compliant because of delaying the start of therapy more than 2 days (2) and not recording that the study medication had been administered (3). The 10 patients using MONISTAT®7 were classified as non-compliant because they used an unknown number of doses or days of therapy (2), used less than 6 days of therapy (5), or delayed the start of therapy more than 2 days (4) (Pt. Number 1703 used less than 6 doses and delayed therapy more than 2 days). The Applicant found that the difference in rates of compliance was not statistically significant (p=0.19).

The total number of adverse events reported were 253 in 91 out of the 138 (66%) patients in the 1200 mg [redacted] group and 231 in 86 out of the 133 patients (45%) in the MONISTAT® 7 arm.

The Applicant tabulated the body systems with the highest incidences of adverse experiences, frequently occurring adverse experiences, and adverse experiences reported by 2% to 5% of patients. The tables are presented below.

Table 58. Body Systems with the Highest Incidence of Adverse Experiences, All Causality (Greater than 10% in Either Treatment Group)

	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 138)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 133)	
Body System	n	%	n	%
Genital/reproductive system	**63**	**45.7**	**63**	**47.4**
Nervous system	**19**	**13.8**	**18**	**13.5**
Respiratory system	**15**	**10.9**	**9**	**6.8**
Gastrointestinal system	**14**	**10.1**	**9**	**6.8**

(Applicant's Table IX from Vol. 1.9, p. 08-000317

The rates of adverse experiences in the genital/reproductive and nervous system are similar for the 2 treatment groups. A greater number of patients reported respiratory and gastrointestinal adverse experiences in the 1200 mg [redacted] arm of the study. The Applicant tabulated adverse experiences by primary term to further investigate the individual adverse experiences. Table 59 shows the adverse experiences reported in more than 5% of patients.

Table 59. Most Frequently Reported Adverse Experiences by Primary Term, All Causality (Greater than 5% in Either Treatment Group)

Adverse Experience	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 138)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 133)	
	n	%	n	%
Burning, female genitalia	39	28.3	34	25.6
Irritation, female genitalia	34	24.6	31	23.3
Pruritus, external female genitalia	22	15.9	36	27.1
Headache	17	12.3	18	13.5
Erythema, female genitalia	10	7.2	13	9.8
Discharge, female genitalia	12	8.7	8	6.0
Edema, female genitalia	7	5.1	6	4.5
Pharyngitis	7	5.1	4	3.0
Infection, urinary tract	7	5.1	0	0.0

(Applicant's Table X from Vol. 1.9, p. 08-000318)

Slightly higher rates of burning and irritation of the female genitalia, discharge, urinary tract infection, and pharyngitis were observed in the 1200 mg [redacted] arm of the study. Patients in the MONISTAT®7 arm reported genital pruritus and genital erythema more frequently.

The Applicant's rates of adverse experiences for the urinary system from Study 97-006 are shown in Table 60.

Table 60. Adverse Experiences Involving the Urinary System

Adverse Experience	Treatment Group Study 97-006			
	1200 mg Vaginal [redacted] (N = 138)		MONISTAT® 7 (N = 133)	
	n/N	%	n/N	%
Dysuria	1/138	0.7	1/133	0.8
Infection, Urinary Tract	7/138	5.1	0/133	0.0
Cystitis	0/138	0.0	1/133	0.8
Urethritis	0/138	0.0	1/133	0.8

(Results summarized from the Applicant's Appendices 7 & 8)

MO Comment: The Medical Officer reviewed the classification of urinary adverse experiences in order to investigate the excess of urinary tract infections reported in the 1200 mg [redacted] arm. The medical officer agreed with the 7 patients classified as having a UTI on the 1200 mg [redacted] arm of the study. One patient in the MONISTAT®7 arm of the study with the adverse event of cystitis (Pt. No. 1303) was treated with Nitrofurantion and was therefore considered to have a UTI. Thus the number of UTIs in each of the study arms was 7 for the 1200 mg [redacted] and 1 for MONISTAT®7 Vaginal Cream.

MO Comment: The adverse experiences involving the urinary system in study 96-002 do not corroborate the findings regarding urinary tract infection from study 97-006. Given that the comparative rates of urinary tract infection in study 97-006 is one of multiple comparisons of adverse experience rates, the possibility of an elevated type I error must be considered. The lack of corroboration with the companion study (96-002) suggests that the elevated rate of urinary tract infection may be a chance occurrence detected in the setting of multiple comparisons.

