CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-827**

MEDICAL REVIEW(S)

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MEDICAL OFFICER REVIEW OF NDA 20-827

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APPLICANT: Advanced Care Products
North Brunswick, NJ

CHEMICAL NAME: Miconazole nitrate

TRADE NAME: MONISTAT®3 Vaginal Cream (4%)

PHARMACOLOGIC CATEGORY: Anti-fungal

DOSAGE FORM: Cream

ROUTE OF ADMINISTRATION: Vaginal

PROPOSED USE: for the treatment of vaginal yeast infections (*candidiasis*)

PROPOSED DOSAGE AND ROUTE OF ADMINISTRATION: one prefilled applicatorful vaginally at bedtime for 3 days in a row.

MEDICAL OFFICER REVIEWERS:
Efficacy Review: Daniel Davis, M.D., M.P.H., DSPIDP (HFD590)
Safety Review: Ling Chin, M.D., M.P.H., DOTCDP (HFD 560)- see Dr. Chin's review

RELATED Miconazole Nitrate NDAs:
- 17-450 (100 mg cream),
- 18-520 (100 mg suppository),
- 18-888 (200 mg suppository),
- 18-592 (100 mg tampon),
- 20-288 (mg suppository and external cream),
- 20-670 (200 mg suppository and external cream).

ABBREVIATIONS used in this report by both the applicant and the medical officer: see p. 0268 of Vol. 1.9.

ACP	Advanced Care Products
AE	Adverse Experience
BHA	Butylated Hydroxyanisole
CMH	Cochran-Mantel-Haenszel (Test)
IRB	Institutional Review Board
IUD	Intra-Uterine Device
KOH	Potassium Hydroxide
MCN	Miconazole Nitrate
M3C	Miconazole Nitrate (4%) 3-day Vaginal Cream
M5C	Miconazole Nitrate (2.8%) 5-day Vaginal Cream
M7C	Miconazole Nitrate (2%) 7-day Vaginal Cream
MO	Medical Officer
OTC	Over-The-Counter (for sale to the public without prescription)
PAP	Papanicolaou (smear)
RV1	Return Visit 1 (8-10 days after completion of treatment)
RV2	Return Visit 2 (30-35 days after completion of treatment)
V1	Entry visit (day of initial evaluation and start of therapy)
VVC	Vulvovaginal candidiasis

All text included in **Times New Roman 11** font represents Advanced Care Products' verbatim overview of two controlled clinical studies (95-005-P, 95-007-P) of miconazole nitrate (4%) vaginal cream in the treatment of patients with vulvovaginal candidiasis.

MO Comment: All medical officer comments and tables are represented using the **Arial 11** font .

I. INTRODUCTION

MONISTAT® vaginal products have been available in the United States since 1974 for the treatment of vulvovaginal candidiasis and it is estimated since 1991 approximately [redacted] courses of treatment have been dispensed annually. Moreover, unlike many antimicrobial agents available over a similar time period, there have been no reports of the development of resistance by *Candida* species to miconazole nitrate, the active ingredient of all MONISTAT® products. Indeed, the results of an essentially continuous clinical program with various MONISTAT® products over the past 25 or more years suggest that miconazole nitrate containing products remain as clinically effective today as when they were first studied for and introduced to the American market. Currently marketed MONISTAT® (miconazole nitrate 2%) Vaginal Cream (the control regimen in both studies summarized here) and currently marketed MONISTAT®7 Vaginal Suppositories have been available by prescription since 1977 and 1982 respectively, and both have been approved for over the counter (OTC) use since 1991. MONISTAT®3 Vaginal Suppositories have been available by prescription since 1984. MONISTAT DUAL-PAK® which combines the 3 Vaginal Suppositories with a 15-

gram tube of MONISTAT DERM® Cream has been available for prescription use since 1986. MONISTAT®3 Combination Pack ("Dual-Pack") was approved for OTC in 1996. Ongoing surveillance of adverse experiences reported for marketed MONISTAT® products suggests that the profile of adverse experiences obtained from clinical studies is representative of adverse experiences occurring in day to day use. However, adverse experience reporting in clinical studies has been much more frequent than with the marketed products. Adverse experiences are not serious or life-threatening and usually resolve promptly.

Vulvovaginal candidiasis remains a common cause of vaginitis (1,2) accounting for between 20 and 33% of all symptomatic cases of vaginitis seen in medical practice (2,3). Three of four women experience at least one episode of vulvovaginal candidiasis in their lifetime (4), and 40 to 50% suffer a second episode (2,5). No studies suggest that these incidences have changed in recent years. While not a serious infection, vulvovaginal candidiasis can present distressing symptoms to the patient that can have significant adverse impact on her quality of life. While the development of resistance by *Candida* species to miconazole nitrate has not been reported, there is no evidence that this infection is becoming less frequent. However, self-diagnosis of re-infection can be accomplished readily and accurately, and the availability of safe and effective OTC medication allows prompt and cost-effective treatment.

MO Comment: The data concerning the accuracy of self-diagnosis of vulvovaginal candidiasis (VVC) are circumstantial at best. There are no actual use studies analyzed by our agency for the use of OTC products for treating VVC. There are data from both the USA and worldwide for the Rx and OTC sales of the various approved products for VVC, but sales do not correlate with accurate self-diagnosis and do not provide any information concerning clinical and mycological cure rates.

The availability of miconazole nitrate (4%) vaginal cream administered for three days would provide the same dosage of miconazole nitrate (200 mg) for the same duration (three days) as MONISTAT®3 Vaginal Suppositories, but provide the consumer with an alternate dosage form.

The purpose of the two clinical studies (95-005-P, 95-007-P) summarized in this report was to assess the safety and efficacy of miconazole nitrate (4%) vaginal cream in the treatment of vulvovaginal candidiasis, and to provide information relative to the risks and benefits of this

1. Paavonen, J., Stamm, W.E. Lower genital tract infections in women. Infect Dis Clin North Am. 1987;1:179-198.
2. Sobel, J.D. Pathophysiology of Vulvovaginal Candidiasis. *J Reprod Med.* 1989;34 (supl 8):572-580.
3. Fleury, F.J. Adult Vaginitis. *Clin Obstet Gynecol.* 1981;24:407.
4. Berg, A.O., Heidrich, R.E., Fihn, S.D., et al. Establishing the Cause of Genitourinary Symptoms in Women in a Family Practice. Comparison of Clinical Examination and Comprehensive Microbiology. *JAMA.* 1984;251:620-625.
5. Hurley, R., DeLouvois, J. *Candida* Vaginitis. *Postgrad Med J.* 1979;55:645-647.

product for OTC use. It was also to fulfill the requirements of the Anti-Infective Drug Division of the FDA for OTC approval of vaginal antifungal drug products.

II. OVERVIEW OF STUDIES

Clinical Study ("Phase III Study Comparing Miconazole Nitrate 4% to MONISTAT®-7 2% Vaginal Cream in the Treatment of Vulvovaginal Candidiasis") with Protocol 95-005-P and Clinical Study ("Phase III Study Comparing Miconazole Nitrate 4% and Miconazole Nitrate 2.8% Vaginal Cream to Currently Marketed MONISTAT®-7 2% Vaginal Cream in the Treatment of Vulvovaginal Candidiasis") with Protocol 95-007-P, were very similar (but not identical) in design, patient population and methods of analysis. Both studies were double-blind, randomized, controlled, parallel group, comparative, multicenter, Phase III studies of patients with documented vulvovaginal candidiasis. Clinical Study Protocol 95-005-P compared three days of miconazole nitrate (4%) vaginal cream administration to seven days administration of currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream, whereas Clinical Study Protocol 95-007-P compared both three days administration of miconazole nitrate (4%) vaginal cream and a five day miconazole nitrate (2.8%) vaginal cream regimen to seven days administration of currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream. All formulations studied were cream formulations. Placebo cream was utilized only for the purpose of blinding the studies. Placebo only treatment of diagnosed vulvovaginal candidiasis was not considered appropriate. Currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream was the active control treatment in both studies.

