8.2.2. Trial # 2: Study 97-006 — A Single-Blind Safety and Efficacy Study Comparing a Single Dose (1200 mg) Miconazole Nitrate Vaginal [redacted] to MONISTAT® 7 Vaginal Cream (100 mg Miconazole Nitrate) in the Treatment of Vulvovaginal Candidiasis (VVC)

MO Comment: Study 97-006 is the second of the two pivotal phase 3 clinical studies. The protocol objectives and study design are virtually identical to Study 96-002. Therefore in the following sections describing Study 97-006, the reader will be referred to the appropriate section of the description of Study 96-002. Where differences occur, they will be noted. The study results for 97-006 will be described in their entirety.

Study 97-006 took place from May 1997 to December 1997.

Objective/Rationale

The study objective was the same as stated for Study 96-002. Please see section 8.2.1., page 15 of this report.

Design

The study design was the same as stated for Study 96-002. Please see section 8.2.1., page 15 of this report.

Study 97-006 enrolled a total of 280 patients. The study involved 17 centers, all within the US.

The clinical supply lot number of the [redacted] used in the study was CS97-099. [redacted] manufactured the bulk miconazole nitrate (1200 mg) [redacted] for Study 97-006.

The clinical supply lot number of the MONISTAT® External Vulvar Cream packaged with the 1200 mg soft gel vaginal insert was CS97-092.

The clinical supply lot number for the MONISTAT®7 Vaginal Cream used in Study 97-006 was CS97-090.

Protocol Overview

The study procedures, evaluability criteria, endpoints, and statistical analyses were the same for Study 97-006 as they were for Study 96-002. Please see page 15 of this report for a detailed description of these elements of the protocol.

Study Results

Demographics

Comparisons of the age and race distributions for the two treatment groups are provided in Table 39.

Table 39. Baseline Demographics, Age and Race, by Treatment Group in The Population of Patients Valid for Safety

	Treatment Group			
Characteristic	1200 mg [redacted]		MONISTAT® 7	
Age (yrs.)				
Mean	35.5		37.0	
Range	17–75		17–76	
Standard Deviation	13.6		13.4	
Race	n/N	(%)	n/N	(%)
White	94/138	(68.1)	97/133	(72.9)
Black	25/138	(18.1)	24/133	(18.0)
Hispanic	13/138	(9.4)	9/133	(6.8)
Other	6/138	(4.3)	3/133	(2.3)
Oral contraceptive use	34/138	(24.6)	26/133	(19.5)

(adapted from Applicant's table 3a, Vol. 1.9, p. 08-000333)

The two groups are similar with regards to age, race, and oral contraceptive use. The rates of intercourse and condom use were comparable between the two treatment arms. The Applicant also analyzed the data for the evaluable for efficacy population. The results were similar to the information presented above for the evaluable for safety population.

Disease severity at admission was compared for the two treatment groups (Table 40).

Table 40. Disease Severity at Admission by Treatment Group in the Population of Patients Valid for Safety

	Treatment Group			
	1200 mg [redacted]		MONISTAT® 7	
Disease Severity	n/N	(%)	n/N	(%)
Very mild	3/138	(2.2)	1/133	(0.8)
Mild	91/138	(65.9)	95/133	(71.4)
Moderate	41/138	(29.7)	35/133	(26.3)
Severe	3/138	(2.2)	2/133	(1.5)

(adapted from the Applicant's table 3a, Vol., 1.9, p. 08-000333)

The distribution of disease severity is similar in each of the treatment groups. Table 40 provides data on the valid for safety patient population. Similar results were found in the valid for efficacy population

Evaluability

A total of 280 patients were enrolled in the study (142 in the 1200 mg [redacted] arm and 138 in the MONISTAT® 7 arm). All but 9 patients were evaluable for safety (4 patients from the 1200 mg [redacted] arm and 5 from the MONISTAT® 7 arm). Two patients, both in the 1200 mg [redacted] arm, did not use the study medication and the remaining 7 were lost to follow-up and provided no safety information.

Comparable numbers of patients were evaluable for efficacy at Return Visit 1 and overall. Table 41 below provides the number of patients in each of the evaluable populations.

Table 41. Summary of Patient Evaluability by Treatment Group

	MCN (1200 mg) Vaginal [redacted]		MONISTAT® 7 (2% MCN) Vaginal Cream		TOTAL	
Evaluability	n	%	n	%	n	%
Total enrolled	**142**		**138**		**280**	
Evaluable for safety	**138**	**97.2**	**133**	**96.4**	**271**	**96.8**
Evaluable for RV1 efficacy	**111**	**78.2**	**94**	**68.1**	**205**	**73.2**
Evaluable for overall efficacy*	**104**	**73.2**	**90**	**65.2**	**194**	**69.3**

(Applicant's table IV from vol. 1.9, p 08-000309)
*evaluable for RV1 and RV2

The reasons that patients were non-evaluable are shown in Table 42. The most frequent reason patients were non-evaluable was the category of "negative or missing KOH smear or BiGGY culture for *Candida* species on admission." The other frequent reasons for non-evaluability were did not return for visits 1 and/or 2, use of prohibited medication, improper use of study medication, and tampon use. Table 42 provides additional details on primary reasons for non-evaluability.

