

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-026**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 21-026/SN-000  
**Drug Name:** Miconazole nitrate, 0.25%  
**Indication(s):** Treatment of diaper dermatitis complicated by *Candidiasis*  
**Applicant:** Barrier Therapeutics, Inc.  
**Dates:** Submitted: November 24, 2004  
Received: November 24, 2004  
User fee: May 24, 2005  
Review completion: April 1, 2005  
**Review Status:** Priority (6-month)  
**Biometrics Division:** Division of Biometrics III (HFD-725)  
**Statistics Reviewer:** Shiojjen Lee, Ph.D.  
**Concurring Reviewers:** Mohamed Alesh, Ph.D.  
**Medical Division:** Dermatologic and Dental Drug Products (HFD-540)  
**Clinical Team:** Brenda Carr, M.D. (HFD-540)  
**Project Manager:** Mildred Wright (HFD-540)

**Keywords:** Overall cure, clinical cure, mycological cure, KOH, *Candida albicans*,

## Table of Contents

1. EXECUTIVE SUMMARY .....	3
1.1 Conclusions and Recommendations .....	3
1.2 Brief Overview of Clinical Studies .....	3
1.3 Statistical Issues and Findings .....	4
2. INTRODUCTION .....	6
2.1 Overview .....	6
2.2 Data Sources .....	7
3. STATISTICAL EVALUATION .....	7
3.1 Evaluation of Efficacy .....	7
3.1.1 Study 10833/10842.33 .....	7
3.1.2 Study 12966.37A .....	8
3.1.3 Study 12966.37B .....	10
3.1.4 Summary of Studies 10833/10842.33, 12966.37A and 12966.37B .....	11
3.1.5 Study BT100 .....	11
3.1.5.1 Study Design .....	12
3.1.5.2 Statistical Methods .....	13
3.1.5.3 Patient Disposition and Baseline Characteristics .....	14
3.1.5.4 Primary Efficacy Endpoint .....	15
3.1.5.5 Missing Data Handling and Sensitivity Analyses .....	16
3.1.5.6 Secondary Efficacy Endpoint .....	17
3.1.6 Results Comparison among Studies .....	19
3.2 Evaluation of Safety .....	19
3.2.1 Extent of Drug Exposure .....	19
3.2.2 Incidence of Adverse Event .....	20
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....	20
4.1 Gender, Race and Age .....	21
4.2 Other Special/Subgroup Populations .....	21
5. SUMMARY AND CONCLUSIONS .....	22
5.1 Statistical Issues and Collective Evidence .....	22
5.2 Conclusions and Recommendations .....	23
APPENDICES .....	25
SIGNATURES/DISTRIBUTION LIST PAGE .....	35

Appears This Way  
On Original

## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

Results of Study BT100 USA/001 (denoted as BT100) were evaluated for the indication of treatment of diaper dermatitis complicated by *Candidiasis*. As vehicle arm had a significantly higher missing data rate than miconazole group on Day 14 (52% vs. 13%), it is difficult to draw a definite conclusion about the efficacy of miconazole nitrate as compared to vehicle ointment with respect to the primary efficacy endpoint, overall cure rate on Day 14.

### 1.2 Brief Overview of Clinical Studies

NDA 21-026 was originally submitted by Johnson & Johnson Consumer Companies, Inc. on August 24, 1998 for the indication of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor. Three studies 12966.37A, 12966.37B and 10833/10842.33 were submitted to support the efficacy claims. Non-approvable (NA) letters were issued on 6/28/1999 and 7/24/2000 based on the studies conducted. The sponsorship of the drug application was later transferred to Barrier Therapeutics, Inc. on 6/21/2002. Barrier conducted one clinical trial, BT100, which is the subject of the current resubmission.

For the three studies submitted in the original NDA, each of studies 12966.37A and 12966.37B was conducted at a single center in Australia during February 1989 – March 1990 and December 1988 – November 1989, respectively; while study 10833/10842.33 was conducted at two sites in the U.S during November 1983 and June 1984. Each study had 7-day treatment duration, but no follow-up visits. Clinical measures were evaluated on Days 1, 3, 5 and 7. *Candida* culture was not done in study 12966.37B, it is impossible to evaluate the efficacy of miconazole nitrate for treating diaper dermatitis complicated by *Candidiasis* for the study. Study 10833/10842.33 enrolled 53 and 54 patients in miconazole and vehicle group, respectively. Twenty-three patients (43%) in each group had positive *Candida albicans* culture at baseline. Study 12966.37A enrolled 101 patients for each of miconazole and vehicle groups. Totals of 28 (28%) and 35 (35%) patients in the miconazole and vehicle group, respectively, were confirmed with *Candida albicans* at baseline.