MO Comment: The results of the miconazole nitrate (2.8%) vaginal cream used as a 5-day treatment in Study 95-007-P were not included in this NDA submission.

All patients studied were outpatients; treatment was self-administered by the patient over seven days, and 46 of 49 investigative centers were in the United States of America (three were in Latin America). Key patient information (including medication use, symptom relief and adverse experiences) was recorded on diary cards. All patients were required to have clinical AND microbiological confirmation of disease. Clinical confirmation required the presence of at least one of the following signs or symptoms:

- vulvovaginal itching
- vulvovaginal burning/irritation
- vulvar erythema
- vulvar edema
- vulvar excoriation
- vaginal erythema
- vaginal edema

Microbiological confirmation of vulvovaginal candidiasis required documentation of *Candida* species by BOTH 10% potassium hydroxide (KOH) preparation and by culture.

MO Comment: In the two studies, very few patients had only one sign or symptom, which would indicate very mild disease. As noted above all patients had to have both a positive KOH prep and *Candida* culture at V1 to enter the study. If either the KOH prep was negative or the yeast culture was negative at V1, the patient was considered to be non-evaluable (invalid) by both the applicant and the MO.

Other vulvovaginal disease was ruled out in both studies by appropriate procedures and tests, including gynecologic examination, wet mount for *Trichomonas vaginalis* and clue cells, testing for *Neisseria gonorrhoeae* and Papanicolaou (PAP) smear. Medications which could confound the interpretation of study results such as systemic antibiotics, other vulvovaginal preparations and investigational drugs (and devices) were prohibited in both studies.

MO Comment: Testing for *Chlamydia trachomatis* and *Herpes simplex* virus was not required by either protocol although both organisms can be a cause of vulvovaginal symptoms similar to those of VVC. Subject 29002 in the 005 study was discontinued (rendered non-evaluable) because of a positive chlamydia culture.

All patients were scheduled to be seen and evaluated on three occasions:

- at admission
- at Return Visit 1, 8-10 days after completion of treatment, and
- at Return Visit 2, 30-35 days after completion of treatment.

MO Comment: The MO allowed larger windows for evaluability. RV1 was enlarged 2 days to include from 7-11 days after Day 7 (applicant's "completion of treatment" whether the subject received 3 or 7 days of active drug). RV 2 was expanded 4 days to include from 28-37 days after Day 7. This allowed more patients to be considered by the MO as evaluable, and eliminated some of the problems associated with scheduling visits due to longer holiday weekends, menses, and patient's individual schedules and transportation arrangements.

No patients in study 95-005-P were rendered invalid by the applicant because of protocol violations due to timing of their visits. Three patients in study 95-007-P were invalid by the sponsor due to the timing of their visits: #3105 had RV2 <20 days after therapy, #5601 and #5801 had RV2 >60 days after therapy. The sponsor did not comply with the evaluability windows as stated in the two protocols.

In sharp contrast to the above listed 3 patients rendered invalid by the sponsor, the MO found 24 patients in the 005 study who had at least one of their visits outside the enlarged MO visit windows, and 47 patients in the 007 study similarly had window violations. These are listed individually with their visit days later in the review.

The key efficacy parameter in each study was the overall therapeutic cure rate. The overall clinical and microbiological cure rates, cure rates at Return Visits 1 and 2, relapse rates, and symptomatic relief were secondary efficacy parameters that were examined in each study. Patients at U.S. centers in Study 95-007-P also completed a product preference survey.

Therapeutic cure was calculated at Return Visit 1, Return Visit 2, and overall. A patient was considered a therapeutic cure at Return Visit 1 or 2 if she was BOTH a microbiological AND a clinical cure at that visit. A negative 10% KOH preparation and negative culture for *Candida* species were both required for a microbiological cure. Clinical cure required significant improvement in signs and/or symptoms at Return Visit 1 and essentially complete return to normal at return Visit 2.

Therapeutic cure was assessed by the following paradigm:

Applicant Criteria (Both Studies)

Clinical Cure	Microbiological Cure	Therapeutic Cure
Cure	Cure	Cure
Cure	Failure	Failure
Cure	Indeterminate	Indeterminate
Failure	Cure	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Cure	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

MO Comment: The primary efficacy endpoint in these two studies was therapeutic cure at return visit 2 (designated RV2 or V3). As can be seen above, a therapeutic cure required both a clinical and microbiological cure. All other combinations resulted in either a determination of failure or indeterminate (non-evaluable). The above applicant table was acceptable to the MO for the applicant's analysis of the study data. All failures, whether clinical or microbiological, were carried forward by the applicant. Most indeterminates were also carried forward, were generally non-evaluable for efficacy (unless they were a failure, either clinical or microbiological), and were evaluable for safety.

The primary efficacy parameter for the MO's analysis in each study was the overall therapeutic cure rate at RV2. Because RV1 was not the test-of-cure visit, clinical and mycological rates at RV1 were not tabulated separately by the MO, even though the applicant did this analysis. The MO used the same above paradigm for both studies to determine therapeutic cure, therapeutic failure, and non-evaluable status at RV2. The difference between the MO and the applicant's overall assessment was seen with the criteria used to define a

clinical cure or failure, a microbiological cure or failure, and a non-evaluable status. These differences are discussed later in this review (see pages 7-9 for MO microbiological and clinical criteria).

If a patient was missing either the 10% KOH preparation or culture results at a given visit and she would otherwise be a microbiological cure, she was classified as indeterminate rather than cure at that visit. Similarly, if a patient had missing information for any of the seven clinical signs or symptoms at a given visit and would otherwise be a clinical cure, she was classified as indeterminate rather than cure at that visit. However, any patient with missing data who would otherwise be classified as a failure was classified as a failure. In addition, if all seven signs and symptoms were classified as normal/absent at baseline for a patient, she was considered invalid for all efficacy analyses and was classified as being indeterminate for clinical cure at both return visits.

MO Comment: If a patient was missing either the 10% KOH preparation or culture results at RV1 and she would otherwise be a microbiological cure, she was assigned a microbiological response of indeterminate rather than a cure at that visit by both the applicant and the MO.

If the KOH prep was positive and the BiGGY culture was negative at RV1 and no RV2 occurred, the patient was considered by the MO to be indeterminate (non-evaluable) rather than a failure. In other words, the negative yeast culture at RV1 carried more weight than the KOH prep at this visit. There were 6 subjects in each study (12 total) who remained indeterminate because of a positive KOH and negative BiGGY at RV1, and no follow-up at RV2. The applicant, however, counted these 12 subjects as microbiological failures because the positive KOH was carried forward as a micro failure.

Patients in the above two situations were analyzed by the MO for the primary efficacy parameter if mycological and clinical data were available at the test-of-cure visit RV2.