[redacted] APPEARS THIS WAY ON ORIGINAL

Table 42. Primary Reason for Non-Evaluability by Treatment Arm

Primary Reason for Non-Evaluability	Treatment: 1200 mg [redacted] (N = 142)* n	(%)	MONISTAT® 7 (N = 138)* n	(%)
Did not use study medication	2	1.4	0	0.0
Lost to follow-up after admission	2	1.4	5	3.6
Total non-evaluable for safety	**4**	**2.8**	**5**	**3.6**
No signs or symptoms on admission	1	0.7	0	0.0
Negative or missing smear or culture for *Candida* sp. on admission ψ	9	6.3	14	10.1
Neisseria gonorrhea culture positive or missing ψ	2	1.4	1	0.7
Other vaginal infection on admission	1	0.7	0	0.0
Did not return for visit 1 and 2	3	2.1	6	4.3
Time to study medication delayed from admission**	3	2.1	3	2.2
Used study medication incorrectly**	0	0.0	4	2.9
Developed other vaginal infection between admission and return visit 1	0	0.0	1	0.7
Used other vulvovaginal drugs, systemic antibiotics or investigational drugs between admission and return visit 1	4	2.8	2	1.4
Used tampon during study	4	2.8	4	2.9
Missing microbiological data at return visit 1	0	0.0	4	2.9
Total non-evaluable for efficacy return visit 1	**31**	**21.8**	**44**	**31.9**
Lost to follow-up after return visit 1	1	0.7	0	0.0
Did not return for return visit 2	3	2.1	2	1.4
Developed other vaginal infection between return visit 1 and return visit 2	1	0.7	0	0.0
Used other vulvovaginal drugs, systemic antibiotics or investigational drugs between return visit 1 and return visit 2	2	1.4	2	1.4
Total non-evaluable for efficacy overall	**38**	**26.7**	**48**	**34.8**

(Table derived from the Applicant's table 2c, Vol. 1.9, p. 08-000331)

*The total number of patients enrolled in each study arm is used as the "nominal" denominator for the above percentages.

** The categories of "Time to study medication delayed from admission and" and "Used study medication incorrectly" capture patients who were non-compliant with study medication use. Because of the temporal hierarchy involved in the designated primary reason for non-evaluability criteria, five patients who were non-compliant with study medication use are listed in other primary reason for non-evaluability categories. In the 1200 mg ovule arm, patients 2305 and 3003 were non-compliant but also did not return for RV1 and RV2 and are therefore listed as "Did not return for visit 1 and 2." Similarly, three patients in the MONISTAT ® 7 arm were non-compliant with study medication use but had another primary reason for non-evaluability; patients 1703, 5202, and 5203 did not return for return visits 1 and 2 and are listed under the category of "Did not return for visit 1 and 2" above. Hence, the number of patients compliant with medication in the evaluable for safety population was 133/138 (96%) for the 1200 mg [redacted] and 123/133 (92%) for MONISTAT®7.

ψ See MO Comments below

MO Comment: In the study report for Study 97-006, the Applicant notes that the small number of patients lacking a *Neisseria gonorrhoeae* culture result from admission will not be excluded from the evaluable population. Under the Applicant's discontinuation criteria as defined in the study report, these three should be scored under their respective other reasons for non-evaluability. These three patients are scored as positive or missing culture for *N. gonorrhoeae* because of the temporally based hierarchy of the non-evaluability scoring system. Under the Applicant's further defined analysis plan allowing patients with missing *Neisseria gonorrhoeae* culture results from admission to remain in the evaluable population, these three would be non-evaluable because of subsequent reasons for non-evaluability. The additional reasons for non-evaluability for these three patients were as follows.

- Pt. No. 01605 (1200 mg) – Did not return for Return Visit 2
- Pt. No. 01701 (1200 mg) – Used other vulvovaginal drug, systemic antibiotic, or investigational drug between admission/Return Visit 1
- Pt. No. 02302 (M7C) – Used other vulvovaginal drug, systemic antibiotic, or investigational drug between admission/RV 1

MO Comment: Regarding the category designated as "negative or missing KOH smear or BiGGY culture for *Candida* sp. on admission." Review of the KOH smear data reveals only one patient in the trial who was non-evaluable because of a negative KOH smear (Pt. No. 3901, 1200 mg [redacted] group). Therefore, the category of "negative or missing KOH smear or BiGGY culture for *Candida* sp. on admission" represents one patient with a negative KOH smear and 22 patients with negative BiGGY cultures at admission.

MO Comment: The distribution of primary reasons for non-evaluability do not suggest the introduction of bias that would invalidate the interpretation of the efficacy data. Of note is the greater number of patients with a negative BiGGY culture at the admission visit in the MONISTAT®7 treatment arm of the study. The distribution of disease severity in the population of patients evaluable for safety is similar in the two treatment arms suggesting the increased number of negative BiGGY cultures in the MONISTAT®7 arm may be a chance occurrence. Also of note is that in Study 96-002, the greater number of negative BiGGY cultures was in 1200 mg vaginal [redacted] arm of the study.

