

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-793

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 50-793

Drug Name: _____ (Clindamycin Phosphate Vaginal Cream, 2.0%)

Indication(s): Treatment of Bacterial Vaginosis

Applicant: KV Pharmaceutical

Date(s): Original Application Submitted: October 31, 2003
Major Amendment Submitted: August 23, 2004
PDUFA Date (with 3 month major amendment extension): November 30, 2004

Review Priority: Standard

Biometrics Division: DB3

Statistical Reviewer: Ruthanna C. Davi

Concurring Reviewers: Mohammad Huque, Division of Biometrics III Director

Medical Division: Division of Special Pathogens and Immunologic Drug Products

Clinical Team: Mary Singer, Medical Reviewer
Leonard Sacks, Medical Team Leader

Project Manager: Christina Chi

Keywords: NDA review, active control/non-inferiority, placebo controlled

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.3 STATISTICAL ISSUES AND FINDINGS	4
2. INTRODUCTION	4
2.1 OVERVIEW.....	4
2.2 DATA SOURCES	5
3. STATISTICAL EVALUATION	5
3.1 EVALUATION OF EFFICACY	12
3.2 EVALUATION OF SAFETY	14
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	14
4.1 GENDER, RACE AND AGE	14
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	15
5. SUMMARY AND CONCLUSIONS	15
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	15
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	15

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of the placebo controlled study indicate that using the MITT analysis group, [REDACTED] is superior to placebo in terms of the following endpoints.

- Therapeutic Treatment Outcome at test-of-cure (TOC) visit
- Clinical Treatment Outcome at TOC visit
- Nugent Outcome at TOC Visit
- Investigator Treatment Outcome at TOC visit

These results are consistent across the other two analysis populations, PP and ITT.

Examination of the primary and secondary efficacy endpoints by race and age did not reveal any problematic subgroup differences in the placebo controlled study.

The results of the active controlled study indicate that using the PP analysis group, [REDACTED] is nearly noninferior to Cleocin in terms of Therapeutic Treatment Outcome at the TOC visit. Although the lower limit for the confidence interval for this endpoint does slightly exceed the non-inferiority margin of -15%, the reader should note that the confidence intervals for each of the following endpoints all satisfy a noninferiority margin of -15% suggesting that [REDACTED] is non-inferior to Cleocin in terms of these endpoints.

- Clinical Treatment Outcome at TOC visit
- Nugent Outcome at TOC Visit
- Investigator Treatment Outcome at TOC visit

The results of all the primary and secondary efficacy endpoints in the MITT population consistently satisfy a noninferiority margin of -15%. Examination of the primary and secondary efficacy endpoints by race and age did not reveal any problematic subgroup differences in the active controlled study.

In the assessment of this reviewer [REDACTED] has been shown to be superior to placebo in terms of the endpoints and patients studied. In light of this demonstration of superiority to placebo and the noninferiority suggested by the secondary endpoints in the active controlled study, in the assessment of this reviewer, although the noninferiority of [REDACTED] to Cleocin was not strictly demonstrated for the primary endpoint, an acceptable level of evidence suggesting noninferior efficacy for [REDACTED] relative to Cleocin has been provided.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of two phase 3 studies to support the use of [REDACTED] for treatment of bacterial vaginosis. The first study was titled, "Safety and Efficacy Comparison of Clindamycin Vaginal Cream, 2% (KV Pharmaceutical Company) and Metronidazole Vaginal Cream, 0.75% [REDACTED] Versus Placebo in Patients With Bacterial Vaginosis: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study". The objectives of the study were to demonstrate that dosing with one applicator full of [REDACTED] administered once on a single day is superior in efficacy and comparable in safety to placebo for the treatment of bacterial vaginosis and to demonstrate that dosing with one

applicator full of metronidazole administered once on a single day is superior in efficacy and comparable in safety to placebo for the treatment of bacterial vaginosis. The second study was titled, "Safety and Efficacy Comparison of Clindamycin Vaginal Cream, 2% (KV Pharmaceutical Company) And Cleocin Vaginal Cream 2% (Pharmacia and Upjohn) In Patients with Bacterial Vaginosis: A Multicenter, Randomized, Single-Blind, Parallel Group Study". The objective of the study was to demonstrate that dosing with one applicator full of [REDACTED] administered once on a single day was comparable in safety and equivalent in efficacy to Cleocin administered daily for seven days for the treatment of bacterial vaginosis.