The rigor of the diagnostic criteria employed for UTI is not specifically stated. Given that patients may experience dysuria as a component of VVC, the clinical diagnosis of UTI could be confounded. Evidence of microbiological confirmation of these diagnoses is not provided.

The Applicant tabulated adverse experiences reported by 2 to 5% of patients (Table 61).

Table 61. Adverse Experience Reported by 2 to 5% of Patients (by Primary Term)

	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 138)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 133)	
Adverse Experience	n	%	n	%
Dysmenorrhea	6	4.3	4	3.0
Cramps, GI	5	3.6	3	2.3
Excoriation/abrasion, female genitalia	2	1.4	6	4.5
Pain, trunk	2	1.4	5	3.8
Sinusitis	4	2.9	2	1.5
Pain, abdominal	1	0.7	4	3.0
Upper respiratory infection	3	2.2	1	0.8
Nausea	1	0.7	3	2.3
Flatulence	3	2.2	0	0.0
Insomnia	3	2.2	0	0.0

(Applicant's Table XI from Vol. 1.9, p. 000318)

Higher rates of flatulence and insomnia were reported in the 1200 mg [redacted] group. Patients in the MONISTAT®7 group reported more excoriations and abrasions of the genitalia and pain located in the trunk and abdomen.

MO Comment: The small differences in rates of adverse experiences reported by 2 to 5% of patients do not suggest a significant difference in the these events for the 2 study arms.

MO Comment: Examination of the tabulated data does not reveal any predominant adverse experience as being the cause of the greater

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The rigor of the diagnostic criteria employed for UTI is not specifically stated. Given that patients may experience dysuria as a component of VVC, the clinical diagnosis of UTI could be confounded. Evidence of microbiological confirmation of these diagnoses is not provided.

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Adverse Experience	n	%	n	%
Dysmenorrhea	6	4.3	4	3.0
Cramps, GI	5	3.6	3	2.3
Excoriation/abrasion, female genitalia	2	1.4	6	4.5
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Sinusitis	4	2.9	2	1.5
Pain, abdominal	1	0.7	4	3.0
Upper respiratory infection	3	2.2	1	0.8
Nausea	1	0.7	3	2.3
Flatulence	3	2.2	0	0.0
Insomnia	3	2.2	0	0.0

(Applicant's Table XI from Vol. 1.9, p. 000318)

Higher rates of flatulence and insomnia were reported in the 1200 mg [redacted] group. Patients in the MONISTAT®7 group reported more excoriations and abrasions of the genitalia and pain located in the trunk and abdomen.

MO Comment: The small differences in rates of adverse experiences reported by 2 to 5% of patients do not suggest a significant difference in the these events for the 2 study arms.

MO Comment: Examination of the tabulated data does not reveal any predominant adverse experience as being the cause of the greater

number of respiratory and gastrointestinal adverse experiences in the 1200 mg [redacted] arm of the study.

The Applicant notes that no other adverse experiences were noted by more than 2 patients in either treatment group.

The Applicant tabulated groupings of the genital/reproductive adverse experiences for the two treatment groups (Table 62).

Table 62. Patients Reporting Selected Groupings of Genital/Reproductive Adverse Experiences

	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 138)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 133)	
Adverse Experience Grouping	n	%	n	%
Itching and Burning	47	34.1	49	36.8
Itching, Burning and Irritation	47	34.1	51	38.3
Itching, Burning, Irritation and Pain	48	34.8	51	38.3

(Applicant's Table XII from Vol. 1.9, p. 08-000319)

The Applicant tested the following adverse experience rates for statistical significance.

- patients reporting at least one adverse experience
- any body system with at least a 10% incidence in either treatment group
- any individual adverse experience with at least a 5% incidence in either treatment group, and
- combined genital/reproductive adverse experiences of specific interest.

Of these multiple comparisons, the Applicant found the difference in the rate of patients reporting urinary tract infections to be significantly higher in the 1200 mg [redacted] arm (7 vs. 0, p=0.015) and the difference in the rate of patients reporting pruritus of the female genitalia was significantly higher in the MONISTAT®7 group (36 vs. 22, p=0.027). (Please note the MO Comment above on the classification of urinary tract infection.)