Evaluability by investigator

The rates of evaluablility at each study center for RV 1 and RV2 (overall) are presented in Table 43 and Table 44.

Table 43. Evaluability for Efficacy by Study Center at Return Visit 1

		Treatment Group					
		1200 mg [redacted]			MONISTAT®7 Vaginal Cream		
		Enrolled	Evaluable at RV1		Enrolled	Evaluable at RV1	
Investigator ID	Investigator #	(N)	(n)	(n/N%)	(N)	(n)	(n/N%)
Albery	1156-1	2	2	100	1	0	0
Aven	1046-1	6	6	100	6	6	100
Gilderman	1160-1	15	15	100	15	12	80
Harrell	1158-1	4	2	50	5	0	0
Hassman	1152-1	12	8	67	11	5	46
Koster	1155-1	14	10	71	13	11	85
Loesch	1162-1	1	0	0	0	0	0
Marbury	1091-1	10	8	80	9	4	44
Moffet	1128-1	10	8	80	12	9	75
Moore	1132-1	11	11	100	9	8	89
Schwebke	1159-1	12	7	58	12	6	50
Swanson	1131-1	14	8	57	15	10	67
Tinsman	1153-1	8	7	88	8	7	88
Trupin-Campbell	1017-1	7	6	86	7	5	71
Tyler	1163-1	8	7	88	7	6	86
Waldbaum	1134-1	8	6	75	8	5	63
Total		142	111	78	138	94	68

(Table derived from the Applicant's data Vol. 1.9, p. 08-000329)

(An additional investigator, John Ondrejicka, MD of Jacksonville, FL, was assigned investigator # 1071-2 but enrolled no patients.)

Table 44. Evaluability for Efficacy by Study Center at Return Visit 2

		Treatment Group					
		1200 mg [redacted]			MONISTAT®7 Vaginal Cream		
		Enrolled	Evaluable at RV2		Enrolled	Evaluable at RV2	
Investigator ID	Investigator #	(N)	(n)	(n/N%)	(N)	(n)	(n/N%)
Albery	1156-1	2	2	100	1	0	0
Aven	1046-1	6	6	100	6	6	100
Gilderman	1160-1	15	14	93	15	12	80
Harrell	1158-1	4	2	50	5	0	0
Hassman	1152-1	12	8	67	11	5	46
Koster	1155-1	14	10	71	13	11	85
Loesch	1162-1	1	0	0	0	0	0
Marbury	1091-1	10	7	70	9	4	44
Moffet	1128-1	10	8	80	12	9	75
Moore	1132-1	11	11	100	9	8	89
Schwebke	1159-1	12	7	58	12	6	50
Swanson	1131-1	14	7	50	15	10	67
Tinsman	1153-1	8	7	88	8	6	75
Trupin-Campbell	1017-1	7	3	43	7	4	57
Tyler	1163-1	8	6	75	7	4	57
Waldbaum	1134-1	8	6	75	8	5	63
Total		142	104	73	138	90	65

(Table derived from the Applicant's data Vol. 1.9, p. 08-000329)

MO Comment: While there is some variation in the percentage of patients evaluable at the different study centers, review of the evaluability data along with the cure rates by study center does not demonstrate any trends that would raise concern as to the validity of the data.

Discontinuation

The proportion of patients discontinued from the study along with the primary reason for study discontinuation is presented in Table 45 below.

Table 45. Number of Patients Discontinued From the Study by Primary Reason for Discontinuation, All Patients

Primary Reason for Discontinuation	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 142)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 138)	
	n	%	n	%
Treatment failure	21	14.8	17	12.3
Protocol violation**	16	11.3	12	8.7
Screening failure Ψ	4	2.8	11	8.0
Developed another infection requiring treatment*	3	2.1	4	2.9
Lost to follow-up	3	2.1	3	2.2
Other	2	1.4	3	2.2
Patient request due to no improvement in symptoms prior to RV1	0	0.0	4	2.9
Adverse experience	1	0.7	2	1.4
Total Number of Patients Discontinued	50	35.2	56	40.6
Total Number of Patients Completing Study	92	64.8	82	59.4

(Applicant's Table III from Vol. 1.9, p. 08-000308)

Ψ All patients with "screening failure" as their primary reason for discontinuation had negative BiGGY cultures at admission. Only one patient in the study (pt. No. 3901) had a negative KOH preparation at admission. This patient's primary reason for discontinuation was "protocol violation."

* One of the 7 patients with a primary reason for discontinuation of "Developed another infection requiring treatment" was noted to have trichomoniasis (Pt. No. 2903, 1200 mg [redacted] group). The others 6 patients were all noted to have clue cells on their wet preparations at RV1.

**Table 46. provides a tabulation of the protocol violations that resulted in patient discontinuation by treatment group.