1.3 Statistical Issues and Findings

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Adjustment for multiple treatment groups in placebo controlled study (ref: *Sections 3.0, 3.1*)
- Definition of noninferiority margin in active controlled study (ref: *Section 3.0*)
- Imputation of missing efficacy outcomes as failures in both studies (ref: *Section 3.1*)

2. INTRODUCTION

2.1 Overview

The sponsor has submitted the results of two phase 3 studies to support the use of [REDACTED] for treatment of bacterial vaginosis. Each of these studies will be summarized and critiqued within this document.

The first study was titled, "Safety and Efficacy Comparison of Clindamycin Vaginal Cream, 2% (KV Pharmaceutical Company) and Metronidazole Vaginal Cream, 0.75% [REDACTED] Versus Placebo in Patients With Bacterial Vaginosis: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study". The objectives of the study were to demonstrate that dosing with one applicator full of [REDACTED] administered once on a single day is superior in efficacy and comparable in safety to placebo for the treatment of bacterial vaginosis and to demonstrate that dosing with one applicator full of metronidazole administered once on a single day is superior in efficacy and comparable in safety to placebo for the treatment of bacterial vaginosis. [REDACTED]

The second study was titled, "Safety and Efficacy Comparison of Clindamycin Vaginal Cream, 2% (KV Pharmaceutical Company) And Cleocin Vaginal Cream 2% (Pharmacia and Upjohn) In Patients with Bacterial Vaginosis: A Multicenter, Randomized, Single-Blind, Parallel Group Study". The objective of the study was to demonstrate that dosing with one applicator full of [REDACTED] administered once on a single day was comparable in safety and equivalent in efficacy to Cleocin administered daily for seven days for the treatment of bacterial vaginosis.

2.2 Data Sources

The sponsor has submitted the results of two controlled clinical trials in support of the efficacy of [REDACTED] for the treatment of bacterial vaginosis. The following data sets were submitted electronically and utilized in the review of this study.

\\Cdsub1\n50793\N_000\2003-10-30\02-005_Placebo\Transport dataset\Transport formatted dataset\B EFFICA.XPT

\\Cdsub1\n50793\N_000\2003-10-30\01-025_Cleocin\Transport dataset\Transport formatted dataset\A EFFICA.XPT

All submitted data sets were found to be clearly documented and well organized.

3. STATISTICAL EVALUATION

The sponsor has submitted the results of two phase 3 studies (one placebo controlled, the other active controlled) to support the use of [REDACTED] for treatment of bacterial vaginosis. Although the designs of these studies are different, they will be described in text simultaneously within this document with the differences in design and analyses highlighted. Results of statistical analyses will be presented separately for each study.

The placebo controlled study was a multicenter, prospective, randomized, double-blind, parallel group phase III clinical trial conducted at 20 centers in the United States. The objectives of the study were to demonstrate that dosing with one applicator full of [REDACTED] administered once on a single day is superior in efficacy and comparable in safety to placebo for the treatment of bacterial vaginosis and to demonstrate that dosing with one applicator full of metronidazole administered once on a single day is superior in efficacy and comparable in safety to placebo for the treatment of bacterial vaginosis.

The active controlled study was a multicenter, prospective, randomized, parallel group phase III clinical trial conducted at 27 centers in the United States. Unlike the double-blind placebo controlled study, the active controlled study was investigator-blind as the dosage regimens for the two treatments differed. The objective of the study was to demonstrate that dosing with one applicator full of [REDACTED] administered once on a single day was comparable in safety and equivalent in efficacy to Cleocin administered daily for seven days for the treatment of bacterial vaginosis.

Patients who fulfilled the following protocol-specified criteria were eligible for inclusion in the studies. There were minor differences in inclusion criteria for each of the studies and those differences are indicated in items 4 and 5 below.

1. Eighteen years of age or older.
2. Clinical diagnosis of BV according to Amsel Criteria, defined as having all of the following findings:
 - a.) Off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina;
 - b.) The presence of "clue cells" \geq 20% of the total epithelial cells on microscopic exam of the saline "wet mount";
 - c.) Vaginal secretion pH of $>$ 4.5;
 - d.) A fishy odor of the vaginal discharge with the addition of a drop of 10% KOH (ie, a positive "whiff test").
3. Willingness and ability to give signed informed consent.
4. Willingness to abstain from alcohol ingestion during the treatment phase (period between the dose of study medication and the Interim Telephone Contact) of the study and for one day thereafter. [This item is applicable to placebo controlled study only.]
5. Willing to abstain from vaginal intercourse during the 7 days after administration of the study medication [for the placebo controlled study] and during the period between the Entry Visit and the Interim Safety Evaluation Visit (7 to 10 days after the beginning of dosing) [for the active controlled study].
6. Willing to abstain from douching and from using intravaginal/vulvovaginal products (eg, a diaphragm, contraceptive creams, gels, foams, sponges, tampons, feminine deodorant sprays, douche, Nonoxynol-9 products, etc) both during the treatment phase of the study and throughout the follow up period (the period between the Interim Telephone Contact and the TOC Visit [for the placebo controlled study] and between the Interim Safety Evaluation Visit and the Test-Of-Cure Visit [for the active controlled study]).