A patient was an overall microbiological cure if both 10% KOH preparation and culture were negative at both return visits. A patient was an overall clinical cure if the clinical signs and symptoms were improved at the first return visit and essentially normal/absent at the second return visit. An overall therapeutic cure was an overall microbiological AND an overall clinical cure. For a patient to be classified as an overall therapeutic cure, all information required by the protocol had to be complete. This concept of overall therapeutic cure is an extremely rigorous criterion of product efficacy.

MO Comment: The MO used different criteria for the analysis of cures and failures. The BiGGY culture results were the MO's most important factor in determining a mycological (microbiological) cure. The table below outlines the MO criteria for a mycological cure, failure, or indeterminate (non-evaluable). Microbiological failures were also carried forward by the MO, and an overall therapeutic cure required both a mycological AND clinical cure at RV2 (the same as stated above by the applicant).

Medical Officer Table for Mycological Interpretation

Visit	If the KOH result is...	and the BIGGY result is...	then the MO Interpretation is...
V1	Negative	Positive	Non-evaluable
	Positive	Negative or missing	Non-evaluable
	Positive or missing	Positive	Assess at V2/V3
V2 (RV1)	Negative or missing	Positive	Micro failure (carried forward)
	Negative or missing	Negative	Micro cure at V2; need V3 data
	Positive	Negative	Indeterminate*; need V3 data
	Positive	Missing	Indeterminate if V3 data available. Failure, if V3 data not available.
V3 (RV2)	Negative or missing	Positive	Micro failure
	Negative or missing	Negative	Micro cure at V3
	Positive	Negative	Micro cure
	Positive	Missing	Micro failure
	Negative	Missing	Micro cure at V3

*Indeterminate = non-evaluable

Clinical signs and symptoms were assigned scores of 1 (normal/absent), 2 (mild), 3 (moderate), or 4 (severe), and disease severity at baseline and clinical cure were defined as follows:

Table II
Combined Applicant and MO Table for Clinical Evaluation in Both Studies

Disease Severity Group per Applicant	Sum of Signs and Symptoms at Baseline per Applicant	Maximum Sum of Signs and Symptoms for Clinical Improvement (RV1) or Cure (RV2)			
		RV1 Applicant	RV1 MO	RV2 Applicant	RV2 MO
Very Mild	8	7	7	7	7
Mild	9-14	8	9	8	8
Moderate	15-20	10	11	8	8
Severe	21-28	15	16	8	9

* Patients could be classified as a clinical cure at Return Visit 2 if one sign or symptom was classified as mild; except for those patients entering the study with only one mild sign or symptom. These patients required normal/absent scores for all signs and symptoms to be classified as a cure at both Return Visits 1 and 2.

MO Comment: See shaded areas in the above table. The MO allowed a slightly higher score than the sponsor for the mild, moderate, and severe groups at RV1, and for the severe group at RV2. This yielded more clinical cures, but still required a marked improvement in the composite sum of the signs and symptoms.

The MO used the exact same criteria at both visits as the applicant to determine a clinical cure in all patients with very mild disease.

The MO and the applicant used the above Table II for the determination of clinical improvement or cure in both studies in this NDA.

Safety was assessed by review and analysis of adverse experiences reported, by review of study discontinuations, and by the results of follow-up gynecologic examinations.

As can be seen in Table I below, 709 patients were enrolled in the two studies, including 280 assigned to receive miconazole nitrate (4%) vaginal cream for three days, 145 assigned to the five day miconazole nitrate (2.8%) vaginal cream regimen, and 284 assigned to currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream for seven days.

Table I
Summary of Patient Enrollment and Treatment Groups per Applicant

Study	Miconazole Nitrate (4%) Vaginal Cream	Miconazole Nitrate (2.8%) Vaginal Cream	MONISTAT®7 (2% MCN) Vaginal Cream
95-005-P	138	Not Done	142
95-007-P	142	145	142
Total = 709	280	145	284

III. SUMMARY OF STATISTICAL METHODS

The Cochran-Mantel-Haenszel (CMH) test was the principal test used to compare the two treatment groups for overall and Return Visit 1 therapeutic cure rates, and for days to symptomatic relief. Comparisons of the two formulations were also investigated using odds ratios, point estimates of the difference, and confidence limits. The CMH Test was used to identify variables affecting the cure rate. Norton's Test (6) was used to determine if there were significant investigator by treatment interactions.

Baseline variables were compared by a two-tailed T-test, Fisher's Exact Test, or Chi-Square Test, as appropriate. Proportions of patients reporting adverse experiences and proportions of patients non-compliant were compared using a two-tailed Fisher's Exact test. All statistical tests were two-sided and the p-value for significance was 0.05, unless specifically stated otherwise.

6. Norton, H.W. Calculation of Chi-Square for Complex Contingency Tables. *Journal of the American Statistical Association.* 1945;40:251-258.

IV. DESCRIPTION OF INDIVIDUAL STUDY 95-005-P ("Phase III Study Comparing Miconazole Nitrate 4% to MONISTAT®-7 2% Vaginal Cream in the Treatment of Vulvovaginal Candidiasis")

LIST OF 17 INVESTIGATORS 95-005-P

Responsible Investigator	Investigator Number	Location
Sofia H. Anthony, M.D.	1098-1	Verona, NJ
Allan B. Aven, M.D.	1046-1	Arlington Heights, IL
Steven C. Bowman, M.D.	1094-1	Clearwater, FL
Dan L. Chichester, M.D.	1092-1	Salt Lake City, UT
Reuben Clay Jr., M.D.	1122-1	San Francisco, CA
Dan C. Henry, M.D.	1090-1	Salt Lake City, UT
Gary R. Jones, M.D.	1121-1	Austin, TX
Frank Maggiacomo, D.O.	1127-1	Providence, RI
Thomas C. Marbury, M.D.	1091-1	Orlando, FL
Robert W. Rhame, M.D.	1120-1	Holly Hill, SC
Ernie Riffer, M.D.	1093-1	Phoenix, AZ
Harold M. Silberman, M.D.	1069-2	Coral Gables, FL
Malcolm Sperling, M.D.	1097-1	Fountain Valley, CA
Gary Steinbach, M.D.	1099-1	Edison, NJ
Elizabeth Trupin-Campbell, M.D.	1095-1	Champaign, IL
Raphael Tshibangu, M.D.	1055-1	Rochester, NY
Derek van Amerongen, M.D.	1014-1	Baltimore, MD

A. Objective

The objective was to determine the efficacy and the safety of miconazole nitrate (4%) vaginal cream administered for three days compared to the efficacy and safety of currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream administered for seven days in the treatment of patients with vulvovaginal candidiasis.

B. Design

This was a randomized, double-blind, parallel group, Phase III, multi-center study of 280 outpatients with documented vulvovaginal candidiasis. It was conducted at 17 centers, each enrolling from two to 30 patients, except for one center that enrolled no patients.

C. Study Medication

The investigational test product was miconazole nitrate (4%) vaginal cream containing 200 mg miconazole nitrate per 5-gram dose, supplied in a water-miscible, white to off-white cream base containing benzoic acid, cetyl alcohol, stearyl alcohol, isopropyl myristate, propylene glycol, polysorbate 60, potassium hydroxide, and purified water. It was administered for three days, followed by four days of identical placebo cream. The total dose of miconazole nitrate administered was 600 mg.