MO Comment: There does not appear to be any apparent bias exhibited by the tabulation of reasons for discontinuation. In Study 97-006, we see a greater number of screening failures in the MONISTAT® 7 arm of the study. In the previous study, 96-002, there was a greater number of screening failures in the 1200 mg vaginal [redacted] arm of the study, suggesting chance variation.

Table 46. Description of Protocol Violations as the Primary Reason for Study Discontinuation by Treatment Group

Description of Protocol Violation	Treatment			
	1200 mg [redacted] N=16		MONISTAT®7 N= 12	
	n	%	n	%
Tampon use between admission and RV1	3	19	3	25
Received an oral antibacterial medication	6	38	4	33
Test for GC not done and admission in the setting of a secondary reason for discontinuation*	4	25	2	17
Used intravaginal medication (not an anti-infective)	0	0	2**	17
Used condoms as method of birth control	1	6	0	0
Had a history of 2 episodes of VVC in a 2-month time period	1	6	0	0
Had a negative KOH smear, medication dispensed in error	1	6	0	0
Used clotrimazole for itching in addition to study drug	0	0	1	8

*Absence of a test for GC alone was not sufficient for discontinuation (see discussion below)
** see MO Comment Below

MO Comment: One patient (Pt. No. 2605) was discontinued from the study because she used an intravaginal medication (an estrogen preparation). However, she appears to have been erroneously retained in the evaluable for efficacy population. The patient was in the MONISTAT®7 arm of the study and was an overall clinical, microbiological, and therapeutic failure. Inclusion of this one patient would not be expected to change the overall study conclusions.

There were nine patients who did not meet all of the inclusion criteria enrolled in Study 97-006. Seven of these nine patients did not have a culture done or a result available for their *Neisseria gonorrhoeae* culture. The Applicant notes that the missing enrollment data, either a culture for *Neisseria gonorrhoeae* was not done (5) or the results for the cultures were unknown (2). Three of the 7 patients were assigned to the 1200 mg vaginal [redacted] arm of the study (Pt. Nos. 01806, 02201, and 03102): four were assigned to the MONISTAT® 7 arm (Pt. Nos. 00601, 01105, 02203, and 02605). Two of the 9 patients were 17-year-old patients enrolled in the study despite the minimum age of 18 years specified in the protocol (Pt. No. 00401, MONISTAT® 7 arm; Pt. No. 0140, 1200 mg vaginal [redacted] arm).

MO Comment: The case report tabulations and comments extracted from the CRFs for the patients with incomplete results for their cultures for *Neisseria gonorrhoeae* were reviewed to investigate the reasons for the incomplete data. The comments from the CRFs suggest that the cultures were inadvertently not obtained in two patients. The CRF comments note the intention to obtain these

cultures at subsequent visits. In the other five a variety of occurrences (unacceptable specimen, inconclusive test results, laboratory mistake, test for GC not performed at the laboratory, specimen not received by the laboratory) are contained in the CRF comments as potential explanations for the missing data.

Cultures for *Neisseria gonorrhoeae* were obtained at the time of admission in 266 of the 288 patients enrolled in the study. Of these 266 patients who were cultured, there was a single positive culture. If this larger population is representative of the smaller population for whom cultures for *Neisseria gonorrhoeae* (GC) were not obtained, allowing these 7 patients whose only missing admission evaluation was a missing culture for GC is not an unreasonable modification. It should however be noted that ideally the data should be analyzed as per the original protocol specifications.

Efficacy

The study was designed to compare the clinical, microbiological, and therapeutic response of patients treated with MONISTAT® DUAL-PAK® to those treated with MONISTAT®7 Vaginal Cream. Clinical and microbiological responses were assessed at Return Visits 1 and 2. The results from the clinical and microbiological responses were combined to determine the therapeutic response endpoint. Results from the endpoints determined at RV1 and RV2 were combined to form an overall response category (see the description of endpoints for efficacy for further explanation, p. 22). In the study report, the Applicant also provides additional information with regards to the time to relief of symptoms.

MO Comment: As noted in the study report, the Applicant widened the allowable time windows for assessments of patients at RV1 and RV2. The Applicant's revised windows for RV1 and RV2 specified that patients were non-evaluable if:

- RV1 was more than 60 days after therapy was completed and the therapeutic response was a failure at RV1
- RV2 was less than 20 days after the end of therapy and the overall therapeutic response was a cure
- RV2 was greater than 60 days after the end of therapy and the therapeutic response was not a failure at RV1, but was a failure at RV2

The study report specified evaluability criteria related to the timing of RV1 and RV2 differ from the protocol-specified windows for RV1 (Study Day 15-19) and RV2 (Study Day 35-43). The Medical Officer

analyzed the number of patient assessments that fell outside the protocol specified windows for RV1 and RV2 (Table 47). The MO performed an additional efficacy analysis because patients were included in the applicant's evaluable for efficacy populations at RV1 and RV2 that were evaluated outside of the protocol specified RV1 and RV2 windows. These analyses include assessments of clinical, microbiological, and therapeutic response rates in the subset of the Applicant's evaluable patients who were compliant with the protocol specified visit window or in a second analysis evaluated within ± 2 days of the protocol specified visit window. These analyses are presented in the section titled MO Efficacy Analysis on page 68 of this report.