MO Comment: The increased rate of urinary tract infection in the 1200 mg [redacted] group and the higher rate of reporting pruritus in the MONISTAT®7 group was found by doing multiple comparisons on the adverse event data as noted above. Given the multiple comparisons performed, one must consider the possibility of an elevated chance of a type I error. Hence, while these findings are noted, the relevance of the p-value calculated without adjusting for multiple comparisons is questionable. The Applicant describes a total of 17 comparisons of adverse event rates from which the cited findings of

urinary tract infection and pruritus are reported. In Study 96-002 the reported rates for adverse effects involving the urinary tract were similar between the 1200 mg [redacted] and MONISTAT®7 groups. (Please also see the MO Comment above on the classification of urinary tract infection).

Three patients were discontinued from the study because of adverse experiences (Table 63).

Table 63. Patients Discontinuing the Study Due to an Adverse Experience

Patient	Age/ Race	Adverse Experience	Study Day of AE Onset*	Severity/ Relation Per Investigator	Action	Outcomes	Other Note
M1200							
03006	40(C)	headache and sinus infection, vulvovaginal burning/irritation, and labial tear	2 (sinus infection)	mild or moderate and not or unlikely related	Counteractive medication	recovered except for ongoing labial tear	
M7C							
00702	23(C)	vulvovaginal burning, irritation & itching and genital herpes eruption	4 (herpetic eruption)	severe or moderate and possibly and not related	study medication discontinued after five doses and counteractive medication given	ongoing	treatment for herpes and for *Gardnerella vaginalis*
04406	22(C)	vulvovaginal burning and irritation, vulvar erythema and edema	3 (burning/ irritation) 5 (erythema/ edema)	mild or moderate and possibly related	study drug discontinued after three days	ongoing	similar previous reaction to MONISTAT®

C = Caucasian
*Study Day of onset for the AE resulting in discontinuation.

(Adapted from the Applicant's Table XIII from Vol. 1.9, p. 08-000320)

Summaries for the patients who experienced a serious event or discontinued the study because of an adverse event are provide below.

Patient 00702

The patient was a 23-year-old female with the diagnosis of vulvovaginal candidiasis confirmed by KOH and culture. She was randomized to and received therapy (5 days) with MONISTAT®7. She developed genital herpes on Study Day 4 and was evaluated at Return Visit 1 on Study Day 8. She was given a prescription for Famvir® for treatment of her genital herpes. She was also noted to have clue cells on her Return Visit 1 examination and was also prescribed po

metronidazole to treat *G. vaginalis*. The patient was discontinued because of genital herpes and accompanying vulvovaginal burning, itching, and irritation. Also noted on the discontinuation form is treatment for *G. vaginalis*.

Patient 03006
The patient was a 40-year-old female with vulvovaginal candidiasis confirmed by KOH and culture. She was randomized to and received the 1200 mg [redacted] On Study Day 9 she started taking Amoxil® for sinusitis. She was discontinued from the study because of her adverse event of sinusitis for which she was prescribed an anti-infective. At the time of her discontinuation, she was noted to have a small labial tear that was judged unlikely to be related to therapy.

Patient 03101
The patient was a 62-year-old woman with a history of diabetes enrolled in the study with the diagnosis of VVC confirmed by KOH and culture. She was treated with MONISTAT®7. At Return Visit 1 she was a clinical cure, microbiological failure, and therapeutic failure. Five to six weeks after completing her study medication the patient died from arteriosclerotic vascular disease. Her death was not considered related to study medication.

Patient 04406
The patient was a 22-year-old female diagnosed with VVC with a confirmatory KOH and culture. She was randomized to MONISTAT®7 and used the medication for 3 days. She stopped using the study medication after day 3 because of increased vulvovaginal symptoms. She returned for an assessment on Study Day 5 and was discontinued from the study for increased burning, irritation, itching, vulvar edema, and erythema. At Return Visit 1, the patient also noted a prior history of adverse reaction when she had previously used MONISTAT®.

The Applicant also notes patient 03803 assigned to MONISTAT®7 who was reported to have a positive pregnancy test at her last visit. The patient did not return calls from the study center; hence the status of her pregnancy remains unknown.

The Applicant tabulated severity of adverse experience by treatment group (Table 64). Most of the adverse experiences classified as severe were vulvovaginal itching, burning, or irritation (31/49 in the 1200 mg [redacted] group and 28/41 in the M7C group).