The active control was currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream containing 100 mg miconazole nitrate per 5-gram dose supplied in a water-miscible, white to off-white cream base containing benzoic acid, butylated hydroxyanisole (BHA), mineral oil, peglicol 5 oleate, pegoxol 7 stearate, and purified water. It was administered for seven days, for a total miconazole nitrate dose of 700 mg.

All medication was dispensed in identical packaging (package A for the first three nights and package B for the subsequent four nights) with tamper-evident seals and two-part, double-blind, tear-off labels. Each package contained prefilled 5-gram applicators with written instructions for use. All medication was self-administered and was to be inserted high in the vagina on retiring.

D. Study Population

Approximately 276 female patients with vulvovaginal candidiasis were to be entered if they:

- were 18 years of age or older with regular menses (if applicable)
- were non-pregnant and non-nursing
- used effective methods of contraception or were at least two years post-menopausal
- exhibited at least one of the 7 previously listed signs or symptoms of VVC
- had a Class I or II Papanicolaou (PAP) smear (no dysplasia) within 30 days of study entry
- met the laboratory requirements previously listed
- provided informed consent in writing and follow-up information.

Patients were excluded for:

- use of any systemic anti-infective or vulvovaginal therapeutic within seven days of admission
- use of water douches within three days of admission

- current history of alcohol or drug abuse
- history of sensitivity to any imidazole or triazole drug, or any component of the cream formulations
- vulvovaginal infections(s) associated with pathogens other than *Candida* species
- active genital herpetic lesions at the time of admission
- active genital condylomata requiring topical treatment within seven days of admission
- recent (within six months) history of abnormal pathology on PAP smear without corrective measures
- use of an experimental drug or device within 30 days prior to study entry, or
- more than one documented yeast infection within a two month period, or yeast infection not clearing with proper treatment.

MO Comment: The MO agreed with and used in the MO analysis the above inclusion and exclusion criteria used by the applicant in both of the studies.

E. Outline of Study Procedures

After finishing admission procedures, patients were treated for 7 consecutive nights, beginning on the day of admission. A gynecologic examination, KOH preparation, BiGGY culture for *Candida* species, and wet smear for *Trichomonas vaginalis* and clue cells were performed at each study visit.

Patients were instructed not to use tampons, not to douche, not to use any other vulvovaginal preparations, and not to use experimental drugs or devices during the study. Patients were also requested to refrain from intercourse, but condoms were supplied should intercourse occur. A diary card was supplied on which to record medication use, symptom relief, and any adverse experiences noted. This card was reviewed at both return visits and collected at the last return visit.

At each visit, patients were questioned regarding presence and severity of symptoms, intercourse, condom use, use of other vaginal or systemic medications, and also the presence and severity of any adverse experiences.

F. Validity, Compliance, Demographics and Discontinuations

Of the 280 patients entered, 138 were randomly assigned to receive miconazole nitrate (4%) vaginal cream and 142 were randomly assigned to receive currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream. All patients who received study medication and who provided safety data were analyzed for safety, and all evaluable patients were analyzed for efficacy. The main reasons for exclusion from the analyses were negative or

missing admission KOH preparation or BiGGY culture for *Candida* species, did not return for visits 1 and/or 2, and use of prohibited medication.

Table III
Study 95-005-P - Summary of Patient Evaluability by Treatment Group - N (%)
per Applicant

	Miconazole Nitrate (4%) Vaginal Cream	MONISTAT®7 (2%) Vaginal Cream	TOTAL
Total enrolled	138	142	280
Evaluable for safety*	135 (98%)	135 (95%)	270 (96%)
Evaluable for RV1 efficacy	97 (70%)	96 (68%)	193 (69%)
Evaluable for overall (RV2) efficacy	87 (63%)	88 (62%)	175 (63%)

MO Comment: *The MO had the same total number of enrolled patients and number evaluable for safety as did the applicant. All subjects who received at least one dose of study medication at any time and who provided any safety data were analyzed by the MO and the applicant for safety.

Evaluable for MO overall efficacy at RV2, however, were 65/138 = 47% in the 4% 3-day arm, and 79/142 = 56% in the 2% 7-day arm. The reason for fewer MO evaluable patients was due to larger numbers of non-evaluable patients who were screening failures at V1, and window violations at V2 and V3 (see Tables MO-1, MO-2 & MO-3). A screening failure, by MO criteria, was any subject at V1 with a negative KOH prep, or a negative BiGGY culture, or no clinical signs and symptoms.

Compliance was high in both treatment groups: 126/135 (93%) in the miconazole nitrate (4%) vaginal cream group and 128/135 (95%) in the currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream group. Reasons for classification as non-compliant were delay in starting medication, insufficient number of doses administered, and unknown medication use.

MO Comment: It is interesting to note that the compliance was actually higher (95% versus 93%) in the 7-day group compared to the 3-day group. One potential advantage with the shorter treatment regimens for treating VVC is the assumption that compliance will be better compared to the longer treatment regimens.

The treatment groups appeared generally comparable at baseline. Just over 70% of women were Caucasian and most of the remaining patients were Black or Hispanic. Mean age was 36-37 years and just over one quarter used oral

contraceptives. Disease severity was mild or moderate in about 90% of patients and severe in 7-8%. Intercourse and condom use between admission and RV1, and between RV1 and 2 appeared comparable as well.

MO Comment: The above data concerning compliance, demographics, disease severity, and use of oral contraceptives and condoms was very similar to the 95-007 study, and acceptable to the MO.

As can be seen in Table IV, screening failure and treatment failure were the primary reasons for study discontinuation. Overall discontinuations were slightly more frequent in the currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream group, which had more patients classified as screening failure or lost to follow-up.

Applicant Table IV
Study 95-005-P - Primary Reasons for Study Discontinuation -
All Patients - Investigator's Determination

Primary Reason for Discontinuation*	MONISTAT®3 (4% MCN) N=138	MONISTAT®7 (2% MCN) N=142
Screening failure	24 (17%)	28 (20%)
Treatment failure	10 (7%)	12 (8%)
Lost to follow-up	2 (1%)	6 (4%)
Personal reasons	2 (1%)	4 (3%)
Protocol violations	3 (2%)	3 (2%)
Adverse experience	3 (2%)	2 (1%)
Development of another infection requiring treatment	4 (3%)	1 (1%)
Patient request due to no improvement in symptoms prior to RV1	2 (1%)	2 (1%)
Other	2 (1%)	2 (1%)
Total	52 (38%)	60 (42%)

*A patient was only counted once: the reason chosen by the applicant was sometimes arbitrarily made.

MO Comment: The above table listed the overall reasons for the applicant's discontinuation of patients from the study. This list included treatment failures at RV1. The applicant did not include in their overview report a table of overall reasons for non-evaluability or evaluability per center.

