

on adverse experiences was collected. The patient diary card (used to record medication use, symptoms and/or adverse experiences) was also reviewed.

At the admission visit, patients were evaluated for symptoms, physical findings, and laboratory evidence of VVC. Patient symptoms were scored in the categories of

- vulvovaginal itching
- vulvovaginal burning or irritation
- unusual vaginal discharge

A complete gynecologic exam (speculum and bimanual) were performed to assess the physical findings of

- vulvar erythema
- vulvar edema
- vulvar excoriation
- vaginal erythema
- vaginal edema
- other abnormal pelvic findings

Each of the above symptoms and physical findings (excluding other abnormal pelvic findings) were scored on a scale of 1-4 (1 = none, 2 = mild, 3 = moderate, and 4 = severe).

Subjects also underwent laboratory testing to determine eligibility and evaluability. A positive 10% KOH smear for yeast was required for study entry. Patients were also required to have a culture positive for *Candida* species (taken at admission) in order to be evaluable. Other tests used to determine eligibility included a negative pregnancy test, a negative wet mount for *Trichomonas vaginalis* and clue cells, a negative test for *N. gonorrhoeae*, and a Papinicolaou smear with no evidence of carcinoma in-situ or worse noted.

The clinical supply lot number of the ovule used in the study was CS96-075. This lot of [redacted] was manufactured by [redacted]. The formula is the same as [redacted] a product currently marketed in Europe.

The clinical supply lot number of the MONISTAT® External Vulvar Cream packaged with the 1200 mg [redacted] was CS95-031.

The clinical supply lot number for the MONISTAT® 7 vaginal cream was CS96-068.

The study compared the MONISTAT® DUAL-PAK to MONISTAT®7 vaginal cream in prefilled applicators. The MONISTAT® DUAL-PAK® consists of one MONISTAT® (miconazole nitrate 1200 mg) soft gel vaginal insert and MONISTAT® (miconazole nitrate 2%) external vulvar cream. The soft gel vaginal insert is used as a one-time dose for the treatment of VVC. The accompanying external vulvar cream can be applied twice daily as needed for up to 7 days for the treatment of involved external vulvar tissue. The comparator, MONISTAT®7, cream in prefilled applicators, contains 100 mg of miconazole nitrate (2%) per 5 gram dose. The applicators are used once daily for 7 days for the treatment of VVC. The MONISTAT®7 comparator is a commercially available over-the-counter (OTC) formulation.

MO Comment: The use of a standard 7-day regimen is in accordance with the recommendations of the aforementioned 1992 IDSA/FDA guidelines (McCutchan, 1992).

Eligible subjects were randomized based on a randomization schedule provided by ACP. The study was designed as an investigator-blind study. However, no attempt was made to maintain the blind after medication had been dispensed.

MO Comment: The single-blind as defined in the study protocol was maintained only until medication was dispensed. Thereafter, no further attempt was made to maintain the investigator-blind (single-blind). The lack of investigator and patient blinding beyond the time of medication dispensing could allow for the introduction of bias, particularly in the case of subjective measurements. A placebo medication was not used because of the potential interference of administering a second intravaginal product. The decision to not use a placebo is in agreement with the Agency's Draft Guidance for Industry, Vulvovaginal Candidiasis — Developing Antimicrobial Drugs for Treatment.

Patients were instructed to follow the instructions provided with the medication. Medication use and symptoms were recorded by patients through Return Visit 2. Patients were also instructed to refrain from intercourse and using intravaginal products for the duration of the study.

At each of the return visits, patients were evaluated for symptoms and physical findings (including a complete gynecologic exam) of VVC. Laboratory tests performed included a 10% KOH wet mount for yeast, a culture for *Candida* spp., and a wet mount to exclude *T. vaginalis* and clue cells.

A schematic of the study procedures is presented in Table 7.