Table 64. Severity of Adverse Experiences

	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] *(N = 254)		MONISTAT® 7 (2% MCN) Vaginal Cream *(N = 231)	
Severity	n	%	n	%
Mild	**106**	**41.7**	**78**	**33.8**
Moderate	**99**	**39.0**	**112**	**48.5**
Severe	**49**	**19.3**	**41**	**17.7**

* number of adverse experiences reported

(Applicant's Table XIV from Vol. 1.9, p. 08-000321)

The Applicant performed a chi-square test on the distribution of adverse experiences between the two treatment groups. No significant difference was found in the distribution of adverse events between the two groups (p = 0.36).

The Applicant tabulated the relationship of adverse experience to study medication (Table 65).

Table 65. Relationship of Adverse Experiences to Study Medication

	Treatment Group			
	MCN (1200 mg) Vaginal [redacted] (N = 254)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 231)	
Relationship	n	%	n	%
Not related	**102**	**40.2**	**97**	**42.0**
Unlikely related	**68**	**26.8**	**48**	**20.8**
Possibly related	**60**	**23.6**	**68**	**29.4**
Probably related	**23**	**9.1**	**18**	**7.8**
Highly probably related	**1**	**0.4**	**0**	**0.0**

(Applicant's Table XV from Vol. 1.9, p. 08-000321)

The Applicant notes that of the adverse experiences classified as probably or highly probably related, 17/24 in the 1200 mg [redacted] group and 17/18 in the MONISTAT®7 group were experiences of vaginal burning, itching or irritation. The distribution of relationship to study medication was analyzed with a chi-square test. The relationship of adverse events to therapy was not significantly different between the two study groups (p = 0.98).

The Applicant notes that follow-up gynecologic examination did not reveal any findings suggestive of drug toxicity in either of the two arms of the study.

Reviewer's Comments/Conclusions for Study 97-006

The patient populations enrolled in the two treatment arms were comparable. The efficacy results show the MONISTAT® DUAL-PAK® to be similar to MONISTAT®7 with regards to clinical, microbiological, and therapeutic response at both Return Visit 1 (RV1) and overall in the Applicant's evaluable for efficacy population. A modified-intent-to-treat (MITT) analysis performed by the Agency's Statistical Reviewer found the two treatment groups to be similar with regards to overall clinical, microbiological, and therapeutic response. The MO's analysis of efficacy in the subset of evaluable patients compliant with the protocol specified visit windows found MONISTAT® DUAL-PAK® and its comparator statistically similar with regards to clinical, microbiological, and therapeutic response at RV1 and overall. The results of these three analyses of the study data support statistically similar efficacy for the MONISTAT® DUAL-PAK® and its comparator, MONISTAT®7 Vaginal Cream. In addition, recurrence rates for patients cured at RV1 were comparable between the two treatment groups.

Review of the safety data finds similar rates for adverse events for the MONISTAT® DUAL-PAK® and MONISTAT®7. There was a higher rate of urinary tract infection in this study (97-006) in the MONISTAT® DUAL-PAK® group, but this finding was not corroborated by study 96-002 suggesting this may be a chance occurrence. The number of patients discontinued from the study because of an adverse event is similar across the two study groups.

Overall, the study supports statistical similarity of safety and efficacy of MONISTAT® DUAL-PAK® to its comparator, MONISTAT®7.

8.2.3. Trial # 3: Study 97-007 — Drug Absorption Study of a Miconazole Nitrate [redacted] in Normal Volunteers

Objective/Rationale

The objective of this study was to measure and compare the safety and drug absorption of miconazole from a 1200 mg miconazole nitrate vaginal [redacted] in normal volunteers by measuring plasma levels of miconazole at various time intervals after intravaginal application of the ovule. A secondary objective was to assess the absorption of miconazole if a woman were to administer two applications of 1200 mg miconazole nitrate vaginal [redacted] 2 days apart, as a measure of safety.

Design

This was an open label, single center, phase 1 study to measure the systemic absorption of drug from the 1200 mg vaginal [redacted] Subjects were to receive either a single dose of the 1200 mg vaginal [redacted] (Dose Group 1) or a first dose of the 1200 mg [redacted] followed by a second dose of the 1200 mg [redacted] administered 48 hours later (Dose Group 2). The planned enrollment was 24 healthy female volunteers in order to obtain 20 evaluable subjects; 10 in Dose Group1 and 10 in Dose Group 2. Plasma samples were obtained to assess systemic absorption and the pharmacokinetic profile of the 1200 mg miconazole nitrate vaginal [redacted] The pharmacokinetic data obtained from this study was compared to historical data from other miconazole nitrate dosage forms for the treatment of VVC.