Sponsor conducted study BT100 following the two NA letters and communication with the Agency. Study BT100 was conducted at 20 sites in the U.S. and Latin/South America during April 2004 and June 2004. The study included a 7-day treatment duration followed by a 3-week follow-up period. The study dosing was after each diaper change (about 5-12 times daily). Clinical measures were evaluated on Days 1, 3, 5, 7, 14, and 28, with Day 14 as the primary time point for efficacy assessment.

A total of 330 patients were enrolled and randomized in study BT100. As a result, 236 patients had positive *Candidiasis* at baseline (112 and 124 patients in miconazole and vehicle group, respectively). These patients defined the modified intent-to-treat (MITT) population which is the primary for efficacy analyses. It should be noted that about 60% and 54% of the MITT patients in miconazole and vehicle group were enrolled from Latin/South America. More than 60% of the MITT patients are Hispanic/Latino origin; while only about 24.6% of the MITT patients are White origin.

### 1.3 Statistical Issues and Findings

#### Statistical Issues

The primary efficacy endpoint in study BT100 is the overall cure rate on Day 14 which was agreed upon with the Division. It is defined as clinical cure (i.e., resolution of signs/symptoms) plus mycological cure (i.e., negative KOH and culture). The proposed missing data handling for the two components were the last observation carried forward (LOCF) for signs/symptoms and treatment failure for mycological endpoint. The Division had requested that missing mycological endpoint be imputed using the LOCF. The results are identical.

The critical statistical issue in the current application is the missing data handling in efficacy analyses. It should be noted that sponsor's sample size calculation for the study at the IND stage assumed a treatment effect of 25%. Patients were assigned to treatments with an equal allocation ratio. Accounting for similar dropouts, totals of 130 patients per arm with confirmed KOH and culture at baseline were planned. The two treatment groups were comparable in terms of missing data rate on Day 7. However, vehicle arm had a significantly higher missing data rate than miconazole group on Day 14 which is the primary time point for efficacy assessment for study BT100. The missing data rates on Day 14 were 52% vs. 13% for vehicle vs. miconazole. Several sensitivity analyses were conducted to evaluate the robustness of efficacy results due to different imputation methods. As a result, a great impact on the efficacy results for the primary efficacy endpoint, overall cure rate on Day 14, is observed.

#### Statistical Findings

The sponsor in this resubmission presented results for study BT100 in support of the efficacy and safety claim of Miconazole nitrate, 0.5% ointment for the treatment of diaper dermatitis complicated by *Candidiasis*. The dosing of miconazole nitrate, 0.5%, is applying to diaper area after each diaper change (about 5 to 12 times daily) for 7 days. Results of the primary efficacy endpoint (i.e., overall cure rate) based on the MITT population with the last observation carried forward (LOCF) method for handling missing data, as well as other sensitivity analyses are presented in Table E.1 for Study BT100.

Table E.1: Comparison of Overall Cure Rate on Day 14 – Study BT100

Imputation	Miconazole	Vehicle	Comparison
LOCF (or treatment failure)	26/112 (23%)	12/124 (10%)	0.005 <sup>a</sup>
Observed cases	26/98 (26.5%)	12/59 (20.3%)	0.406 <sup>a</sup>
Imputing missing based on the observed cure rate	30/112 (26.8%)	25/124 (20.2%)	0.281 <sup>b</sup>

Source: Table 6 in this review and sponsor's data sets at \\cdsesub\21026\000\Hpbio\NDA\_21-026\BT100-USA-001.

<sup>a</sup> p value from CMH test adjusting for investigational group.

<sup>b</sup> p value from Fisher's exact test.

The following summarizes the results:

1. As vehicle arm had a significantly higher missing data rate on Day 14 than miconazole arm (i.e., 52% vs. 13% with  $p < 0.001$ ), efficacy results of the overall cure rate are sensitive to different imputation methods. This is evident from the summary stated in the following:
  - Imputing missing by LOCF method or treatment failure yielded superiority outcome of miconazole to vehicle. The overall cure rates are 23% vs. 10% for miconazole vs. vehicle

- with  $p = 0.005$ . It should be noted that imputing missing by failures would be in favor of miconazole group, as vehicle arm had a significantly higher missing data rate than miconazole (52% vs. 13%).
- However, the superiority of miconazole to vehicle is not established based on the observed cases. The observed overall cure rates are 26.5% vs. 20.3% for miconazole vs. vehicle with  $p = 0.406$ . The observed treatment effect is 6.2% which is smaller than the assumed 25% in the sample size calculation.
  - The superiority of miconazole to vehicle is not established by imputing missing based on the observed cure rate in the respective group. The resulted p value is 0.281 based on the Fisher's exact test. Alternatively, a simulation based on 10,000 simulated trials is performed by imputing missing data with the observed cure rate in the respective group. The probability (or power) that miconazole is superior to vehicle is found to be only about 8%.
2. Study BT100 enrolled more than 60% of MITT patients as Hispanic/Latino origin and only about 24.6% of White origin. It is a clinical judgment if the study population sufficiently represents the demographics of the U.S. population.