Table 47. Proportion of Patient Assessments within Varying Windows for RV1 and RV2.

Visit Window	Treatment Group 1200 mg Insert n/N	%	MONISTAT®7 Cream n/N	%
RV1 (Day 15-19)	94/111*	85	81/94*	86
cure <35 days	3		5	
cure >43 days	10		7	
failure <35 days	2		0	
failure >43 days	2		1	
RV1 ± 2 days (Day 13-21)	101/111*	90	90/94*	96
cure <35 days	2		0	
cure >43 days	6		3	
failure <35 days	1		0	
failure >43 days	1		1	
RV2 (Day 35-43)	67/87**	77	64/74**	86
cure <35 days	1		1	
cure >43 days	11		6	
failure <35 days	4		2	
failure >43 days	4		1	
RV2 ± 2 days (Day 33-45)	77/87**	89	68/74**	92
cure <35 days	1		0	
cure >43 days	4		5	
failure <35 days	2		1	
failure >43 days	3		0	

*The denominators for RV1 represent the patients valid for efficacy at RV1.

**The denominators for RV2 represent the patients valid for efficacy at RV2 that actually underwent an RV2. (Note: Patients valid for efficacy at RV2 who were declared treatment failures and discontinued from the study prior to RV2 are not included in the RV2 denominators.)

Clinical

The Applicant's clinical, microbiological, and therapeutic cure rates at RV1 in patients valid for efficacy at RV1 are presented in Table 48.

Table 48. Summary of the Applicant's Cure Rates by Treatment Group, Patients Valid for Efficacy at Return Visit 1

	Treatment Group				
	Miconazole Nitrate (1200 mg) Vaginal [redacted] N=111		MONISTAT® 7 (2% MCN) Vaginal Cream N=94		
Type of Cure	n	%	n	%	P-value*
Clinical	98	88.3	79	84.0	
Microbiological	88	79.3	76	80.9	
Therapeutic	82	73.9	68	72.3	0.92

* The Cochran-Mantel-Haenszel Test, stratified by investigator, was used to detect any difference between the treatment groups.

(Applicant's Table VII from Vol.1.9, p. 08-000315)

The Applicant calculated 95% confidence intervals to investigate the comparability of the cure rates for the two treatment groups. The differences in the point estimates and their 95% confidence intervals are presented below (Table 49).

Table 49. Difference in the Applicant's Return Visits 1 Cure Rates and 95% Confidence Intervals for Patients Evaluable for Efficacy at Return Visit1

Response	Point Estimate of the Difference in Cure Rates*	95% Confidence Limits of the Difference in Cure Rates*
Clinical	4%	(-5%, 14%)
Microbiological	-2%	(-13%, 9%)
Therapeutic	2%	(-11%, 14%)

*The difference is miconazole nitrate 1200 mg [redacted] minus MONISTAT®7

(Table adapted from the Applicant's data Vol. 1.9, p. 08-000354)

The point estimates of the difference in the clinical, microbiological, and therapeutic cure rates are contained within the 95% confidence interval and within the lower bound of the specified delta of -20%. Therefore, the Applicant's cure rates for clinical, microbiological, and therapeutic outcomes support that the two treatments produce statistically similar response rates at RV1.

MO Comment: The Statistical Reviewer Cheryl Dixon calculated confidence intervals with a continuity correction. Please see her review for the analyses. The conclusion regarding equivalence were unchanged using confidence intervals with a continuity correction.

The Applicant's overall clinical, microbiological, and therapeutic cure rates for patients evaluable for efficacy overall are presented in Table 50a.

Table 50a. Summary of the Applicant's Overall Cure Rates by Treatment Group, Patients Valid for Overall Efficacy

	Treatment Group				
	Miconazole Nitrate (1200 mg) Vaginal [redacted] N= 104		MONISTAT®7 Vaginal Cream N= 90		
Type of Cure	n	%	n	%	P-value*
Clinical	72	69.2	63	70.0	
Microbiological	72	69.2	62	68.9	
Therapeutic	64	61.5	55	61.1	0.78

* The Cochran-Mantel-Haenszel Test, stratified by investigator, was used to detect any difference between the treatment groups.

(Applicant's Table V, from Vol. 1.9, p. 08-000312)

In order to investigate the comparability in the overall clinical, microbiological, and therapeutic cure rates, the Applicant calculated 95% confidence intervals for the difference in the point estimates of the cure rates (Table 50b).

Table 50b. Difference in the Applicant's Overall Cure Rates and 95% Confidence Intervals for Patients Evaluable for Efficacy Overall

Response	Point Estimate of the Difference in Cure Rates*	95% Confidence Limits of the Difference in Cure Rates*
Clinical	−1%	(−14%, 12%)
Microbiological	0%	(−13%, 13%)
Therapeutic	0%	(−13%, 14%)

*The difference is miconazole nitrate 1200 mg [redacted] minus MONISTAT®7

(Table adapted from the Applicant's Table 13, Vol. 1.9, p. 08-000348)

The point estimate of the difference in the Applicant's overall clinical, microbiological, and therapeutic cure rates falls within the respective 95% confidence interval and is within the lower bound of −20% as specified by the delta. Therefore, the overall cure rates demonstrated statistical similarity between the treatment groups.