Protocol Overview

Population, procedures

Patients were required to meet the following inclusion and exclusion criteria for study participation.

Noteworthy inclusion criteria

- to be 18 years of age or older, premenopausal, with regular menses
- to be non-pregnant and non-nursing. A negative pregnancy test was required in all women of childbearing potential within one day of administration of study medication
- to be using an effective method of contraception (oral contraceptives, levonorgestrel implants, IUD, Depo-Provera™ injections, abstinence or sterilization of either partner)
- to have a Papanicolaou smear taken at or within six months (with documentation) of admission and to be Class I or II, (or show no dysplasia or more advanced disease with the Bethesda System)
- to have negative tests for HIV, hepatitis (HBsAg), and *Neisseria gonorrhoeae*
- a negative wet mount for *Trichomonas vaginalis* and clue cells
- a negative KOH preparation for yeast, and

- to have laboratory test results within ± 10% of the normal limits of the laboratory used

Noteworthy exclusion criteria

- use of any systemic antibiotic or vulvovaginal therapeutic, vaginal or cervical contraceptive device, vaginal lubricant, foam, jelly, ointment, medicated douche or feminine sprays within seven days of admission; or use of water douches within three days of admission
- a recent history of alcohol or drug abuse
- a history of sensitivity to the imidazole or triazole classes of drugs, or any component of the ovule formulation
- any vulvovaginal infection(s)
- active genital herpetic lesions at the time of admission
- active genital condylomata which require topical treatment within 7 days of admission
- any significant history of any chronic illnesses or chronic vulvovaginal infection
- acute illness within seven days of study admission
- any diseases or condition which could result in excess accumulation, impaired metabolism, or excretion of study drugs, and
- use of an experimental drug or device within 30 days prior to study admission

The initial contact with study subjects was a screening visit. Potential subjects received a full explanation of the study and if interested in study participation, provided informed consent.

Within 2 weeks of study admission, subjects underwent the following evaluations:

- a review of the subject's medical history (including the date of the subjects last menstrual period)
- a complete gynecologic examination
- Papanicolaou smear (unless done with an available report within the last 6 months)
- Testing for HIV, HBsAg, and *Neisseria gonorrhoeae*

Eligible subjects were instructed to refrain from sexual intercourse from 48 hours prior to admission through the end of the study and not to use water douche from three days prior to admission or vulvovaginal therapeutic agent from seven days prior to admission and through the end of the study. The study was scheduled to be performed from 1-12 days after the end of each subject's menstrual flow, and study subjects from both groups were confined to the study site starting the day before dosing of study drug and ending 24 hours after dosing of study drug. Dose Group 2 was confined again starting 12 hours prior to Day 3 dosing and ending again at 24 hours after the second dosing of study drug. Alcohol containing beverages were not allowed from 12 hours prior to study drug administration until completion of the study.

At the time of study admission all subjects underwent the following evaluations:

- complete gynecologic and physical examination including temperature, pulse, respiration rate, and blood pressure
- A wet mount for *Trichomonas vaginalis* and clue cells and a 10% KOH slide preparation for yeast were performed
- A [redacted] pregnancy test (or test of equal or greater sensitivity) was performed, if applicable
- The following laboratory tests were performed at study admission (and again prior to discharge from the study)
  - Hematology: hemoglobin, hematocrit, MCV, MCH, MCHC, RBC, WBC with differential and platelet counts.
  - Biochemistry: Glucose, BUN, creatinine, uric acid, sodium, potassium, chloride, CO_2, total protein, albumin, total bili, alk. phos, GGTP, SGOT, SGPT and LDH.
  - Urinalysis: pH, specific gravity, glucose, protein, bilirubin, ketones, blood, nitrites and leukocyte esterase.

Subjects were assigned to open label study medication in numerical order. They self-administered the study medication under the supervision of the clinical study manager in order to assure compliance. Subjects were instructed to remain in a supine or reclining position for 4 hours following drug administration.