Table 7. Schematic of Study Procedures

Procedure	Admission (Day 1)	Return Visit 1 (Day 15-19)	Return Visit 2 (Day 35-43)
Medical history	X		
Gynecologic examination	X	X	X
Evaluation of signs and symptoms	X	X	X
KOH preparation	X	X	X
BiGGY culture for <i>Candida</i> species	X	X	X
Wet mount for <i>T. vaginalis</i> and clue cells	X	X	X
Test for <i>Neisseria gonorrhoeae</i>	X		
PAP smear	X		
Pregnancy test	X		
Review concurrent medication use	X	X	X
Drug administration 1200 mg ovule MONISTAT® Cream	X(Day 1) X(Day 1-7)		
Dispense/review/collect diary card	X	X	X
Diary card completion by patient (daily)	X	X	X
Adverse experiences		X	X

(Adapted from the Applicant's Figure 1, Vol. 1.9, p. 08-000192)

Patients were discontinued from the study protocol for the following reasons:

- Clinically significant adverse experiences
- Patient request
- Screen failures due to
 - negative culture results for *Candida* species at admission
 - PAP smear at admission shows dysplasia or more advanced disease
 - positive test for *Neisseria gonorrhoeae*
- Validity compromised due to the Papanicolaou smear taken at admission shows presence of another condition which requires treatment
- Protocol violation, including but not limited to, treatment with an anti-infective, vulvovaginal therapeutic, douche, feminine spray or experimental drug/device
- Patient develops another vulvovaginal infection at Return Visit 1 from a pathogen other than *Candida* species and requires treatment for this infection.

- Treatment failure as evidenced by one of the following:
 - no improvement of clinical signs or symptoms of the vulvovaginal infection at first return visit
 - positive KOH prep for yeast at first return visit
 - positive culture result for *Candida* species at first return visit

At the time of study discontinuation patients underwent an evaluation that included a gynecologic examination and completing a study discontinuation/completion form.

The Applicant notes the following patients were included in the study although they did not meet all of the inclusion and exclusion criteria ("minor deviations").

- Patient 00305 (M 1200) used condoms as a means of contraception
- Patient 00313 (M7C) used no contraception and was less than one year post-menopausal
- Patient 01204 (M1200) had a missing test for *Neisseria gonorrhoeae*

MO Comment: Queries of the Applicant's database demonstrate that patients 00305 and 00313 are the only two patients in the study who do not meet the criteria for contraceptive method used during the study. The lack of use of one of the specified methods of contraception in these two patients should not have a significant effect on the efficacy results. The protocol notes that patients will be instructed to refrain from intercourse during the study period and that if intercourse is anticipated that the condoms provided to study participants should be used. In the event that condoms are not used the protocol notes that this will not be grounds for discontinuation.

MO Comment: The Applicant's protocol-specified discontinuation criteria states that patients with a positive culture for *Neisseria gonorrhoeae* meet the criteria for discontinuation. The clinical report further defines this criteria and allows patients with missing culture results to remain in the study. Patient 01204 was the only patient in the study missing a culture for *Neisseria gonorrhoeae*. The remaining 277 patients in the study all had negative cultures for *N. gonorrhoeae*. Given the lack of positive cultures for *N. gonorrhoeae* in the study population, the effect of including the one patient with a missing culture for *N. gonorrhoeae* should be minimal.

Safety information was collected from follow-up evaluations and the patient diary. The patient diary cards were reviewed at each of the return visits. Adverse experiences were evaluated in terms of relationship to the study drug (not related, unlikely, possible, probable, highly probable) and the severity of the event (mild, moderate, and severe). The study compared the number, type, and severity of adverse experiences between the two treatment arms of the study.