MO Comment: The Statistical Reviewer, Cheryl Dixon, performed a modified intent-to-treat (MITT) analysis in order to evaluate efficacy in a MITT population. The results of her MITT analysis found the 1200 mg [redacted] to be statistically similar to MONISTAT®7 with regards to clinical, microbiological, and therapeutic response rates overall (Table 51). Please see the Statistician's Review for details of the analysis.

Table 50a. Summary of the Applicant's Overall Cure Rates by Treatment Group, Patients Valid for Overall Efficacy

	Treatment Group				
	Miconazole Nitrate (1200 mg) Vaginal [redacted] N= 104		MONISTAT®7 Vaginal Cream N= 90		
Type of Cure	n	%	n	%	P-value*
Clinical	72	69.2	63	70.0	
Microbiological	72	69.2	62	68.9	
Therapeutic	64	61.5	55	61.1	0.78

* The Cochran-Mantel-Haenszel Test, stratified by investigator, was used to detect any difference between the treatment groups.

(Applicant's Table V, from Vol. 1.9, p. 08-000312)

In order to investigate the comparability in the overall clinical, microbiological, and therapeutic cure rates, the Applicant calculated 95% confidence intervals for the difference in the point estimates of the cure rates (Table 50b).

Table 50b. Difference in the Applicant's Overall Cure Rates and 95% Confidence Intervals for Patients Evaluable for Efficacy Overall

Response	Point Estimate of the Difference in Cure Rates*	95% Confidence Limits of the Difference in Cure Rates*
Clinical	−1%	(−14%, 12%)
Microbiological	0%	(−13%, 13%)
Therapeutic	0%	(−13%, 14%)

*The difference is miconazole nitrate 1200 mg [redacted] minus MONISTAT®7

(Table adapted from the Applicant's Table 13, Vol. 1.9, p. 08-000348)

The point estimate of the difference in the Applicant's overall clinical, microbiological, and therapeutic cure rates falls within the respective 95% confidence interval and is within the lower bound of −20% as specified by the delta. Therefore, the overall cure rates demonstrated statistical similarity between the treatment groups.

MO Comment: The Statistical Reviewer, Cheryl Dixon, performed a modified intent-to-treat (MITT) analysis in order to evaluate efficacy in a MITT population. The results of her MITT analysis found the 1200 mg [redacted] to be statistically similar to MONISTAT®7 with regards to clinical, microbiological, and therapeutic response rates overall (Table 51). Please see the Statistician's Review for details of the analysis.

Table 51. FDA Statistician's Overall Clinical, Microbiological, and Therapeutic Cure Rates by Modified Intent-to-Treat Analysis for Study 97-006

Type of Cure N (%)	1200 mg [redacted] N=120	M7C N=129	Corrected 95% CI
Clinical	76 (58%)	70 (57%)	(-13%, 13%)
Microbiological	78 (59%)	66 (54%)	(-8%, 18%)
Therapeutic	68 (52%)	59 (48%)	(-10%, 16%)

MO Efficacy Analysis

The MO performed an analysis to examine clinical, microbiological, and therapeutic efficacy in the subset of the Applicant's evaluable population whose visits occurred within the protocol specified visit windows or in a second analysis within ± 2 days of the protocol specified windows. The analyses were performed using the Applicant's assessments of cure, failure, and indeterminate. The following criteria were used to perform the analyses.

For the analysis of cure rates at RV1

1. A patient's RV1 must occur within Study Days 15-19, inclusive
2. If the patient was declared a failure prior to the specified RV1 window, the patient is included in the analysis as a failure.
3. If a patient's RV1 occurred after Study Day 19, the patient was not included in the analysis regardless of whether the patient was scored as cure, indeterminate, or failure.

For Analysis of overall cure rates

1. Patients must meet all of the above criteria for RV1
2. RV2 must occur within Study Days 35-43
3. Patients whose RV2 assessment occurred prior to the specified RV2 window and who were scored as failures were included in the analysis.
4. If a patient's RV2 occurred after Study Day 43, the patient was not included in the analysis regardless of whether the patient was scored as cure, indeterminate, or failure.

A second analysis was performed using the rules above but allowing the protocol specified RV1 and RV2 windows to be widened by ± 2 days.

The results of the MO's analyses are presented for the clinical, microbiological, and therapeutic (composite clinical and microbiological results) cure rates (Table 52a-c).

None of these additional covariables had a statistically significant effect on cure rate.

MO Comment: A total of 9 patients 65 years of age and older were enrolled in study 97-006 (1200 mg [redacted] (6), MONISTAT®7 (3)). The proportion of patients 65 years of age and older valid for overall efficacy classified as overall therapeutic cures was 2/4 in the 1200 mg ovule group and 1/2 in the MONISTAT®7 group.