Blood samples for miconazole levels were obtained from patients in the single-dose arm of the study at the following time points: 0 (just prior to study drug administration), and 2,4,8,12,16,24,48,72, and 96 hours following drug administration. Patients in the two-dose arm of the study underwent blood draws at the following time points 0 hours (just prior to initial drug administration), and 2,4,8,12,16,24, and 36 hours following initial drug administration and at baseline 0 hours (just prior to the second drug administration), and 2,4,8,12,16,24,48,72 and 96 hours following the second drug administration.

Following drug administration, subjects were asked to report the development, severity and abatement of any adverse experiences. Adverse experiences were also assessed by periodic questioning and examining the subjects. Relationship to treatment and severity were determined by the investigator using the explanations defined in the study protocol.

At the end of the study, patients underwent the following evaluations:

- a gynecologic examination, temperature, pulse, respiration rate, blood pressure
- a laboratory evaluation including hematology, serum chemistries, and a urinalysis were repeated (same tests as described at study admission)

- a study discontinuation/completion form was completed

The study formulation of the 1200 mg vaginal [redacted] was formulation PD-F-0408, [redacted] Lot # SF048570. The Clinical Supply lot number was CS97-009.

Evaluability criteria

Subjects were to be discontinued from the study for the following reasons.

- protocol violations
- clinically significant adverse experiences
- subject's request
- menses

Endpoints defined

The goal of the study was to gather information on the absorption and pharmacokinetic profile in each of the two study groups. Therefore no pre-defined criteria for efficacy were defined.

Safety information was collected from patients by patient report, periodic questioning, and examination in order to detect adverse events.

Statistical considerations

The Applicant chose a sample size of ten patients per group based on an estimated coefficient of variation of 40% and the goal of estimating the peak concentration to within 29% of the true value with 95% confidence.

Statistical analyses of the study results were descriptive only.

Study Results

Demographics

The study enrolled females 18 to 45 years of age. The mean age in the single dose group was 30.3 years and the mean age in the two-dose group was 29.5 years. In the single-dose group (Dose Group 1) 50% of the subjects were caucasian and 50% were black. In the two-dose group (Dose Group 2) 80% of the 10 subjects were caucasian and 20% were black. The subject's baseline medical histories and physical examinations were unremarkable. All Papanicolaou smears were Class I or II. All admission KOH preparations, wet mounts, cultures for *N. gonorrhoeae,* pregnancy tests, HIV tests, and HBsAg tests were negative.

Evaluability

A total of 23 of the 24 subjects enrolled completed the study. All 24 subjects were included in the safety analysis. The pharmacokinetic analysis was performed on the first 10 patients in each of the two study groups to complete the study. The one patient who did not complete the study was withdrawn on Study Day 1 after she experienced an acute anxiety episode judged by the principal investigator not to be related to the study medication.

Pharmacokinetics

(For a complete description of the pharmacokinetic analyses please see Dr. Phil Colangelo's Biopharmaceutics Review.)

The Applicant presents the pharmacokinetics of the 1200 mg vaginal [redacted] in study subjects. The results are presented for the group of patients who received only one [redacted] and then for the group of patients who received a second [redacted] at 48 hours. The administration of a second ovule at 48 hours was to provide additional safety data on a potential misuse situation. The plasma concentration results are presented graphically below.

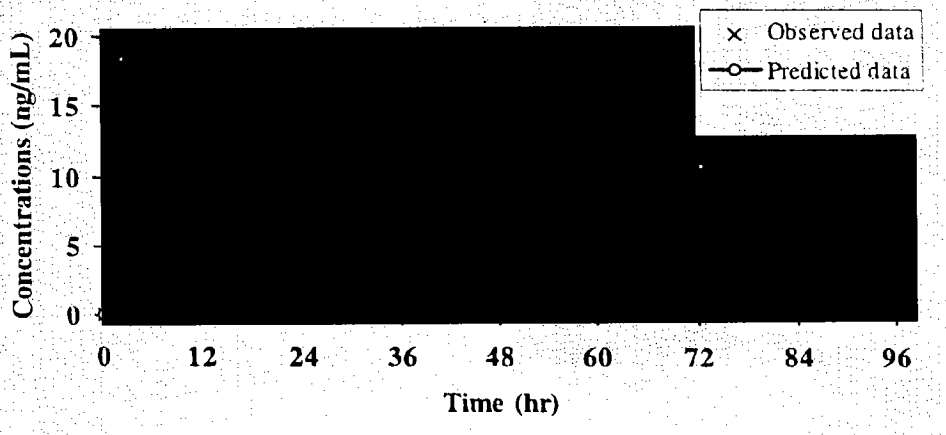

Figure I

Observed and predicted plasma miconazole concentration-time profiles following a single intravaginal application of 1200 mg miconazole vaginal [redacted] (Dose Group 1, A_1 = 67133.85, A_2 = 17.53029, ka = 0.257914, λ_1 = 0.257996, λ_2 = 0.025917).
(Applicant's Figure I from Vol. 1.9, p. 08-000113)