Evaluability criteria (as per the Applicant)

Efficacy

In order to be evaluable for efficacy, a patient must meet the following criteria

- inclusion and exclusion criteria must be satisfied at the time of admission
- patients must have a BiGGY culture positive for *Candida* sp. at the time of admission
- medication must be started within 2 days of admission
 - patients using the ovule must insert the [REDACTED] correctly
 - patients using MONISTAT® 7 cream must insert the cream appropriately and must use 6 to 7 doses over 6 to 8 days – patients could not skip more than one day of study medication
- patients must return for both Return Visits 1 and 2 unless the patient is discontinued as a failure at an earlier point in time
- patients must not develop another vulvovaginal infection during the study
- patients must not use systemic antibiotics, vulvovaginal drugs, or other investigational drugs during the study
- patients must not use tampons between admission and Return Visit 1
- patients must have complete clinical and microbiological data at both return visits unless the patient is found to be a failure
- Return Visit 1 must occur within 60 days after therapy and cannot be an overall therapeutic failure
- Return Visit 2 must not occur less than 20 days after therapy is completed and the overall therapeutic response is a cure
- Return Visit 2 must not occur more than 60 days after therapy is completed if the patient was not a failure at Return Visit 1 and was a failure at Return Visit 2

MO Comment: The evaluability criteria are only partially specified in the study protocol. The complete listing of the evaluability criteria for efficacy are in the study report.

Ideally a complete listing of the evaluability criteria would have been specified in the study protocol.

The Applicant widened the allowable visit windows for RV1 and RV2 compared with the protocol specified windows. The MO performed an additional efficacy analysis using the protocol specified visit windows to assess the effects of the Applicant's widening of the allowable visit windows (see MO Efficacy Analyses p.38).

Other than the noted concern regarding the Applicant's widening of the allowable visit windows, the evaluability criteria as stated above are acceptable.

Safety

All patients who used at least a single dose of the study medication and provided safety information to the investigator were valid for the safety analysis. Therefore, the only reasons for non-evaluability for safety are not using the study medication or being lost to follow-up after admission.

Endpoints defined

Efficacy

The protocol defined efficacy parameters include clinical, microbiological, and therapeutic cure rates of vulvovaginal candidiasis at Return Visits 1 and 2. A third category of "overall" clinical, microbiological, and therapeutic response was determined by combining the results from the RV1 and RV2 efficacy parameters. The study report provides additional description as to how clinical, microbiological, and therapeutic cures are determined.

MO Comment: The protocol does not provide detailed definitions for clinical, microbiological, or therapeutic cure. The detailed definitions of endpoints are presented in the study report. The definitions as provided in the study report are similar to those provided in the Agency's Draft Guidance, Vulvovaginal Candidiasis — Developing Antimicrobial Drugs for Treatment, US DHHS, FDA, CDER, July 1998.

The principle criterion of response was therapeutic cure, which is a composite endpoint of both clinical and microbiological response. The combined endpoint was scored as the least favorable outcome of all of its constituents. The table below provides the schema for the composite endpoint of "therapeutic cure" (Table 8).

Table 8. Determination of Therapeutic Cure

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

(Applicant's Table I from Vol., 1.9, page 08-000198)

Within the categories of clinical or microbiological response, if any data was missing within the category and the patient was otherwise considered a cure, the response of the respective category was indeterminate. In the case where only partial data was collected but the patient would otherwise be classified as failure, the patient would be classified as failure.

The clinical response criteria considered the severity of the patient's disease at enrollment in specifying the required degree of improvement at each of the return visits. The clinical score was composed of the sum of 7 clinical signs or symptoms each scored from 1 to 4 (1 = none, 2 = mild, 3 = moderate, 4 = severe). The table below provides the required degree of improvement in a patient's clinical score at each of the return visits based on the severity of disease at admission (baseline) (Table 9).

Table 9. Maximum Sum of Scores at RV1 and RV2 for Clinical Cure

Disease Severity Group At Baseline	Sum of Signs and Symptoms At Baseline	Maximum Sum of Signs and Symptoms for Clinical Improvement or Cure	
		RV1	RV2
Very Mild	8	7	7
Mild	9-14	8	8
Moderate	15-20	10	8
Severe	21 or more	15	8

(Applicant's Table II from Vol. 1.9, p. 08-000200)

The microbiological response criteria were scored as "cure" (no yeast on the KOH smear and culture negative for *Candida* sp.) or "failure" (yeast on the KOH smear or *Candida* sp. on culture). The category

of "indeterminate" was assigned if the microbiological data for a visit was incomplete and if none of the available microbiological data (if any) demonstrated findings consistent with the presence of *Candida* sp.