Table MO-1
Evaluability per Center (per MO)

	Miconazole Nitrate (4%)		Monistat® 7 (2%)		MO Comment
Investigator 005-P Study	E/N = Evaluable/ Enrolled	%	E/N = Evaluable/ Enrolled	%	
Anthony	0/2	0	0/2	0	
Aven	4/9	44	6/9	67	5 window violations in 4% arm
Bowman	1/6	17	3/6	50	
Chichester	2/8	25	5/8	63	
Clay	1/3	33	2/5	40	
Henry	7/11	64	5/10	50	
Jones	5/11	45	4/12	33	10/23 had negative BiGGY at V1
Maggiacomo	4/4	100	2/3	67	
Marbury	8/12	67	11/14	79	
Rhame	0/0	–	0/0	–	
Riffer	5/15	33	9/15	60	
Silberman	4/12	33	4/12	33	
Sperling	7/15	47	9/15	60	8/30 had a negative BiGGY at V1
Steinbach	0/1	0	0/1	0	
Trupin-Campbell	4/8	50	2/8	25	
Tshibangu	3/6	50	5/7	71	
van Amerongen	10/15	67	12/15	80	
TOTALS	65/138	47%	79/142	56%	

MO Comment: The total number enrolled (both arms) per site ranged from 0 to 30. The percentage deemed evaluable was 47% and 56% overall (range 0 to 100%) in the two arms, but the two arms were comparable. The two major reasons for non-evaluable subjects were negative BiGGY cultures at V1 (28 in MCN 4%; 33 in MCN 2%) and window violations (17 in MCN 4%; 7 in MCN 2%). These data and other reasons are listed in Table MO-2 below.

Table MO-2
95-005 Study: Medical Officer Non-Evaluability Table

Primary Reason for MO Non-Evaluability*	MONISTAT®3 (4% MCN) N=138	MONISTAT®7 (2% MCN) N=142
Negative baseline BiGGY culture	28 (21%)	33 (23%)
Window (visit) violation	17 (12%)	7 (5%)
Lost to follow-up	8 (6%)	14 (10%)
Patient request to leave study	1 (2%)	0
Protocol violations	0 –	0
Late start study medication	5 (4%)	0
Adverse experience	1 (1%)	0
Development of another infection requiring systemic antibiotic Rx	7 (5%)	1 (1%)
Used other meds: see Exclusions	4 (3%)	6 (4%)
Abnormal V1 lab (e.g., +GC or CT)	2 (1%)	2 (1%)
Total	73/138 = (53%)	63/142 = (44%)

*No subject is counted twice; the reason chosen by the MO was arbitrarily made.
GC = *Neisseria gonorrhoeae;* CT = *Chlamydia trachomatis.*

MO Comment: The applicant had 51/138 = 37% non-evaluable subjects in the MCN 4% 3-day arm, and 54/142 = 38% non-evaluable in the 2% 7-day arm. By comparison, the MO had a much larger number of non-evaluable subjects due to more screening failures (negative BiGGY culture at V1), many more window violations, and more subjects lost to follow-up.

Table MO-3
MO list of Window Violations in M7C (2% cream, 7-day) Subjects (N=7)

Patient ID Number	Day of RV1, RV2 Visits*	Overall Evaluation if Included
04002	17,–	Non-Evaluable
09002	15,33	Therapeutic Cure
41003	09,38	Therapeutic Cure
46005	14,42	Therapeutic Cure
36005	17,32	Therapeutic Cure
21004	10,38	Therapeutic Cure
09001	12,28	Therapeutic Cure

Protocol windows were 8-10 and 30-35 days after completing treatment.
*MO windows were 7-11 (RV1) and 28-37 (RV2) days after completing treatment.

MO Comment: The above 7 subjects were included as evaluable by the applicant. All were considered non-evaluable by the MO because of the window violations; if counted, there would have been 6 cures and 1 non-evaluable subjects.

Table MO-4
MO list of Window Violations* in M3C (4% cream, 3-day) Subjects (N=17)

Patient ID Number	Day of RV1, RV2 visits	Overall Evaluation if Included
02002	8,50	Therapeutic Cure
02005	5,–	Non-Evaluable
03003	8,41	Non-Evaluable
04005	14,31	Therapeutic Cure
04006	5,32	Therapeutic Cure
05001	14,33	Therapeutic Cure
05002	21,–	Non-Evaluable
09004	12,32	Therapeutic Cure
44002	08,39	Therapeutic Cure
44004	–,39	Therapeutic Cure
13002	15,35	Therapeutic Cure
15004	9,38	Therapeutic Cure
15005	12,–	Non-Evaluable
54003	1,29	Therapeutic Cure
54006	1,29	Therapeutic Cure
35004	11,41	Therapeutic Cure
20005	13,34	Therapeutic Cure

Protocol windows were 8-10 and 30-35 days after completing treatment.
*MO windows were 7-11 (RV1) and 28-37 (RV2) days after completing treatment.

MO Comment: The above 17 subjects were counted as evaluable by the applicant. All were considered non-evaluable by the MO because of the window violations; if counted, there would have been 13 cures and 4 non-evaluable subjects.

H. <u>Overall Clinical, Microbiological and Therapeutic Cure Rates</u>

Overall clinical, microbiological and therapeutic cure rates appear in Table VI. Although these were all higher in the miconazole nitrate (4%) vaginal cream group, there was no statistically significant difference between treatment groups (p=0.422) in the overall therapeutic cure rate.

Table VI*
Study 95-005- Overall Clinical, Microbiological and Therapeutic Cure Rates per Applicant

	MONISTAT® 3	MONISTAT® 7	95% C.I.
Clinical Cure	67/87 (77%)	61/88 (69%)	
Microbiological Cure	63/87 (72%)	57/88 (65%)	
Therapeutic Cure	58/87 (67%)	52/88 (59%)	(-6.69, 21.85)

*Modified by MO to include the sponsor's 95% C.I. as an added column.

The 95% C.I. provides strong assurance that miconazole nitrate (4%) vaginal cream is at least therapeutically equivalent to currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream.

MO Comment: The overall MO clinical, microbiological and therapeutic cure rates at V3 (RV2) differ from the sponsor's because of the different criteria used for defining clinical and mycological cures, the different windows allowed for the 2 follow-up visits, and the smaller number of MO evaluable subjects in both arms of the 005-P study. The table below lists the overall MO cure rates.

Table MO-5
Study 95-005-P Overall Clinical, Microbiological and Therapeutic Cure Rates (per MO)

	MONISTAT®3	MONISTAT®7	95% C.I.*
Clinical Cure	54/65 (83%)	62/79 (78%)	(-9.66, 18.85)
Microbiological Cure	52/65 (80%)	55/79 (70%)	(-5.07, 25.83)
Therapeutic Cure	45/65 (69%)	49/79 (62%)	(-9.70, 24.11)

*Alpha = .05 and Continuity Correction Factor is used.

The cure rates at Return Visit 1 in patients evaluable for overall efficacy and the proportions of patients cured at Return Visit 1 who remained cured at Return Visit 2 appear in Table VII.

Table VII
Study 95-005-P - Cure Rates at Return Visit 1 and Return Visit 2 - Patients Evaluable for Overall Efficacy per Applicant

	MONISTAT®3	MONISTAT®7
Return Visit 1		
Clinical Cure	80/87 (92%)	76/88 (86%)
Microbiological Cure	75/87 (86%)	69/88 (78%)
Therapeutic Cure	73/87 (84%)	63/88 (72%)
Return Visit 1 Therapeutic Cures Remaining Cured at Return Visit 2		
Clinical Cure	65/73 (89%)	56/63 (89%)
Microbiological Cure	62/73 (85%)	53/63 (84%)
Therapeutic Cure	58/73 (79%)	52/63 (83%)

As would be expected, cure rates in both treatment groups were higher at Return Visit 1 than overall. However, as with the overall analyses, cure rates were consistently higher in the miconazole nitrate (4%) vaginal cream group. Proportions of patients cured at Return Visit 1 who remained cured at Return Visit 2 were similarly high in both treatment groups. This suggests a low

relapse rate (or perhaps, more correctly, a low re-colonization rate) with both treatment regimens.