Patients with other infectious causes of vulvovaginitis or another vaginal or vulvar condition which would confound the interpretation of clinical response were excluded from the studies. In addition, patients with a Nugent score $<$ 4 were to be excluded from the studies; however, the exclusion criteria noted that although efforts should be made to have the patients wait to self-administer study medication until after the Nugent Score is known, this may not have always been practical. In these, cases, patients were allowed to begin self-administration of the study medication prior to the Nugent score being known. If a patient was then determined to have a baseline Nugent score $<$ 4, the investigator should have had the patient return to the site when it was convenient for the investigator and patient to undergo an Early Discontinuation Visit. At this visit, the investigator should have made the following assessments: drug accountability, adverse events, and concomitant medications. The exclusion criteria were not limited to three items. (For complete listing of exclusion criteria, please see study protocol.)

After the inclusion/exclusion criteria were satisfied, patients were randomly assigned (within center in a 1:1:1 ratio with blocks of size six) to receive one of the following three treatments for the placebo controlled study.

- (1.) (clindamycin phosphate) vaginal cream, 2%, 100 mg, self-administered once on a single day, intravaginally

(2.) Metronidazole cream, 0.75%, 37.5 mg, self-administered once on a single day, intravaginally

(3.) Placebo vaginal cream

Subjects in the active controlled study were randomly assigned (within center in a 1:1 ratio with blocks of size four) to receive one of the following two treatments.

(1.) (Clindamycin phosphate vaginal cream, 2%) 100 mg, self-administered once on a single day, intravaginally

(2.) Cleocin cream 2%, 100 mg, self-administered once daily in the evening for 7 days, intravaginally

The primary efficacy variable in both the placebo controlled and active controlled studies was therapeutic treatment outcome (cured / failure). The secondary efficacy variables were clinical (cure / failure), Nugent score (cure / failure), and investigator treatment outcomes (cure / failure). These efficacy variables were assessed at the test-of-cure (TOC) visit (i.e., 21 to 30 days after study entry).

The primary endpoint, therapeutic outcome, was determined based on a combination of the clinical outcome and the Nugent score. The patient was considered a therapeutic cure if that patient was both a clinical cure (as defined below) and a Nugent cure (as defined below). Otherwise, the patient was considered a therapeutic failure.

Clinical cure as assessed by Amsel criteria was defined as resolution of the following clinical findings:

- The original discharge characteristic of BV has returned to a normal physiological discharge which varies in appearance and consistency depending on the menstrual cycle;
- The whiff test is negative for any amine (“fishy”) odor;
- The saline wet mount is negative for clue cells (<20% clue cells);
- The pH is <4.7, using pH paper that measures at least from 4.0 to 6.0.

Clinical failure was defined as a patient who did not meet the definition of clinical cure or:

- In whom an antimicrobial drug for the treatment of BV not allowed per protocol was received during the study period because the patient was not responding to the study treatment, or
- If the investigator answered “yes” to the question, “In your opinion, does the patient require additional treatment for BV infection at this time?” during the Interim Telephone Visit (i.e., 7 to 10 days after study entry) or at the TOC or Early Discontinuation Visit.
- If at the TOC or Early Discontinuation Visit the patient required additional treatment for BV, the investigator supplied the patient with appropriate marketed standard-of-care therapy provided by sponsor.

Nugent cure was defined as a Nugent score of 0 to 3 at the TOC visit. If the TOC Nugent score was greater than 3, the patient was a Nugent failure. This system used a 0 to 4 point scale for the evaluation of the vaginal flora and was based on the weighted sum of the following 3 bacterial morphotypes scores calculated from slide exam under oil immersion: lactobacillus, gardnerella / bacteroides, and mobiluncus. The total Nugent score was derived by adding individual scores for each morphotype.

The Investigator treatment outcome was determined by the yes or no answer by the investigator to the question, “In your opinion, does the patient require additional treatment for BV at this item?”

asked at the TOC or Early Discontinuation Visit. If the investigator answered no to the above question, the patient was considered an investigator treatment cure. If the investigator answered yes to the above question, the patient was considered an investigator treatment failure.