Efficacy assessments were made at both Return Visit 1 (RV1) and Return Visit 2 (RV2). The assessments made at RV1 and RV2 were combined to determine "overall" response. The overall clinical, microbiological, and therapeutic responses were designated as the least favorable response from either of the 2 return visit assessments. For example, if either assessment was failure the overall response was failure. If one of the responses was indeterminate and the other was cure, the overall response was indeterminate. The assessment of cure was required at both return visits to attain an overall assessment of "cure."

MO Comment: The Applicant's endpoint definitions for efficacy are acceptable. The endpoints are defined in a manner that is similar to the recommendations of the Agency's Draft Guidance, Vulvovaginal Candidiasis — Developing Antimicrobial Drugs for Treatment, US DHHS, FDA, CDER, July 1998. (The Draft Guidance would not have been available at the time the Applicant's studies were being designed.)

Safety

All patients who used at least 1 dose of study medication and provided safety information were evaluable for safety. Information on adverse experiences was obtained by both questioning and examining the study participants. The protocol required that any new or continuing adverse experiences not present at the time of admission must be recorded. The protocol also required that any baseline medical condition that deteriorated during the study should be recorded as a new adverse experience.

Adverse events were assessed by the investigator in the following 4 categories:

- severity — mild, moderate, severe, serious
- cause — probability of relationship to study medication
- actions taken to manage the adverse event
- outcome of the adverse event

The protocol defines a serious adverse experience as any experience that is fatal or life-threatening, permanently disabling, requires or prolongs hospitalization, is a congenital anomaly, cancer, or causes

an overdose. Rates for adverse events were compared for the two treatment arms of the study.

Statistical Considerations

The study had a targeted enrollment of 276 patients. The sample size was determined using the following criteria and assumptions. The study was designed to detect a 20% difference in the cure rates of the two groups with a power of 80% at an alpha level of 0.05 assuming a 63% cure rate. The sample estimates were further adjusted to allow for a 33% drop-out rate. The result is a sample estimate of 138 patients per treatment group. The Applicant enrolled a total of 278 patients in the study (140 1200 mg insert, 138 MONISTAT®7).

MO Comment: Please see Dr. Cheryl Dixon's Biostatistical Review.

The protocol provides the following description of proposed statistical procedures:

The objective of the statistical analysis of efficacy is to examine the cure rates for comparability between the vaginal [redacted] (1200 mg) group and the MONISTAT® 7 Vaginal Cream group. The 95% confidence intervals will be constructed for the difference in clinical, microbiological and therapeutic cure rates, between each of the vaginal [redacted] group (1200 mg) and MONISTAT® 7 Vaginal Cream group.

Safety evaluations will be based on the incidence and type of adverse experiences. The proportions of patients experiencing at least one adverse experience and the proportion of patients experiencing a given type of adverse experience will be compared.

The study report provides additional details with regards to the statistical analysis plan for efficacy. The report states the null hypothesis as the equivalence of therapeutic cure rates between the 1200 mg vaginal [redacted] and MONISTAT®7 cream and the two-sided alternate hypothesis that the cure rates are not equal. Confidence intervals (80%, 90%, and 95%) based on the normal distribution were used to assess the equivalence of the two groups. The therapeutic cure rates and days to symptomatic relief were compared for the two treatment groups using the Cochran-Mantel-Haenszel test.

Comparability of baseline variables of age and oral contraceptive use for the two treatment groups was assessed using either a T-test or a

Fisher's Exact Test (two-tailed). The variables of race, intercourse, and condom use were analyzed using the chi-square test. Covariables influencing treatment response were identified using the Cochran-Mantel-Haenszel Test or its generalization. The data were stratified by treatment group in order to assess the effects of the covariables on the therapeutic cure rates. An alpha level of 0.10 was used in these testing procedures. For any covariable demonstrating significance at the $\alpha = 0.05$ level, the data for overall therapeutic cure rates were stratified and cure rates between the two treatment groups were compared.