MO Comment: Dr. Linda Gosey, FDA microbiologist, comments on possible relapse and re-colonization rates with both treatment regimens in her microbiology review.

MO Comment: The MO-6 table that follows below, looks at the number of patients found evaluable by the MO and the number of therapeutic cures per site/ investigator.

The percentage of therapeutic cures was 69% and 62% overall (range 0 to 100%) in the two arms, but there were no obvious outliers and the two arms were comparable. Data from the applicant showed similar findings, but was not presented in the table format created by the MO and shown below.

Table MO-6
005 Study Therapeutic Cure Rate per Center (per MO)

	Miconazole Nitrate 4%		Monistat® 7 (2%)	
Investigator 005-P Study	C/E = Cure/ Evaluable	%	C/E = Cure/ Evaluable	%
Anthony	0/0	–	0/0	—
Aven	4/4	100	5/6	83
Bowman	1/1	100	0/3	0
Chichester	0/2	0	3/5	60
Clay	0/1	0	1/2	50
Henry	4/7	57	3/5	60
Jones	4/5	80	3/4	75
Maggiacomo	4/4	100	2/2	100
Marbury	4/8	40	7/11	64
Rhame	0/0	–	0/0	–
Riffer	2/5	40	5/9	56
Silberman	3/4	75	4/4	100
Sperling	5/7	71	5/9	56
Steinbach	0/0	–	0/0	–
Trupin-Campbell	3/4	75	0/2	0
Tshibangu	2/3	67	3/5	60
van Amerongen	10/10	100	8/12	67
TOTALS	45/65	69 %	49/79	62 %

I. Effects of Key Covariables on Overall Therapeutic Cure Rates

The Cochran-Mantel-Haenszel Test was used to identify any covariables affecting the cure rate. There were no effects of oral contraceptive use, disease severity on admission, condom use and intercourse between admission and Return Visit 1, or condom use and intercourse between Return Visits 1 and 2 on the therapeutic cure rates overall, at the 0.10 level of significance.

J. Symptomatic Relief

The cumulative percentages of patients experiencing symptomatic relief (complete relief of itching and burning/irritation) on Days 3 and 7 of treatment appear in Table VIII.

Table VIII
Study 95-005-P - Symptomatic Relief in Patients Evaluable for Overall Efficacy - N (%) per Applicant

	MONISTAT®3	MONISTAT®7
Day 3	19/85 (22%)	19/85 (22%)
Day 7	66/85 (78%)	54/85 (64%)

Although more patients in the miconazole nitrate (4%) vaginal cream group experienced symptomatic relief at Day 7, there was no statistically significant difference between treatment groups at either Day 3 or Day 7.

K. Adverse Experiences- see Dr. Chin's safety review.

M. Speciations of Cultures

The distribution of species at admission and at return visits (treatment failures) were evaluated. Approximately 87% of admission species were *Candida albicans* and 7% were *Torulopsis glabrata*. Most treatment failures were still due to *Candida albicans* strains.

MO Comment: The microbiology review by Linda Gosey, FDA microbiologist, observed that 160/170 = 94% of her mycologically-evaluable patients had V1 cultures positive for *Candida albicans*. 7/170 = 4% grew *Candida glabrata* at V1. The remaining 2% were due to other species of *Candida*. By her criteria, 14/21 = 67% of mycological failures were due to *Candida albicans*, and 6/21 = 29% of mycological failures were due to C. *glabrata*. See Dr. Gosey's review for details.

N. Conclusions

Both treatment regimens provided prompt, safe and effective treatment of vulvovaginal candidiasis. Miconazole nitrate (4%) vaginal cream

administered for three days was as safe, and at least as efficacious, as currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream administered for seven days.

STUDY 95-007-P: "Phase III Study Comparing Miconazole Nitrate 4% and Miconazole Nitrate 2.8% Vaginal Cream to Currently Marketed MONISTAT®-7 2% Vaginal Cream in the Treatment of Vulvovaginal Candidiasis."

LIST OF INVESTIGATORS 95-007-P

Responsible Investigator	Investigator Number	Location
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Paul S. Bradley, M.D.	1114-1	Savannah, GA
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≈John Gillespie, M.D.*	1100-1	Dover, NH
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James H. Maxwell, M.D.	1072-1	Colorado Springs, CO
Mary L. Minar, D.O.	1133-1	Long Beach, CA
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Donald Moore, M.D.	1132-1	Seattle, WA
Jose Moreno Isturiz, M.D.	1112-1	Caracas, Venezuela
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Kevin Patrick, M.D.	1119-1	San Diego, CA
Howard A. Reisman, M.D.	1011-1	Roswell, GA
≈James Rice, M.D.	1107-1	Renton, WA
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Fred W. Schnepper, M.D.	1136-1	Chula Vista, CA
Gerald Shockey, M.D.	1139-1	Mesa, AZ
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Stephen G. Swanson, M.D.	1131-1	Lincoln, NE
Arthur S. Waldbaum, M.D.	1134-1	Denver, CO
Harry C. Watters, D.O.	1105-1	Chandler, AZ
Victor Weinstein, M.D.	1117-1	Charleston, SC
Ronald L. Young, M.D.	1109-1	Houston, TX
≈Edward A. Zbella, M.D.	1021-2	Clearwater, FL

≈No subjects were enrolled by these investigators.

This study was conducted at 29 centers in the United States of America and 3 centers in Latin America. Although patients in this study were randomly assigned to one of three treatment groups, only the results of the two groups, miconazole nitrate (4%) vaginal cream and currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream, are presented in this submission.

MO Comment: No data from the miconazole nitrate (2.8%) 5-day treatment arm were submitted with this NDA. So the comparison here in Study 95-007-P was between the 3-day 4% MCN cream and the 7-day 2% cream comparator arm. Because of the 3-arm design of the study, however, the MO and the FDA statistician, Cheryl Dixon, used Dunnett's adjustment (statistical analysis for multiple comparisons) with a smaller alpha value ($\alpha = 0.027$).

A. Objectives

The objectives were to determine the efficacy and the safety of miconazole nitrate (4%) vaginal cream administered for three days (and miconazole nitrate (2.8%) vaginal cream administered for five days) compared to the efficacy and safety currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream administered for seven days in the treatment of women withVVC.

B. Design

This was a randomized, double-blind, parallel group, Phase III, multi-center study of 429 outpatients with documented vulvovaginal candidiasis. It was conducted at 32 centers, each enrolling from 0 to 28 patients. The list of all potential investigators is provided on the next page.

C. Study Medication: the same as in the 95-005 study.

D. Study Population: Approximately 414 female patients with vulvovaginal candidiasis were to be entered if they met the same inclusion/exclusion criteria listed for the 95-005 study.

E. Outline of Study Procedures

The procedures were the same for both studies.

F. Validity, Compliance, Demographics and Discontinuations

Of the 429 patients entered, 142 were randomly assigned to receive miconazole nitrate (4%) vaginal cream, 145 to receive miconazole nitrate (2.8%) vaginal cream, and 142 to receive currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream. Only the results of patients receiving miconazole nitrate (4%) vaginal cream and currently marketed

MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream are reported here. All patients who received study medication and who provided safety data were analyzed for safety, and all evaluable patients were analyzed for efficacy. The main reasons for exclusion from the efficacy analyses were negative or missing KOH preparation or BiGGY culture for *Candida* species at the entry visit and use of prohibited medication.

