return visit however, efficacy was classified either as a cure or a failure in that an improvement in symptoms at the "test of cure" visit is not an appropriate evaluation. The results of the Medical Officer's final analysis are shown below.

Treatment Outcome - Evaluable Patients
By Medical Officer

Outcome	Clindamycin-3	Clindamycin-7	95% CI
Cure	124/167(74%)	139/161(86%)	(-21.2, -3.00)
Failure	43/167(26%)	22/161(14%)	

Of significance in the Applicant's analysis is the number of failures found in the clindamycin 3-day group of 19% as compared to a 9% failure rate in the clindamycin 7-day group. This would indicate that the treatment of BV once-a-day for 3 consecutive days is not equivalent to the treatment of BV once-a-day for 7 consecutive days.

Additionally, if all of the patient assessed by the Applicant as improved at the follow-up visit were classified as cures, the cure rate obtaind in the Applicant analyses would be 81% in the three day clindamycin group and 91% in the seven day clindamycin

group with a 95% confidence Interval of (-18.89, -0.52) which fails to demonstrate equivalence.

When the improvement category is assessed as either a cure or a failure, as in the Medical Officer's analyses, the cure rate obtained in the 3-day treatment group is clearly not equivalent to the 7-day regimen. Statistically the 3-day regimen of clindamycin phosphate vaginal cream 2% is inferior to the 7-day regimen because both, the upper and lower limits of the 95% confidence interval, are negative and fail to meet the criteria that has been established by the Agency as demonstrating equivalence between two drug products.

Consultation with the Division of Biometrics confirms the findings of the Medical Officer and the complete statistical review of this supplement by the statisticians may be found in their review dated November 30, 1995.

Conclusion: From the evaluation of the Medical Officer, it may be concluded that the 3-day clindamycin vaginal cream 2% is superior to placebo in treating BV however, it does not demonstrate equivalence to the 7-day treatment. There appears to be no safety advantage for the three day regimen over the seven day regimen.

Recommendation: I recommend non approval of this supplement for the use of clindamycin vaginal cream 2% once-a-day for three days in the treatment of Bacterial Vaginosis.

/S/

Joseph K. Winfield, M.D.
Reviewing Medical Officer

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