The data for the therapeutic cure rates for each of the two treatment groups at RV1 and overall were stratified by investigator and compared using the Cochran-Mantel-Haenszel Test. Norton's Test was performed to test for interaction between investigator and treatment response.

The study report also describes a secondary response variable of days to relief of vulvovaginal itching and burning/irritation. The variable was computed by calculating the difference in the date of symptom relief and the date that study medication was initiated. The cumulative percent of patients experiencing relief of symptoms was calculated and the distribution of days to relief were compared between the two treatment groups. The median time to relief of symptoms and the cumulative percent of patients experiencing relief of symptoms at 3 and 7 days were determined. The proportion of patients in the following categories were also calculated:

- reported no itching and no burning at Return Visit 1 (relief date unknown)
- reported itching or burning at Return Visit 1, but no itching or burning at Return Visit 2
- reported itching or burning at Return Visit 1 (data missing at Return Visit 2)
- reported itching or burning at both Return Visits 1 and 2
- reported no itching or burning at Admission and Return Visit 1.

The number of patients satisfying the criteria for the secondary response variables were compared between the two treatment groups using two-tailed Fisher's Exact Tests.

MO Comment: The results from analyses of secondary response variables defined *post-hoc* should be interpreted with caution. Similarly, the results of multiple comparisons should take into consideration the effect of multiple comparison bias.

MO Comment: The clinical study as designed should allow for a meaningful comparison of the safety and efficacy of the 1200 mg [redacted] with MONISTAT® 7. Other than the caution noted above and the Applicant's widening of the allowable visit windows, the reviewer agrees with the design and conduct of the study as presented by the Applicant.

Study Results

Demographics

Comparison of the age and race distributions for the two treatment groups are provided in Table 10.

Table 10. Baseline Demographics, Age and Race, by Treatment Group in The Population of Patients Valid for Safety

Characteristic	Treatment Group			
	1200 mg [redacted]		MONISTAT® 7	
Age (yrs.)				
Mean	34.1		32.4	
Range	18-79		18-70	
Standard Deviation	12.4		12.7	
Race	n/N	(%)	n/N	(%)
White	79/134	(59.0)	80/132	(60.6)
Black	18/134	(13.4)	22/132	(16.7)
Hispanic	31/134	(23.1)	23/132	(17.4)
Other	6/134	(4.5)	7/132	(5.3)
Oral contraceptive use	52/134	(38.8)	46/132	(34.8)

(adapted from data presented in the Applicant's table 3a p. 08-000228)

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 demographic 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 11).

Table 11. Disease Severity at Admission by Treatment Group in the Population of Patients Valid for Safety

Disease Severity	Treatment Group			
	1200 mg Ovule		MONISTAT® 7	
	n/N	(%)	n/N	(%)
Very mild	6/134	(4.5)	2/132	(1.5)
Mild	76/134	(56.7)	71/132	(53.8)
Moderate	46/134	(34.3)	50/132	(37.9)
Severe	6/134	(4.5)	9/132	(6.8)

(adapted from data provided in the Applicant's table 3a, p. 08-000228)

The distribution of disease severity is similar in each of the treatment groups. Table 11 provides data on the valid for safety patient population. Similar results were found in the valid for efficacy population.

Evaluability

A total of 278 patients were enrolled in the study (140 in the 1200 mg [REDACTED] arm and 138 in the MONISTAT® 7 arm). All but 12 patients were evaluable for safety (6 patients from each group). One of the 12 did not use the study medication and 11 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 12 below provides the number of patients in the evaluable populations.