The summary with respect to the adverse event incidence is stated below. P values are listed for reference purpose only as the study was not designed for detecting significant safety parameters.

- The overall adverse event incidence rates were 22% vs. 19% for miconazole vs. vehicle with  $p = 0.585$  (Fisher's exact test).
- The majority events were mild in severity and all events were judged to be unlikely or unrelated to the study drug.
- The most frequent adverse event was related to infections and infestations with the incidence rates of 12% vs. 10% for miconazole vs. vehicle with  $p = 0.728$ .

Appears This Way  
On Original

## 2. INTRODUCTION

### 2.1 Overview

The New Drug Application (NDA) 21-026 was originally submitted by Johnson & Johnson Consumer Companies, Inc. on August 24, 1998 for the indication of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor. Three studies, 12966.37A, 12966.37B, and 10833/10842.33, were submitted to support the efficacy claims. Based on the studies conducted, a non-approvable letter was issued on 6/28/1999. On 1/21/2000, sponsor filed an amendment that provided a response to the non-approvable letter. The Agency issued a second non-approvable letter on 7/24/2000 following an Advisory Committee Meeting for the NDA on 6/30/2000. In the 2<sup>nd</sup> non-approvable letter, the Agency cited the need of an adequate and well-controlled clinical trial to establish the safety and efficacy where the severity of the disease is adequately defined and *Candida albicans* involvement is proven. The responsibility of the drug product was transferred from Johnson & Johnson Consumer Companies, Inc. to Barrier Therapeutics, Inc. on 6/21/2002.

A Guidance meeting between the Division and Barrier Therapeutics, Inc. was held on 10/7/2002. Sponsor submitted a Phase 3 study protocol and requested the Division's comments and agreement about their proposed plan to address the deficiency outlined in the non-approvable letter (dated 7/24/2000). One of the key issues in the meeting discussion was whether the study drug were considered to be a combination drug, as it contains zinc oxide and petrolatum in addition to miconazole nitrate. Zinc oxide has been marketed and widely used for diaper rash. The Division had teleconference with the sponsor on 12/18/2003 concerning the combination drug issue. The Division stated that the sponsor did not need to do a specific study to demonstrate the contribution of zinc oxide and petrolatum. They could rely on evidence already known regarding the contribution of zinc oxide and petrolatum to the combination.

Studies 10833/10842.33, 12966.37A and 12966.37B were included in the original NDA submission (dated 8/24/1998). Both studies 12966.37A and 12966.37B were conducted in Australia, and study 10833/10842.33 was conducted in the U.S. As there were some deficiencies in the study design, it is impossible to evaluate the efficacy results with respect to the claimed indication. The deficiencies were:

- The primary efficacy endpoint was not specified in the protocols.
- About 57% and 69% of patients in studies 10833/10842.33 and 12966.37A, respectively, did not have *Candida albicans* at baseline. There was no *Candida* culture assessment in study 12966.37B.
- Studies 12966.37A and 12966.37B were single-center; while study 10833/10842.33 had two sites. The generalization of efficacy results was limited.

For the complete statistical review of studies 10833/10842.33, 12966.37A and 12966.37B, refer to the Statistical Review dated 2/29/1999.

The Agency requested an adequate and well-controlled clinical trial be conducted (dated 7/24/2000). In response to the Agency's non-approvable letter, the sponsor conducted Study BT100 in the U.S., Latin America and South America to support the efficacy claim of miconazole nitrate, 0.25%. Results of study BT100 are submitted in the current NDA. The

overview of the clinical studies conducted under application NDA 21-026 is presented in Table 1.

**Table 1: Overview of Clinical Studies Conducted in NDA 21-026**

Study	Conducted country (duration)	Enrollment	Comments
10833/10842.33	U.S. (2 sites) (Nov. 1983 – June 1984)	Active: 53 Vehicle: 54	Twenty-three patients in each group had positive <i>Candida albicans</i> at baseline.
12966.37A	Australia (single center) (Feb. 1989 – March 1990)	Active: 101 Vehicle: 101	Thirty-eight and 42 patients in the respective group had positive culture at baseline.
12966.37B	Australia (single center) (Dec. 1988 – Nov. 1989)	Active: 98 Vehicle: 98	No culture was done.
BT100-USA-001	U.S., Latin/South America (20 sites) (April 2004 – June 2004)	Active: 166 Vehicle: 164	112 and 124 patients in the respective group had positive <i>Candidiasis</i> at baseline.