The co-primary efficacy objectives of the placebo controlled study were to demonstrate that [REDACTED] is superior to placebo and metronidazole is superior to placebo in terms of the therapeutic outcome at the TOC visit in women with BV. A separate analysis was to be performed for each investigational product to placebo comparison. For each comparison, a two-sided 95% confidence interval on therapeutic cure rate treatment difference (investigational product minus placebo) was to be utilized to determine if the investigational product is statistically superior to placebo using the primary efficacy analysis. Statistical superiority was defined as the lower limit of the confidence interval being greater than zero. Prior to submission of the NDA, the sponsor had been advised by the Agency that a multiple comparison correction would be needed to account for the multiple investigational treatment groups in this study (even though the sponsor's interest in the metronidazole-to-placebo comparison had diminished). [IND comments, September 2002 and July 2003]. However, no multiple comparison correction procedure is clearly selected and documented in the protocol or implemented in the primary analysis results that are given in the study report. Therefore, a Bonferroni adjustment is utilized in the primary analysis presented in this review.

The primary efficacy objective of the active controlled study was to demonstrate that [REDACTED] is noninferior to Cleocin in terms of the therapeutic outcome at the TOC visit in women with BV. A two-sided 95% confidence interval on therapeutic cure rate treatment difference ([REDACTED] minus Cleocin) was to be utilized to determine if [REDACTED] is noninferior to Cleocin for the primary efficacy analysis. Statistical noninferiority was defined as the lower limit of the confidence interval being greater than -20%. While the noninferiority margin defined for the primary efficacy analysis was 20%, the sponsor's sample size calculation assumed a noninferiority margin of 15%. Prior to submission of the NDA, the sponsor had been advised by the Agency that this was not appropriate and that we would consider a noninferiority margin of 15% in interpreting the primary efficacy results. [IND comments, April 2002].

Three analysis populations were defined in the protocols as follows.

Intent-to-treat (ITT): The ITT analysis population consisted of all randomized patients who administered at least one dose of study drug.

Modified intent-to-treat (MITT): The MITT analysis population was a subpopulation of the ITT population including only those patients whose baseline Nugent score was at least 4.

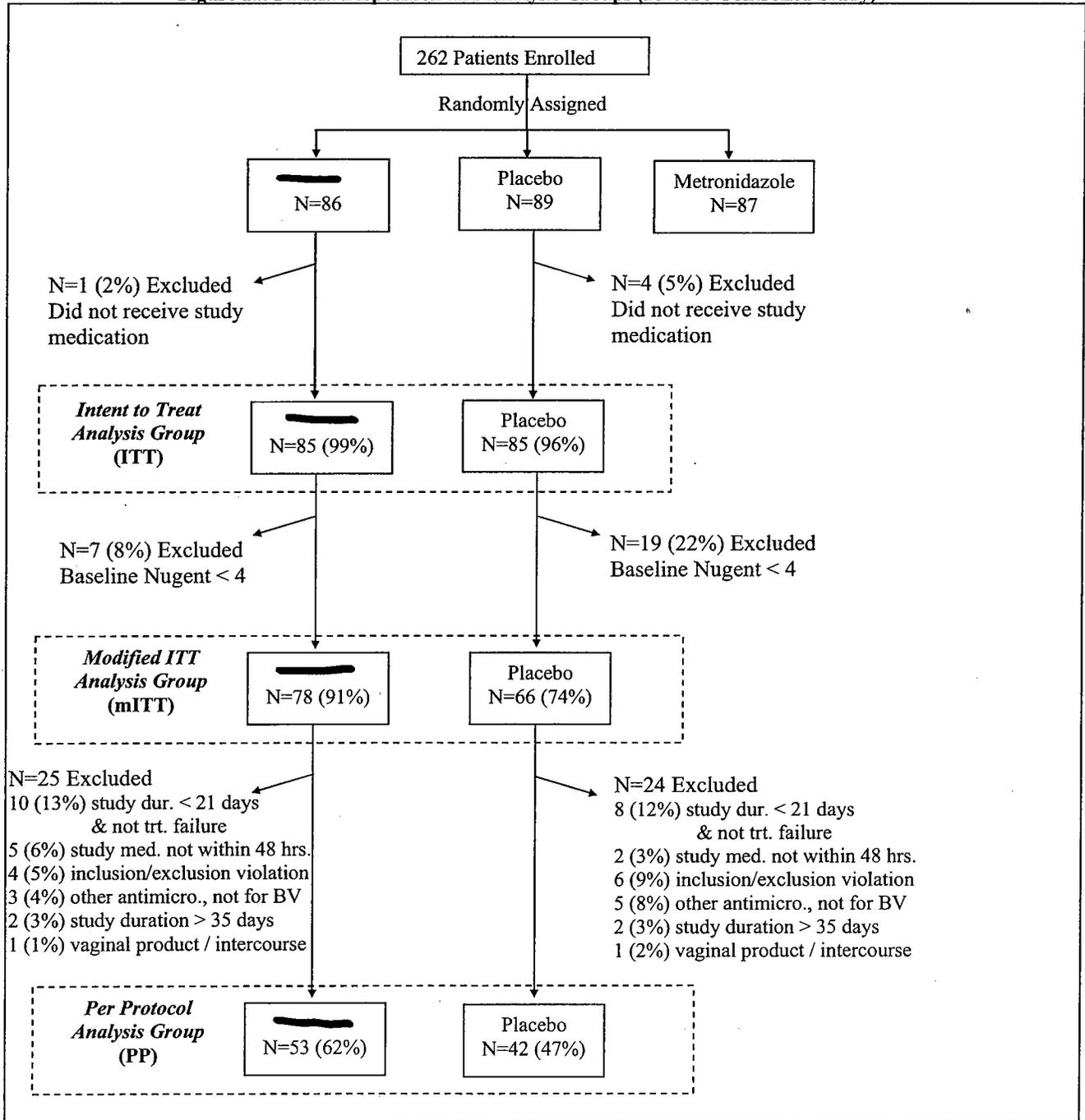
Per protocol (PP): The PP analysis population refers to patients randomized to study medication that completed the study without significant protocol violations.