The Applicant analyzed the secondary variable of time to relief of symptoms by examining

- days to relief of vulvovaginal itching and burning/irritation (days 1-8)
- proportion of patients reporting no itching and no burning at RV1
- proportion of patients who reported itching or burning at RV1, but no itching or burning at RV2
- proportion of patients who reported itching or burning at RV1 and data for RV2 missing
- proportion of patients who reported itching or burning at both RV1 and RV2
- proportion of patients who reported no itching or burning at Admission and RV1

The Applicant presents the following data for days to relief of itching and burning (Table 57). This endpoint is defined as the first day that relief is achieved for both itching and burning/irritation.

Table 57. Cumulative Days to Relief of Itching and Burning/Irritation, Patients Valid for Overall Efficacy

Group	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
[redacted]	14	41	51	58	63	66
N = 100	14.0%	41.0%	51.0%	58.0%	63.0%	66.0%
M7C	7	19	31	39	52	59
N = 85	8.2%	22.4%	36.5%	45.9%	61.2%	69.4%
* = patients exhibiting symptoms at admission						

(Applicant's Table VIII from Vol. 1.9, p. 08-000316)

The Applicant notes that the proportion of patients meeting the criteria for the relief of itching and burning when compared at Day 3 is significantly different between the two treatment groups ($p = 0.008$). The Applicant also notes that the median time to relief of symptoms is 3 days for the 1200 mg [redacted] and 4 days for MONISTAT®7.

MO Comment: The study was not designed to test hypotheses with regards to the secondary variable of time to relief of symptoms defined *post hoc*. These results should be interpreted with caution

Table 52a. MO's Clinical Cure Rates by Visit Window

Visit Window	Cure Rate by Treatment Group				Difference in Cure Rates	95% CI*
	1200 mg [redacted]		MONISTAT® Cream			
	n/N	%	n/N	%		
Cure Rate at RV1						
RV 1 (Day 15-19)	83/95	87	67/81	83	4	(-7, 16)
RV 1 ± 2 days (Day 13-21)	89/102	87	76/90	84	3	(-8, 14)
Overall Cure Rate						
RV 1 (Day 15-19) & RV 2 (Day 35-43)	51/67	76	46/62	74	2	(-15, 18)
RV 1 ± 2 days (Day 13-21) & RV 2 ± 2 days (Day 33-45)	60/79	76	54/71	76	0	(-15, 15)

Table 52b. MO's Microbiological Cure Rates by Visit Window

Visit Window	Cure Rate by Treatment Group				Difference in Cure Rates	95% CI*
	1200 mg [redacted]		MONISTAT® Cream			
	n/N	%	n/N	%		
Cure Rate at RV1						
RV 1 (Day 15-19)	75/96	78	64/81	79	-1	(-14, 12)
RV 1 ± 2 days (Day 13-21)	80/102	78	73/90	81	-3	(-15, 10)
Overall Cure Rate						
RV 1 (Day 15-19) & RV 2 (Day 35-43)	51/79	65	53/80	66	-1	(-18, 14)
RV 1 ± 2 days (Day 13-21) & RV 2 ± 2 days (Day 33-45)	58/88	66	47/74	64	2	(-14, 18)

Table 52c. MO's Therapeutic Cure Rates by Visit Window

Visit Window	Cure Rate by Treatment Group				Difference in Cure Rates	95% CI*
	1200 mg [redacted]		MONISTAT® Cream			
	n/N	%	n/N	%		
Cure Rate at RV1						
RV 1 (Day 15-19)	69/96	72	56/81	69	3	(-12, 17)
RV 1 ± 2 days (Day 13-21)	74/102	73	65/90	72	1	(-13, 14)
Overall Cure Rate						
RV 1 (Day 15-19) & RV 2 (Day 35-43)	46/82	56	41/73	56	0	(-17, 17)
RV 1 ± 2 days (Day 13-21) & RV 2 ± 2 days (Day 33-45)	53/91	58	48/82	59	-1	(-16, 16)

*The 95% confidence intervals with a continuity correction were calculated by the Agency's Statistical Reviewer, Dr. Cheryl Dixon.

MO Comment: The difference in the denominator at RV1 for the RV1 clinical cure rates is secondary to one patient who was declared a clinical cure and a microbiological and therapeutic failure prior to RV1. Hence, this patient is included as a failure in the microbiological and

therapeutic analyses but is not included in the clinical analysis. The differences in denominators at RV2 are secondary to failures being carried forward and patients who were discontinued after being declared failures at RV1. For example, a patient who was declared a microbiological failure and a clinical cure at RV1 would be scored as a microbiological and therapeutic failure at RV1, meets the criteria for discontinuation from study, and the microbiological and therapeutic failure scores would be carried forward to RV2. However, the cure determination at RV1 is not carried forward and the absence of an RV2 clinical assessment would not allow this patient to be included in the overall clinical response population because of the absence of a clinical outcome assessment at RV2.