The results show the range of observed and the predicted serum levels of miconazole nitrate in the single dose study group

MO Comment: In the single dose 1200 mg [redacted] there is considerable variability in the observed serum levels of miconazole with levels up to 18.3 ng/ml in one of the ten patients. The mean Cmax for this group was 10.7 ng/ml. The levels attained with the 1200 mg vaginal ovule are within the range of the levels attained with the 200 mg miconazole nitrate cream (MONISTAT®3 vaginal cream, Table 66) and are well below the peak serum levels attained in the setting of therapy with IV miconazole. Serum levels attained following IV administration range from a peak serum level of 1600 ng/mL following a dose of 200 mg to peak serum levels of 5000-13,000 ng/mL after a 10-12 mg/kg dose (Kucers A, et. al., *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, and Antiviral Drugs*. - 5th ed. Butterworth-Heinemann, Oxford 1997. pp. 1445-59.).

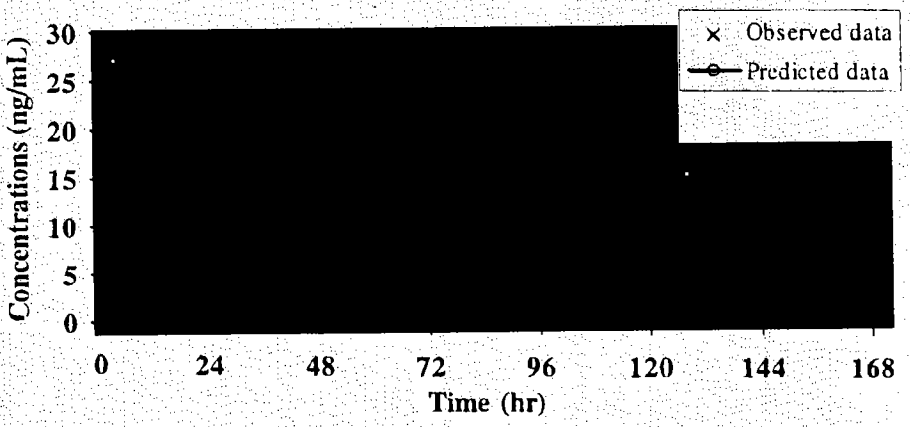

Figure II

Observed and predicted plasma miconazole concentration-time profiles following two intravaginal application of 1200 mg miconazole vagina[redacted]on Days 1 and 3 (Dose Group 2, $A_1 = 1415.502$, $A_2 = 15.74005$, ka = 0.255124, $\lambda_1 = 0.258213$, $\lambda_2 = 0.025551$).
(Applicant's Figure II from Vol. 1.9, p. 08-000113)

The results above show the range of observed serum levels of miconazole nitrate in the two-dose study group.

MO Comment: The levels attained under the misuse situation of a second ovule administered 48 hours after the first produced a mean Cmax of 11.98 ng/mL on Day 3. This value is comparable to the Cmax level observed with 200 mg MCN cream shown in Table 66 below (MONISTAT®3 vaginal cream). Again the range of values observed for serum levels of miconazole was considerable. One patient (Subject

02011) attained a peak serum level of 28 ng/mL. This patient demonstrated a more gradual and persistent rise in serum miconazole level. Although this level is higher than the levels for other patients in the study, it remains well below levels that would be attained with IV miconazole therapy. This patient did not report any adverse experiences.

The maximum concentration (Cmax) attained and the area under the curve (AUC) for the 1200 mg vaginal ovule compared to other miconazole nitrate containing MONISTAT® products used in the treatment of VVC are shown in Table 66.