Efficacy analyses were conducted using all three populations; however, the protocol-specified population that was to be used in the primary efficacy analysis in the placebo controlled study was the MITT population. For the active controlled study, the PP population was to be used in the primary efficacy analysis but again, efficacy analyses were conducted using all three populations.

The placebo controlled study enrolled 262 patients at 20 centers in the United States. Eighty five patients were randomly assigned to treatment with [REDACTED] and 85 were randomly assigned to receive placebo. [REDACTED]

Patient inclusion in or exclusion from the intent-to-treat (ITT), modified intent-to-treat (MITT), and per-protocol (PP) analysis data sets are described in Figure 1a.

Figure 1a: Patient Disposition and Analysis Groups (Placebo Controlled Study)

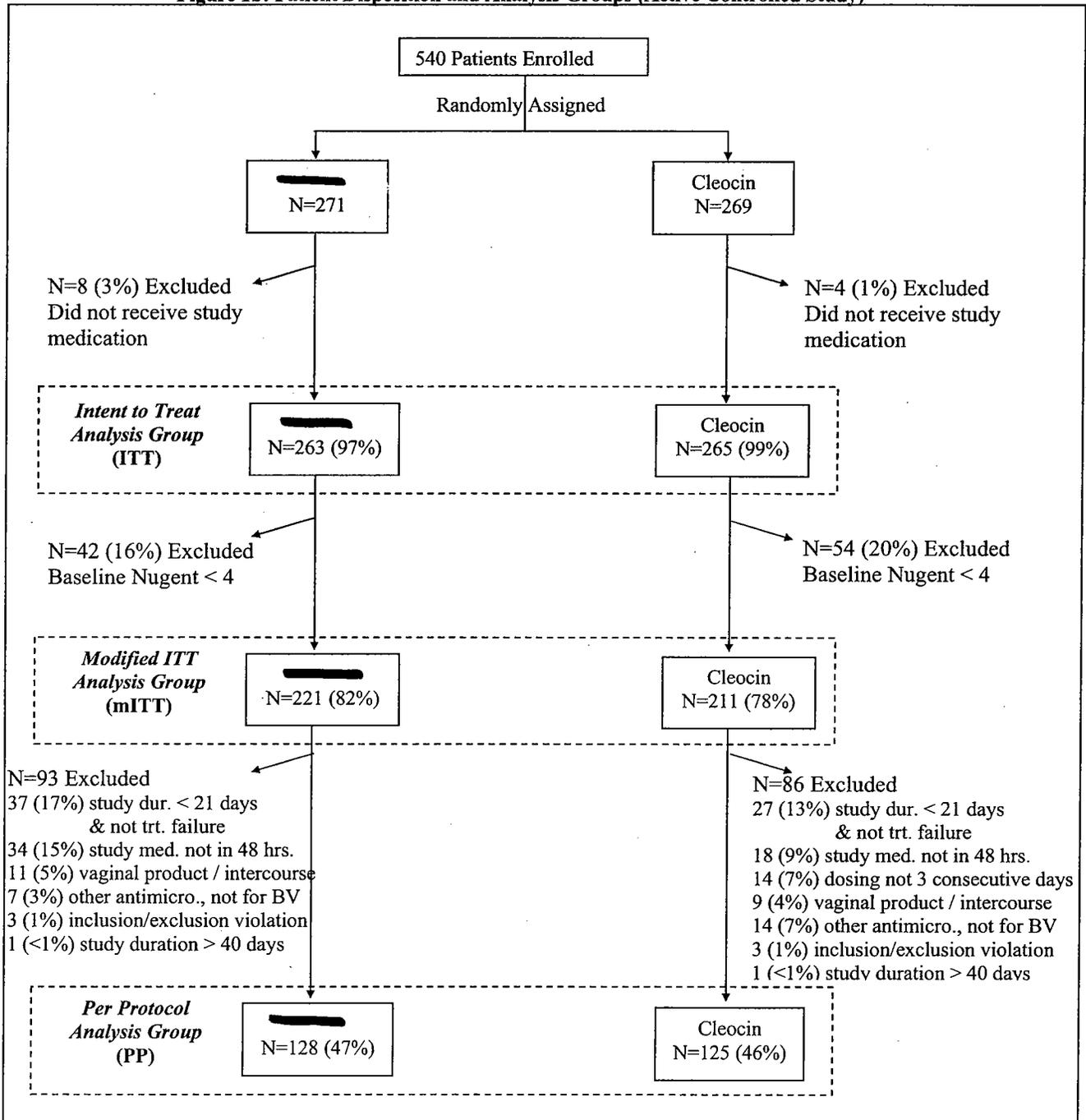


As indicated in Figure 1a, four ██████ subjects and one placebo subject were excluded from the ITT analysis group in the placebo controlled study, as they did not receive study medication. The only reason for further exclusions from the mITT analysis group in both treatments groups was a patient's baseline Nugent score was reported as being less than 4. The placebo group had a higher rate of patients (22%) with baseline Nugent score < 4 compared with the ██████ group (8%). The reason for this imbalance is unclear as all evaluation of the baseline Nugent score was conducted blinded to treatment assignment. Further exclusions from the PP analysis group were made for the follow reasons; study duration was less than 21 days and patient was not a treatment failure, study medication was not administered within 48 hours of enrollement, violation of inclusion or exclusion criteria, patient received other antimicrobial but not for treatment of BV, study duration was greater than 35 days, and patient used another vaginal product or had sexual intercourse. The rates of these exclusions were similar between the two treatment groups.