The results of the MO's analyses finds the clinical, microbiological, and therapeutic cure rates statistically similar with the lower bound of the confidence interval within the delta of -20%. These analyses using the protocol specified windows for RV1 and RV2 corroborate the findings of the Applicant's efficacy analyses and support that the 1200 mg [redacted] (MONISTAT® DUAL-PAK) is therapeutically similar to its comparator (MONISTAT® 7 Vaginal Cream).

Recurrence Rates

The Applicant also investigated recurrence rates by examining the proportion of patients who developed clinical or microbiological evidence of VVC at RV2 who had previously been assessed as overall therapeutic cures at RV1 (Table 53).

Table 53. Recurrence Rates at Return Visit 2 for Patients Assessed as Overall Therapeutic Cures at Return Visit 1 (per Applicant).

Response Category	Recurrence Rate by Treatment Group			
	1200 mg [redacted] (N=75)		MONISTAT®7 Vaginal Cream (N=64)	
	(n/N)	(%)	(n/N)	(%)
Clinical	7/75	9.3	2/64	3.1
Microbiological	8/75	10.7	8/64	12.5
Therapeutic	11/75	14.6	9/64	14.1

(Table derived from the Applicant's Table VI, Vol. 1.9, p. 08-000314)

The overall recurrence rates are within the range of comparable values for the two treatment groups.

MO Comment: In the first study (96-002) the rates of clinical recurrence were 4.9% for the 1200 mg [redacted] and 10.3% for the MONISTAT®7 Vaginal Cream. In the current study (97-006) the

differences in clinical recurrence rates are reversed suggesting the difference observed is likely secondary to chance variation.

MO Comment: In this study (97-006) the organisms obtained on BiGGY culture were not speciated. Therefore, it is difficult to assess true relapse, the recurrence of the same organism as previously isolated. Similarly, without speciation it is not possible to determine if there are certain *Candida* spp. that were less responsive to therapy in this study.

The overall therapeutic cure rates by race were examined for each of the treatment groups (Table 54).

Table 54. Overall Therapeutic Cure Rate by Race (per Applicant)

Race	Overall Therapeutic Cure Rate			
	1200 mg [redacted] (N = 104)		MONISTAT®7 Vaginal Cream (N = 90)	
	n/N	%	n/N	%
Caucasian	42/70	60	41/68	60
Black	11/18	61	9/13	69
Hispanic	7/11	64	3/6	50
Other	4/5	80	2/3	67

(Adapted from the Applicant's table 9, Vol. 1.9, p. 08-000340)

The overall therapeutic cure rates for each of the treatment groups stratified by race are comparable to the overall therapeutic cure rates for the entire study (considering the small number of patients per race strata). The Applicant performed a CMH test for overall therapeutic cure rate by race stratified by treatment group and did not find a significant difference ($p = 0.831$).

The Applicant also analyzed overall therapeutic cure rates by disease severity (Table 55).

Table 55. Overall Therapeutic Cure Rate by Disease Severity (per Applicant)

Disease Severity	Overall Therapeutic Cure Rate			
	1200 mg [redacted] (N = 104)		MONISTAT®7 Vaginal Cream (N = 90)	
	n/N	%	n/N	%
Very Mild	0/1	0	0/1	0
Mild	46/73	63	35/62	57
Moderate	18/29	62	20/26	77
Severe	0/1	0	0/1	0

(Adapted from the Applicant's table 8, Vol. 1.9, p. 08-000339)

since they represent analyses defined *post hoc*. In addition, the comparison of multiple time points in the above *post hoc* analysis may lead to an inflated Type I error.

The findings noted for itching and burning involve subjective patient reported determinations. In the current trial patients were not blinded to the study medication. Therefore the potential for biased reporting of symptoms is a possibility in this single-blind study.

Given the variability as to the time of administration of the study medication, the time of recording of symptoms, and the subjectivity of the measure, one must question the precision of the methods employed to measure the transient finding cited.

Given that the study was not designed to assess time to relief of symptoms, the analysis of these secondary variables were defined *post hoc*, the multiple analyses performed may result in an elevated Type I error, the information that the Applicant presents should be interpreted with caution.

Microbiology

At the time of admission to the study patients were evaluated with a KOH smear and a BiGGY vaginal culture to confirm the presence of *Candida* sp. The culture isolates were not further speciated.

The results for microbiological response rates are included in the clinical section above.

MO Comment: Given the absence of information on speciation of the mycologic isolates, efficacy of the treatments with regards to particular *Candida* spp. cannot be performed.

Safety

All patients who received study medication and for whom safety data was available were analyzed for safety. A total of 9 (4 from the 1200 mg [redacted] arm and 5 from the MONISTAT® 7 arm of the study) of the 280 patients enrolled did not provide safety data. Two patients did not use the study medication (both in the 1200 mg [redacted] group) and 7 were lost to follow-up without providing any safety information.

In the patients evaluable for safety, satisfactory medication compliance was achieved in 96% (133/138) of the patients in the 1200 mg [redacted] group and 92% (123/133) of the patients in the MONISTAT® 7 arm of the study. The 5 patients who were assigned to the 1200 mg [redacted] were classified as non-