Table X
Study 95-007-P - Summary of Patient Evaluability by Treatment Group - N (%) per Applicant

	Miconazole Nitrate (4%) Vaginal Cream	MONISTAT®7 (2%) Vaginal Cream	TOTAL
Total enrolled	142	142	284
Evaluable for safety	139 (98%)	137 (96%)	276 (97%)
Evaluable for RV1 efficacy	104 (73%)	107 (75%)	211 (74%)
Evaluable for overall efficacy	98 (69%)	100 (70%)	198 (70%)

MO Comment: The MO had the same total number of enrolled patients and number evaluable for safety. Evaluable for overall MO efficacy at RV2 were 78/142 = 55% in the 4% 3-day arm, and 84/142 = 59% in the 2% 7-day arm.

Compliance was high in both treatment groups: 131/139 (94%) in the miconazole nitrate 4% group and 130/137 (95%) in the MONISTAT®7 group. Reasons for classification as non-compliant were delay in starting medication, skipped more than one day of medication, and insufficient number of doses administered.

Although the mean age of women receiving miconazole nitrate (4%) vaginal cream (34.6 years) was about two years older than women receiving currently marketed MONISTAT®7 (2%) Vaginal Cream (32.7 years) and oral contraceptive use was greater in women receiving currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream (36.5% vs. 28.8%), the two treatment groups were generally comparable at baseline. About 60% were Caucasian, 20% Black and 20% Hispanic. Most patients had disease of mild or moderate severity, but slightly more currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream patients had severe disease (11% vs. 6%). Intercourse and condom use appeared comparable between treatment groups from admission to RV1, and between RV1 and 2.

MO Comment: The above data concerning compliance, demographics, disease severity, and use of oral contraceptives and condoms was very similar to the 95-005 study, and acceptable to the MO.

As can be seen in Table XI, treatment failure and screening failure were the most frequent reasons for study discontinuation. Overall discontinuations were slightly more frequent in the miconazole nitrate (4%) vaginal cream

group and this appeared to be due primarily to more patients discontinuing this treatment for adverse experiences, and for development of other infections requiring treatment.

Table XI
Study 95-007-P - Primary Reasons for Study Discontinuation - All Patients - Investigator's Determination per Applicant

Primary Reason for Discontinuation*	Miconazole Nitrate (4%) N=142		MONISTAT®7 (2% MCN) N=142	
Treatment failure	23	(16%)	22	(15%)
Screening failure	22	(15%)	19	(13%)
Protocol violation	3	(2%)	5	(4%)
Adverse experience	6	(4%)	1	(1%)
Lost to follow-up	2	(1%)	4	(3%)
Patient request due to no improvement in symptoms prior to RV1	1	(1%)	3	(2%)
Development of another infection requiring treatment	4	(3%)	0	(0%)
Other	1	(1%)	1	(1%)
Personal reasons	0	(0%)	1	(1%)
Total	**62**	**(44%)**	**56**	**(39%)**

*A patient was counted only once: the reason chosen by the applicant was sometimes arbitrarily made.

MO Comment: The above table listed the overall reasons for the applicant's discontinuation of patients from the study. This list included treatment failures at RV1. The applicant did not include in their overview report a table of overall reasons for non-evaluability or evaluability per center.

Table MO-7
007-P Study Therapeutic Evaluability per Center (per MO)

	Miconazole Nitrate 4%		Monistat 7 (2%)		MO Comment
Investigator ⇓	E/N =Evaluable/ Enrolled	%	E/N = Evaluable/ Enrolled	%	
Baker	1/5	20	2/6	33	5 Neg. V1 cultures
Bradley	1/4	25	2/4	50	
Deabate	0/3	0	0/3	0	6 Neg. V1 cultures
Estess	2/4	50	4/4	100	2 Window violations
Jiminez-Torrealba	9/10	90	8/10	80	
Joseph	2/2	100	1/3	33	
Kroll	3/4	75	0/4	0	2 Neg. V1 cultures 2 Window violations
Lui	0/3	0	1/4	25	2 Neg. V1 cultures 4 Window violations
Maxwell	10/10	100	7/11	64	
Minar	0/4	0	0/4	0	4 Neg. V1 cultures 4 Window violations
Moffet	4/5	80	3/4	75	
Moore	3/7	43	3/7	43	5 Window violations
Moreno	3/7	43	2/5	40	5 Neg. V1 cultures 2 Window violations
Novelovitz	2/3	67	2/3	67	
Patrick	7/14	50	13/14	93	6 Follow-up violations
Reisman	2/6	33	3/6	50	7 Window violations
Rivlin	0/2	0	2/2	100	
Schnepper	12/13	92	11/14	79	
Shockey	0	–	1/1	100	
Singleton	5/7	71	3/7	43	
Swanson	1/1	100	0/1	0	
Waldbaum	4/7	57	5/6	83	
Watters	1/5	20	0/4	0	3 Neg. V1 cultures 3 Window violations
Weinstein	5/10	50	9/9	100	
Young	1/6	17	2/6	33	6 Neg. V1 cultures 2 Window violations
TOTALS→	78/142	55	84/142	59	

MO Comment: The total number enrolled (both arms) per site ranged from 0 to 28. The percentage deemed evaluable was 55% and 59% overall (range 0 to 100%) in the two arms respectively, but the two arms were comparable. The

two major reasons for non-evaluable subjects were negative BiGGY cultures at V1 (26 in MCN 4%; 23 in MCN 2%) and window violations (23 in MCN 4%; 24 in MCN 2%). These data and other reasons are listed in Table MO-8 below.

Table MO-8
95-007 Study: Medical Officer Non-Evaluability Table

Primary Reason for MO Non-Evaluability	Miconazole Nitrate (4%) 3-day N=142	MONISTAT®7 (2% MCN) 7-day N=142
Negative baseline BiGGY culture	26 (18%)	23 (16%)
Window (visit) violation*	23 (16%)	24 (17%)
Lost to follow-up RV1	5 (4%)	4 (3%)
Lost to follow-up RV2	8 (6%)	5 (4%)
Patient request to leave study ᶻ	0	0
Protocol violations	1 (1%)	1 (1%)
Late start study medication ᶻ	0	0
Adverse experience ᶻ	0	0
Development of another infection requiring antibiotic treatment ᶻ	0	0
Used other meds: see Exclusions ᶻ	0	0
Abnormal V1 lab (e.g., +GC or PAP)	1 (1%)	1 (1%)
Total	64/142 = (45%)	58/142 = (41%)

* Many of these subjects also had other criteria for non-evaluability.
ᶻ These subjects had other criteria for non-evaluability and are not counted twice.
GC = *Neisseria gonorrhoeae*.

MO Comment: The applicant had 44/142 = 31% non-evaluable subjects in the MCN 4% 3-day arm, and 42/142 = 30% non-evaluable in the 2% 7-day arm. By comparison, the MO had a much larger number of non-evaluable subjects due to more screening failures (negative BiGGY culture at V1), many more window violations, and more subjects lost to follow-up.