The active controlled study enrolled 540 patients at 27 centers in the United States. Two hundred seventy one patients were randomly assigned to treatment with ██████ and 269 patients were randomly assigned to treatment with Cleocin. Patient inclusion in or exclusion from the intent-to-treat (ITT), modified intent-to-treat (MITT), and per-protocol (PP) analysis data sets are described in Figure 1b.

**Appears This Way
On Original**

Figure 1b: Patient Disposition and Analysis Groups (Active Controlled Study)



As indicated in Figure 1b, eight ██████ subjects and four Cleocin subjects were excluded from the ITT analysis group in the active controlled study, as they did not receive study medication. The only reason for further exclusions from the mITT analysis group in both treatments groups was a patient's baseline Nugent score was reported as being less than 4. The rate of this exclusion was fairly balanced across treatment groups with 20% in the Cleocin group and 16% in the ██████ group. Further exclusions from the PP analysis group were made for the follow reasons; study duration was less than 21 days and patient was not a treatment failure, study medication was not administered within 48 hours of enrolment, patient did not dose on three consecutive days (applies to the Cleocin group only), violation of inclusion or exclusion criteria, patient received other antimicrobial but not for treatment of BV, study duration was greater than 40 days, and patient used another vaginal product or had sexual intercourse. The rates of these exclusions were similar between the two treatment groups.

3.1 Evaluation of Efficacy

The primary efficacy comparison in both the placebo controlled and active controlled studies was therapeutic treatment outcome (cured / failure) assessed at the TOC visit. The secondary efficacy comparisons were clinical (cure / failure), Nugent score (cure / failure), and investigator treatment outcomes (cure / failure) assessed at the TOC visit. These efficacy comparisons are summarized in Tables 1a for the placebo controlled study and 1b for the active controlled study.