Table 12. Summary of Patient Evaluability by Treatment Group

Evaluability	MCN (1200 mg) Vaginal [REDACTED]		MONISTAT® 7 (2% MCN) Vaginal Cream		TOTAL	
	n	%	n	%	n	%
Total enrolled	140		138		278	
Evaluable for safety	134	95.7	132	95.7	266	95.7
Evaluable for RV1 efficacy	107	76.4	100	72.5	207	74.5
Evaluable for overall efficacy	99	70.7	97	70.3	196	70.5

(Applicant's table IV from Vol. 1.9, p 08-000204)

The reasons that patients were non-evaluable are shown in Table 13. 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 use of prohibited medication, improper use of study medication, did not return for Return Visits 1 and 2, and tampon use.

MO Comment: Regarding the category designated as "negative or missing KOH smear or BiGGY culture for *Candida* species 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. (This patient was also lost to follow-up and is scored under the lost to follow-up category in the Applicant's hierarchical scheme of scoring primary reason for discontinuation.) Therefore the category of "negative or missing KOH smear or BiGGY culture for *Candida* species on admission" represents patients who had negative BiGGY cultures at admission.

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Table 13. Primary Reason for Non-Evaluability by Treatment Arm

Primary Reason for Non-Evaluability	Treatment			
	1200 mg [REDACTED] (N = 140)*		MONISTAT® 7 (N = 138)*	
	n	(%)	n	(%)
Did not use study medication	1	0.7	0	0.0
Lost to follow-up after admission	5	3.6	6	4.3
Total non-evaluable for safety	6	4.3	6	4.3
Failed non-diagnostic entrance criteria	1	0.7	0	0.0
Negative or missing smear or culture for <i>Candida</i> sp. on admission	17	12.1	8	5.8
Did not return for visit 1 and 2	1	0.7	1	0.7
Time to study medication delayed from admission**	5	3.6	2	1.4
Used study medication incorrectly**	0	0.0	6	4.3
Developed other vaginal infection between admission and return visit 1	1	0.7	1	0.7
Used other vulvovaginal drugs, systemic antibiotics or investigational drugs between admission and return visit 1	2	1.4	8	5.8
Used tampon during study	0	0.0	5	3.6
Missing microbiological data at return visit 1	0	0.0	1	0.7
Total non-evaluable for efficacy return visit 1	33	23.6	38	12.7
Did not return for return visit 2	3	2.1	1	0.7
Developed other vaginal infection between return visit 1 and return visit 2	0	0.0	1	0.7
Used other vulvovaginal drugs, systemic antibiotics or investigational drugs between return visit 1 and return visit 2	4	2.9	1	0.7
Missing clinical data at return visit 2	1	0.7	0	0.0
Total non-evaluable for efficacy overall	41	29.3	41	29.7

(Applicant's Table 2c from Vol. 1.9, p. 08-000226 and 08-000227)

* 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, two 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, patient 604 was non-compliant but also had a negative culture at admission and is therefore listed as "Negative or missing smear or culture for *Candida* sp." Another patient in the 1200 mg [REDACTED] arm, patient 414 was non-compliant with study medication but also did not return for return visits 1 and 2 and therefore her primary reason for non-evaluability is "Did not return for visit 1 and 2." Similarly, two patients in the MONISTAT® 7 arm were non-compliant with study medication use but had another primary reason for non-evaluability; patient 501 had a negative culture for *Candida* sp. at admission and patient 910 did not return for return visit 1 and return visit 2. Hence, the number of patients compliant with medication in the evaluable for safety population was 127/134 (95%) for the 1200 mg [REDACTED] and 122/132 (92%) for MONISTAT®7.

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 1200 mg [] arm of the study. The distribution of disease severity in the population of patients evaluable for safety is similar in the 2 treatment arms suggesting the increased number of negative BiGGY cultures in the 1200 mg [] arm may be a chance occurrence (see Table 11).

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Evaluability by investigator

The rates of evaluability at each study center for Return Visit 1 (RV 1) and Return Visit 2 (RV 2) are presented in Tables 14 and 15 below.