Table MO-9
MO list of Window Violations* in MC3 (4% cream, 3-day) Subjects (N=23)

Patient ID Number	Day of RV1, RV2 visits	Overall Evaluation if Included
8004	9,23	Therapeutic Cure
9204	12,32	Therapeutic Cure
9504	6,32	Therapeutic Cure
0906	9,44	Micro Failure at RV2
5505	9,23	Therapeutic Cure
9303	11,25	Therapeutic Cure
1702	9,25	Therapeutic Cure
3202	21,36	Therapeutic Cure
0106	5,29	Therapeutic Cure
0505	15,48	Therapeutic Cure
0705	18,34	Therapeutic Cure
0706	15,42	Therapeutic Cure
7002	12,52	Clinical Failure
7005	15,39	Therapeutic Cure
2902	10,44	Micro Failure
3005	9,50	Micro Failure
3501	14,30	Therapeutic Cure
3105	8,16	Therapeutic Cure
8104	4,–	Non-Evaluable
3504	8,42	Therapeutic Cure
0605	18,–	Non-Evaluable
6504	4,–	Non-Evaluable
5703	2,–	Non-Evaluable

*MO criteria and comments concerning allowable visit windows:
The protocol allowed an RV1 window of day 8-10, and RV2 from days 30-35.
The MO expanded the RV1 window to days 7-11, and RV2 from days 28-37.
The applicant used an RV1 window of days 1-26, and RV2 from days 16-52.

MO Comment: The above 23 subjects were counted as evaluable by the applicant. All were considered non-evaluable by the MO because of the window violations; if counted, there would have been 15 cures, 4 failures, and 4 non-evaluable subjects.

Table MO-10
MO list of Window Violations* in M7C (2% cream, 7-day) Subjects (N=25)

Patient ID Number	Day of RV1, RV2 visits	Overall Evaluation if Included
1603	5,30	Therapeutic Cure
2702	12,43	Therapeutic Cure
2704	9,55	Therapeutic Cure
2206	19,26	Therapeutic Cure
5503	8,22	Therapeutic Cure
5504	30,83	Therapeutic Cure
4904	3,31	Therapeutic Cure
7102	16,31	Therapeutic Cure
9302	13,28	Therapeutic Cure
4405	8,40	Therapeutic Cure
0602	9,25	Therapeutic Cure
0701	14,32	Therapeutic Cure
7504	15,37	Therapeutic Cure
1406	13,34	Therapeutic Cure
4302	2,36	Non-Evaluable
4304	6,32	Non-Evaluable
5101	2,28	Non-Evaluable
0506	18,–	Non-Evaluable
1904	15,–	Non-Evaluable
2801	8,22	Non-Evaluable
5306	1,22	Therapeutic Cure
5106	25,–	Non-Evaluable
7105	14,–	Non-Evaluable
1402	13,–	Non-Evaluable

*MO criteria and comments concerning allowable visit windows:
The protocol allowed an RV1 window of day 8-10, and RV2 from days 30-35.
The MO expanded the RV1 window to days 7-11, and RV2 from days 28-37.
The applicant used an RV1 window of days 1-26, and RV2 from days 16-52.

MO Comment: The above 24 subjects were counted as evaluable by the applicant. All were considered non-evaluable by the MO because of the window violations; if counted, there would have been 15 cures and 9 non-evaluable subjects by the MO criteria.

H. Overall Clinical, Microbiological and Therapeutic Cure Rates

Although overall clinical, microbiological and therapeutic cure rates were all slightly higher in the currently marketed M7C group, there was no statistically significant difference between treatment groups (p=0.478) in the overall therapeutic cure rate.

Table XIII*
Study 95-007 Overall Clinical, Microbiological and Therapeutic Cure Rates per Applicant

Applicant data	MONISTAT®3	MONISTAT®7	95% C.I.
Clinical Cure	65/98 (66%)	70/100 (70%)	
Microbiological Cure	61/98 (62%)	66/100 (66%)	
Therapeutic Cure	57/98 (58%)	63/100 (63%)	(-18.44, 8.76)

*Modified by MO to include the sponsor's 95% C.I. as an added column.

These provide assurance that miconazole nitrate (4%) vaginal cream is therapeutically equivalent to currently marketed MONISTAT®7.

MO Comment: The overall MO clinical, microbiological and therapeutic cure rates at V3 (RV2) listed below differ from the sponsor's listed above because of the different criteria used for defining clinical and mycological cures (see pages 6-8), the different windows allowed for the 2 follow-up visits, and the subsequent smaller number of evaluable subjects in both arms of the 007-P study.

The MO used the exact same criteria for evaluability and cure/failure for both arms of both studies. The table below lists the overall cure rates at RV2 in the 007-P study as determined by the MO.

Table MO-11
Study 95-007-P Overall Clinical, Microbiological and Therapeutic Cure Rates (per MO)

MO data	MONISTAT®3	MONISTAT®7	97.3% C.I.
Clinical Cure	64/78 (82%)	71/84 (86%)	
Microbiological Cure	51/78 (65%)	55/84 (65%)	
Therapeutic Cure	46/78 (59%)	49/84 (58%)	(-17.2, 19.6)*

* This C.I. adjusts for multiple comparisons (a 3-arm study) using Dunnett's adjustment to alpha. The adjusted alpha is 0.027.

MO Comment: Both the applicant's 95% and the MO's 97.3% confidence intervals demonstrate that miconazole nitrate 4% cream is therapeutically equivalent to the comparator (currently marketed miconazole nitrate 2% cream).

MO Comment: Table MO-12 below analyzed the number of subjects found evaluable by the MO, and the number of therapeutic cures **per site/ investigator**. The total number enrolled (both arms) per site ranged from 0 to 28. The percentage deemed evaluable was 55% and 59% overall (range 0 to 100%) in the 4% and comparator 2% arms respectively, but there appeared to be no obvious outliers and the two arms were comparable. The two reasons for the largest number of non-evaluable subjects were negative BiGGY cultures at V1 (26 in MCN 4%; 23 in

MCN 2%) and window violations (23 in MCN 4%; 24 in MCN 2%). These data and other reasons are listed in Table MO-8 on page 26.

The percentage of therapeutic cures was 59% and 58% overall (range 0 to 100%) in the 4% and comparator 2% arms, respectively, but there were no obvious outliers and the two arms were comparable. Per center data from the applicant showed similar findings, but was not presented in the table format created by the MO and shown below.

Table MO-12
007-P Study Therapeutic Cure Rate per Center (per MO)

	Miconazole Nitrate 4%		Monistat® 7 (2%)	
Investigator ⇓	C/E = Cure/ Evaluable	%	C/E = Cure/ Evaluable	%
Baker	1/1	100	1/2	50
Bradley	0/1	0	0/2	0
Deabate	0	–	0	–
Estess	2/2	100	4/4	100
Jiminez-Torrealba	7/9	78	3/8	38
Joseph	1/2	50	0/1	0
Kroll	0/3	0	0	–
Lui	0	–	1/1	100
Maxwell	7/10	70	7/7	100
Minar	0	–	0	–
Moffet	2/4	50	2/3	67
Moore	2/3	67	2/3	67
Moreno	1/3	33	1/2	50
Novelovitz	2/2	100	2/2	100
Patrick	4/7	57	8/13	62
Reisman	1/2	50	1/3	33
Rivlin	0	–	1/2	50
Schnepper	8/12	67	5/11	45
Shockey	0	–	0/1	0
Singleton	1/5	20	0/3	0
Swanson	1/1	100	0	–
Waldbaum	1/4	25	3/5	60
Watters	0/1	0	0	–
Weinstein	5/5	100	7/9	78
Young	0/1	0	1/2	50
TOTALS→	46/78	59%	49/84	58%