The protocol-defined primary analysis population for the placebo controlled study was the MITT group. Note that the results in Table 1a differ from the analyses of this endpoint provided in the sponsor's submission as they have been adjusted (using the Bonferroni method) for multiple treatment groups (i.e., two-sided 97.5% confidence intervals are presented rather than two-sided 95% confidence intervals).

Table 1a: Primary and Secondary Efficacy Analyses of Placebo Controlled Study (MITT Analysis Population)			
	██████ N=78	Placebo N=66	97.5% Confidence Interval for Difference in Proportions
Therapeutic Treatment Cure at the TOC Visit (primary efficacy endpoint)	23 (29.5%)	2 (3.0%)	(14.0%, 39.0%)
Clinical Treatment Cure at the TOC Visit (secondary efficacy endpoint)	32 (41.0%)	13 (19.7%)	(4.7%, 38.0%)
Nugent Treatment Cure at the TOC Visit (secondary efficacy endpoint)	35 (44.9%)	4 (6.1%)	(24.6%, 53.1%)
Investigator Treatment Cure at the TOC Visit (secondary efficacy endpoint)	51 (65.4%)*	24 (36.4%)*	(11.1%, 47.0%)

* Missing Investigator Treatment Outcomes for four ██████ and two placebo subjects were imputed as failures in this analysis.

The results in Table 1a indicate that ██████ is clearly superior to placebo in terms of all the endpoints examined, including the Therapeutic Treatment Outcome (primary endpoint) as well as Clinical Treatment Outcome, Nugent Outcome, and Investigator Treatment Outcome (secondary endpoints). Statistically, these conclusions are demonstrated by exclusion of zero from the confidence intervals. Although the adjustment for multiple treatment arms implemented by this reviewer has resulted in quantitative differences in the estimation of the confidence intervals, it has not changed the qualitative conclusions of the sponsor regarding the superiority of the efficacy of ██████ relative to placebo. Of note, the by-treatment group differences in these cure rates in the PP and ITT populations were also consistently and statistically significantly (using 97.5% confidence intervals) in support of the superiority of ██████ relative to placebo.

The protocol-defined primary analysis population for the active controlled study was the PP group; however, the results for the MITT group are also presented as it is the understanding of the Division that use of the MITT population is important to allow evaluation of the product in a group of patients with protocol violations.

Table 1b: Primary and Secondary Efficacy Analyses of Active Controlled Study (PP and MITT Analysis Populations)						
	PP Population*			MITT Population		
	██████ N=128	Cleocin N=125	95% Confidence Interval for Difference in Proportions	██████ N=221	Cleocin N=211	95% Confidence Interval for Difference in Proportions
Therapeutic Treatment Cure at the TOC Visit (primary efficacy endpoint)	53 (41.4%) ¹	57 (45.6%)	(-16.4%, 8.0%)	73 (33.0%)	78 (37.0%)	(-12.9%, 5.1%)
Clinical Treatment Cure at the TOC Visit (secondary efficacy endpoint)	81 (63.3%) ²	79 (63.2%)	(-11.8%, 12.0%)	118 (53.4%)	114 (54.0%)	(-10.0%, 8.8%)
Nugent Treatment Cure at the TOC Visit (secondary efficacy endpoint)	70 (54.7%) ³	71 (56.8%) ³	(-14.4%, 10.1%)	101 (45.7%)	104 (49.3%)	(-13.1%, 5.8%)
Investigator Treatment Cure at the TOC Visit (secondary efficacy endpoint)	114 (89.1%)	108 (86.4%)	(-5.4%, 10.7%)	178 (80.5%)	170 (80.6%) ⁴	(-7.5%, 7.4%)

* The population to be used for the primary efficacy comparison was defined in the protocol to be PP.

1. Missing Therapeutic Treatment Outcomes for two ██████ subjects were imputed as failures in this analysis.
2. Missing Clinical Treatment Outcomes for two ██████ subjects were imputed as failures in this analysis.
3. Missing Nugent Treatment Outcomes for four ██████ and two Cleocin subjects were imputed as failures in this analysis.
4. Missing Investigator Treatment Outcomes for five Cleocin subjects were imputed as failures in this analysis.