Table 66. Pharmacokinetic Parameters from Selected MONISTAT® Preparations

Parameter	MONISTAT® 7 Original Cream (N=14)		MCN 100 mg NewBase Cream (N=14)		MCN 200 mg Cream (N=14)		MCN 1200 mg [redacted] (N=10)
Dose	1st	7th	1st	7th	1st	3rd	single
Cmax (ug/L)	1.99	2.54	6.81	8.84	9.48	12.68	10.7
Tmax (Hrs.)	12.29	10.29	10.57	10.00	12.29	12.57	18.4
AUC (ug.h/L)	32.09 [a]	82.76 [b]	91.43 [a]	241.47 [b]	136.04 [a]	365.64 [b]	477.3 [c]

1st results are after a single dose, 7th or 3rd results are after the last dose for that regimen reported in study 95-009-P.
MCN = miconazole nitrate
a = AUC 0-24 hours b = AUC 0-72 hours c = AUC 0-96 hours
(Applicant's Table from Vol. 1.9 p. 08-000140)

MO Comment: The Cmax levels attained with the 1200 mg ovule are comparable to those of the MCN 200 mg cream (MONISTAT®3 Vaginal Cream). The $AUC_{0\text{-}96h}$ produced by the MCN 1200 mg [redacted] is higher than the $AUC_{0\text{-}72h}$ of the MCN 200 mg cream. The biopharmaceutics reviewer also calculated an $AUC_{0\text{-}72h}$ for the MCN 1200 mg ovule of 419.0±136.6 in order to provide a comparable comparison. The Tmax of 18.4 hours for the MCN 1200 mg [redacted] reflects the more gradual and prolonged absorption produced by the ovule.

The Applicant also provided computer simulations to extrapolate expected serum miconazole levels in situations of misuse. Please see the Biopharmaceutics review by Phil Colangelo for comments regarding this information.

Safety

The Applicant tabulated all adverse events reported during the study. No serious adverse experiences were reported during the study. All adverse events that were reported by more than one patient are shown in Table 67.

Table 67. SUMMARY OF ADVERSE EXPERIENCES (N=24)

Adverse Experience by Body System	Number	Percent
Genital/Reproductive System:		
Vaginal Burning	2	8.3
Nervous System:		
Dizziness	2	8.3
Headache	8	33.3

(Applicant's Table VIII from Vol. 1.9, p. 08-000139)

MO Comment: Given the small numbers of patients in the study and the lack of a control group, it is difficult to draw conclusions regarding the adverse experiences reported. Comparing the data with the two pivotal trials we see similar rates for headache and rates of vaginal burning that are somewhat less than observed in the clinical trials in patients with VVC. This difference may reflect that this pharmacokinetics study 97-007 enrolled normal subjects. The etiology of the dizziness reported by 2 patients is unclear. As noted, no serious adverse experiences were reported.

The Applicant notes that the rates for reporting adverse events are similar for both the one and two-dose study groups.

One subject was discontinued from the study (subject no. 02008) because of an anxiety attack judged by the Principal Investigator to be not related to the study drug.

MO Comment: Subject 02011 demonstrated serum levels of miconazole greater than the other patients in the two-dose arm of the study. Despite these higher levels, this subject did not report any adverse experiences during the study.

The Applicant also monitored the study subject's laboratory studies, findings on gynecologic examination, and vital signs during the study. The results of hematology, chemistry, and urinalysis studies were either within normal limits or judged by an investigator to be not clinically significant. The gynecologic examinations both at admission and post-study were judged to be either normal or acceptable. Vital signs were monitored during the study and no significant changes were noted.

Reviewer's Comments/Conclusions for Study 97-007

Study 97-007 demonstrated that the 1200 mg vaginal [redacted] attains serum miconazole levels that are comparable to the 200 mg MCN cream (MONISTAT®3 vaginal cream*). These levels are well below the levels that were attained with IV miconazole therapy. The study also provides information on the serum levels of miconazole nitrate attained in the misuse situation where a second 1200 mg vaginal [redacted] is administered 48 hours after the first. The average peak serum levels attained in this misuse situation are comparable to levels observed with the MONISTAT®3 formulation. There were no serious adverse experiences reported during the study period.

In conclusion, the study demonstrates that the serum levels that are associated with use of the 1200 mg [redacted] are similar to those that are attained with the over-the-counter marketed formulation, MONISTAT®3. This information supports the safety of the 1200 mg [redacted] formulation for prescription use.

*MONISTAT®3 Vaginal Cream was approved under NDA 20-827 for over-the-counter treatment of VVC.