Table 14. Evaluability for Efficacy by Study Center at Return Visit 1
(According to the Applicant's Evaluability Criteria)

Investigator ID	Investigator #	Treatment Group					
		1200 mg Ovule			MONISTAT®7 Vaginal Cream		
		Enrolled (N)	Evaluable at RV1 (n) (n/N%)		Enrolled (N)	Evaluable at RV1 (n) (n/N%)	
Caplan	1140-1	14	8	57	16	11	69
Chichester	1092-1	7	6	86	7	5	71
Henry	1090-1	12	6	50	12	5	42
Martin/Bradley	1014-1	12	11	92	12	9	75
Maxwell	1072-1	12	10	83	14	9	64
Patrick	1119-1	12	12	100	13	12	92
Reisman	1011-1	5	5	100	6	5	83
Riffer	1093-1	12	5	42	12	10	83
Rodriguez	1147-1	13	12	92	11	10	91
Schnepper	1136-1	13	11	85	11	8	73
Sideropoulos	1141-1	8	5	63	9	5	56
Sperling	1091-1	17	13	77	13	10	77
Weinstein	1117-1	3	3	100	2	1	50
Total		140	107	76	138	100	73

(Table derived from the Applicant's data Vol. 1.9, p. 08-000224)

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Table 15. Evaluability for Efficacy by Study Center at Return Visit 2
(According to the Applicant's Evaluability Criteria)

Investigator ID	Investigator #	Treatment Group					
		1200 mg			MONISTAT®7 Vaginal Cream		
		Enrolled (N)	Evaluable at RV2 (n) (n/N%)		Enrolled (N)	Evaluable at RV2 (n) (n/N%)	
Caplan	1140-1	14	8	57	16	10	63
Chichester	1092-1	7	5	71	7	5	71
Henry	1090-1	12	5	42	12	4	33
Martin/Bradley	1014-1	12	10	83	12	9	75
Maxwell	1072-1	12	9	75	14	9	64
Patrick	1119-1	12	11	92	13	11	85
Reisman	1011-1	5	5	100	6	5	83
Riffer	1093-1	12	5	42	12	10	83
Rodriguez	1147-1	13	11	85	11	10	91
Schnepper	1136-1	13	10	77	11	8	73
Sideropoulos	1141-1	8	4	50	9	5	56
Sperling	1091-1	17	13	77	13	10	77
Weinstein	1117-1	3	3	100	2	1	50
Total		140	99	71	138	97	70

(An additional investigator, Theodore Blackwelder, MD of Tempe, AZ, was shipped study medication but enrolled no patients.)

(Table derived from the Applicant's data Vol. 1:9, p. 08-000224)

MO Comment: While there is some variation in the percentage of patients evaluability 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 cause question as to the validity of the data.

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Discontinuation

The proportion of patients discontinued from the study along with the primary reason for study discontinuation are presented in Table 16 below.

Table 16. 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 = 140)		MONISTAT [®] 7 (2% MCN) Vaginal Cream (N = 138)	
	n	%	n	%
Screening failure ψ	18	12.9	9	6.5
Treatment failure	14	10.0	11	8.0
Lost to follow-up	7	5.0	5	3.6
Protocol violation**	5	3.6	4	2.9
Adverse experience	2	1.4	2	1.4
Developed another infection requiring treatment*	3	2.1	0	0.0
Patient request due to no improvement in symptoms prior to RV1	1	0.7	2	1.4
Other	1	0.7	2	1.4
Total Number of Patients Discontinued	51	36.4	35	25.4
Total Number of Patients Completing Study	89	63.6	103	74.6

(Applicant's Table III from Vol. 1.9, p. 08-000203)

ψ The primary reasons for screening failures were as follows:

- Pt. No. 1516 (randomized to MONISTAT[®] 7) had a negative KOH smear and a negative BiGGY culture at admission.
- All of the other patients classified as screening failures had positive KOH smears and negative BiGGY cultures at admission.