A strict interpretation of the results for the Therapeutic Treatment Outcome (primary endpoint) in Table 1b indicate that noninferiority of [REDACTED] to Cleocin has not been established (as evidenced by the lower limit of the confidence interval in the PP population exceeding the noninferiority margin of -15%). However, the reader should note that all of the secondary endpoints examined, including Clinical Treatment Outcome, Nugent Outcome, and Investigator Treatment Outcome, satisfy a noninferiority margin of -15% suggesting that ClindaOne is non-inferior to Cleocin in terms of these endpoints. In addition, the results of all the endpoints in the MITT population consistently satisfy a noninferiority margin of -15%.

3.2 Evaluation of Safety

Since clindamycin has a well-know historically-established safety profile, no safety endpoints were pursued through statistical hypothesis testing methods. Therefore, the reader is referred to the clinical review for a discussion and summary of the safety of [REDACTED]

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The relationship between primary and secondary efficacy variables including Therapeutic Treatment Outcome, Clinical Treatment Outcome, Nugent Outcome, and Investigator Treatment Outcome, and race and age were examined by the sponsor using each of the analysis populations, PP, MITT and ITT.

Although there were some strata in which the numbers of observations were insufficient for inferential analysis, when the analyses were feasible, statistically significant treatment group differences in favor of [REDACTED] relative to placebo were observed for all primary and secondary efficacy endpoints in all analysis populations, while controlling for race in the placebo controlled study. In addition, the cure rates were consistently higher in the [REDACTED] treated patients across all racial subgroups examined in the placebo controlled study. For each analysis population and primary and secondary efficacy outcome, statistically significant treatment group differences in favor of [REDACTED] were also detected while controlling for age in the placebo controlled study. No analyses by gender were appropriate since the placebo controlled study enrolled only women.

No statistically significant treatment group differences between [REDACTED] and Cleocin were observed in any of the primary and secondary efficacy endpoints in all analysis populations, while controlling for race in the active controlled study. In addition, no statistically significant differences in cure rates were observed between [REDACTED] and Cleocin in any of the racial subgroups examined in the active controlled study. For each analysis population and primary and secondary efficacy outcome, no statistically significant treatment group differences were detected while controlling for age in the active controlled study. No analyses by gender were appropriate since the active controlled study enrolled only women.

4.2 Other Special/Subgroup Populations

Other subgroup analyses conducted by the sponsor for both the placebo controlled and active controlled studies included analyses according to sexual behavior, recalcitrant status, height, and weight. None of these analyses suggested any subgroups in which a differing treatment effect might exist.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Adjustment for multiple treatment groups in placebo controlled study (ref: *Sections 3.0, 3.1*)
- Definition of noninferiority margin in active controlled study (ref: *Section 3.0*)
- Imputation of missing efficacy outcomes as failures in both studies (ref: *Section 3.1*)

5.2 Conclusions and Recommendations

The results of the placebo controlled study indicate that using the MITT analysis group, [REDACTED] is superior to placebo in terms of the following endpoints.

- Therapeutic Treatment Outcome at TOC visit
- Clinical Treatment Outcome at TOC visit
- Nugent Outcome at TOC Visit
- Investigator Treatment Outcome at TOC visit

These results are consistent across the other two analysis populations, PP and ITT.

Examination of the primary and secondary efficacy endpoints by race and age did not reveal any problematic subgroup differences in the placebo controlled study.

The results of the active controlled study indicate that using the PP analysis group, [REDACTED] is nearly noninferior to Cleocin in terms of Therapeutic Treatment Outcome at the TOC visit. Although the lower limit for the confidence interval for this endpoint does slightly exceed the non-inferiority margin of -15%, the reader should note that the confidence intervals for each of the following endpoints all satisfy a noninferiority margin of -15% suggesting that [REDACTED] is non-inferior to Cleocin in terms of these endpoints.

- Clinical Treatment Outcome at TOC visit
- Nugent Outcome at TOC Visit
- Investigator Treatment Outcome at TOC visit

The results of all the primary and secondary efficacy endpoints in the MITT population consistently satisfy a noninferiority margin of -15%. Examination of the primary and secondary efficacy endpoints by race and age did not reveal any problematic subgroup differences in the active controlled study.

In the assessment of this reviewer [REDACTED] has been shown to be superior to placebo in terms of the endpoints and patients studied. In light of this demonstration of superiority to placebo and the noninferiority suggested by the secondary endpoints in the active controlled study, in the

assessment of this reviewer, although the noninferiority of [REDACTED] to Cleocin was not strictly demonstrated for the primary endpoint, an acceptable level of evidence suggesting noninferior efficacy for [REDACTED] relative to Cleocin has been provided.

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ruth Davi
11/29/04 12:49:35 PM
BIOMETRICS

Mohammad Huque
11/30/04 01:33:30 PM
BIOMETRICS