* The three patients with "Developed another infection..." as their primary reason for discontinuation developed the following infections:

- Pt. No. 401, Treated for bacterial vaginosis with metronidazole at RV1
- Pt. No. 502, The patient was noted to have clue cells at RV1
- Pt. No. 1411, Developed a urinary tract infection and was treated with an antibiotic

** Table 17. provides a description of the protocol violations that resulted in discontinuation from the study.

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Table 17. Description of Protocol Violations as the Primary Reason for Study Discontinuation by Treatment Group

Description of Protocol Violation	Treatment			
	1200 mg N = 5		MONISTAT®7 N = 4	
	n	%	n	%
Received an oral antibacterial medication	4	80	3	75
Used an intravaginal therapeutic (not an anti-infective)	0	0	1	25
Had a history of a vaginal yeast infection not clearing with proper therapy	1	20	0	0

MO Comment: There is no apparent bias exhibited by the tabulations of primary reasons for discontinuation. The excess of screening failures is addressed above under the heading of evaluability.

MO Comment: Patients who are discontinued from the study because of treatment failure remain in the evaluable for efficacy population (scored as failures and observations are carried forward as failures). Hence, the total number of patients completing the study may be less than the total number of patients valid overall for efficacy, because patients discontinued for treatment failure remain evaluable unless there are other reason for the patient to be non-evaluable.

Efficacy

The study was designed to compare the clinical, microbiological, and therapeutic response of patients treated with the 1200 mg soft gel vaginal insert 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). In the study report, the Applicant also provides additional information with regards to an analysis to investigate 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 18). 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 38 of this report.

Table 18. Proportion of Patient Assessments within Varying Windows for RV1 and RV2.

Visit Window	Treatment Group			
	1200 mg ██████ n/N	%	MONISTAT®7 Cream n/N	%
RV1 (Day 15-19)	90/107*	84	91/100*	91
cure < 15 days	2		1	
cure > 19 days	12		7	
failure > 19 days	3		1	
RV1 ± 2 days (Day 13-21)	104/107*	97	98/100*	98
cure > 21 days	2		2	
failure > 21 days	1		0	
RV2 (Day 35-43)	79/88**	90	82/91**	90
cure < 35 days	2		2	
cure > 43 days	3		4	
failure < 35 days	2		3	
failure > 43 days	2		0	
RV2 ± 2 days (Day 33-45)	83/88**	94	86/91**	95
cure < 33 days	1		0	
cure > 45 days	1		2	
failure < 33 days	2		3	
failure > 45 days	1		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 19.

Table 19. Summary of the Applicant's Cure Rates by Treatment Group, Patients Valid for Efficacy at Return Visit 1

Type of Cure	Treatment Group				P-value*
	Miconazole Nitrate (1200 mg) Vaginal [REDACTED] N=107		MONISTAT® 7 (2% MCN) Vaginal Cream N=100		
	n	%	n	%	
Clinical	99	92.5	97	97.0	0.20
Microbiological	94	87.9	92	92.0	
Therapeutic	90	84.1	90	90.0	

* 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. 08-000209)

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 20. Difference in the Applicant's Return Visit 1 Cure Rates and 95% Confidence Intervals for Patients Evaluable for Efficacy at Return Visit 1

Response	Point Estimate of the Difference in Cure Rates*	95% Confidence Limits of the Difference in Cure Rates*
Clinical	-4%	(-10%, 2%)
Microbiological	-4%	(-12%, 4%)
Therapeutic	-6%	(-15%, 3%)

*The difference is miconazole nitrate 1200 mg [REDACTED] minus MONISTAT®7
(Table adapted from the Applicant's data Vol. 1.9, p. 08-000249)

The point estimate of the differences in the Applicant's overall clinical, microbiological, and therapeutic cure rates are contained within their respective 95% confidence interval and are all within the lower bound of -20% as specified by the delta. Therefore, the Applicant's clinical, microbiological, and therapeutic cure rates for the two treatment groups support that the two treatments are therapeutically similar 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.