## 2.2 Data Sources

The data analyzed in this review is based on the sponsor's NDA submission Volumes 2, 7-17, 41-45 (stamped receipt date 11/24/04), electronic data submission in the Electronic Document Room location of \\cdsesub1\n21026\N\_000\HPbio\NDA\_21-026\BT100-USA-001 and information request received dated 2/15/05.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

For efficacy claims, Studies 10833/10842.33, 12966.37A and 12966.37B were submitted in the original NDA submission (dated 8/24/1998). Both studies 12966.37A and 12966.37B were conducted in Australia; while study 10833/10842.33 was conducted in the U.S. The efficacy results of Studies 10833/10842.33, 12966.37A and 12966.37B, as presented in the Statistical Review (dated 2/29/1999), are summarized in this section.

#### 3.1.1 Study 10833/10842.33

The study was double-blind, vehicle-controlled and randomized conducted in the U.S. during November 1983 and June 1984. Only two investigational sites were included. The objective was to evaluate the comparative efficacy of miconazole nitrate versus vehicle in the treatment of acute infantile diaper dermatitis and in the prevention of the onset of severe diaper dermatitis due to *Candida albicans*. The treatment duration was 7-day. Clinical measures were assessed on Days 1, 3, 5 and 7. No post-treatment follow-up assessment was evaluated.

Totals of 53 and 54 patients were randomized to receive miconazole and vehicle ointment, respectively. Fifty-one (96%) and 48 (89%) patients in the respective group completed the study. It should be noted that 23 patients (43%) in each treatment group had positive *Candida albicans* culture at baseline. The efficacy parameters in the protocol included

- Total rash score;
- Overall rating by investigator;

c. Microbiological status (presence/absence of *Candida albicans*)

However, there was no primary efficacy endpoint specified in the protocol.

Results of the three efficacy endpoints on Day 7 are summarized from Statistical Review (dated 2/29/1999) and presented in Table 2 for patients with and without *Candida albicans* culture at baseline. For missing data handling, the last observation carried forward (LOCF) method was applied. The summary is:

- The superiority of miconazole to vehicle is **not** established with respect to the proportion of patients with total rash score of 0 regardless of confirmed *Candida albicans* culture at baseline. The success rates are 35% vs. 13% with  $p = 0.087$  for patients having *Candida albicans* culture at baseline; while they are 67% vs. 61% with  $p = 0.665$  for patients without *Candida albicans* at baseline.
- For patients with *Candida albicans* at baseline, the overall rating by investigator is significantly better in miconazole group than that in vehicle group ( $p = 0.014$ ). However, two treatment groups are **not** significantly different for patients without *Candida albicans* culture at baseline ( $p = 0.940$ ).
- For patients who had *Candida albicans* at baseline, there is a marginal significance between active and vehicle groups in the proportion of patients who had negative *Candida albicans* culture on Day 7. The negative culture rates are 52% vs. 13% with  $p = 0.064$ .

**Table 2: Number (%) of Patients for Efficacy Endpoints on Day 7 – Study 10833/10842.33**

Efficacy endpoint	Patients with <i>Candida albicans</i> at baseline			Patients without <i>Candida albicans</i> at baseline		
	Active (n = 23)	Vehicle (n = 23)	p-value <sup>b</sup>	Active (n = 30)	Vehicle (n = 31)	p-value <sup>b</sup>
<b>Total Rash Score = 0</b>	8 (35%)	3 (13%)	0.087	20 (67%)	19 (61%)	0.665
<b>Overall Rating by Investigator<sup>a</sup></b>			0.014			0.940
Cured	8 (35%)	3 (13%)		20 (69%)	20 (67%)	
Improved	9 (39%)	5 (22%)		5 (17%)	6 (20%)	
No change	1 (4%)	4 (17%)		0	1 (3%)	
Worse/recurred	5 (22%)	11 (48%)		4 (14%)	3 (10%)	
<b>No <i>Candida albicans</i></b>	12 (52%)	3 (13%)	0.064	NA	NA	NA

**Source:** Data summary is based on the Statistical Review (dated 2/29/1999), Tables A.1.3, A.1.4, A.1.8, A.1.9, and A.1.10.  
<sup>a</sup>The overall rating by investigator for patients without *Candida albicans* at baseline was based on 29 and 30 patients in the respective group. One in each group had a missing measurement.  
<sup>b</sup>p values were from Mantel-Haenszel chi-square test.

**3.1.2 Study 12966.37A**

Study 12966.37A was double-blind, vehicle-controlled and randomized conducted at a single center in Australia during February 1989 and March 1990. The study objective was to evaluate the comparative efficacy of miconazole vs. vehicle in the treatment of acute diaper dermatitis in infants and in the prevention of the onset of severe diaper dermatitis and to assess the role of *Candida*. The treatment duration was 7-day. Clinical measures were assessed on Days 1, 3, 5 and 7. No post-treatment visits were conducted.

A total of 202 patients were enrolled and randomized equally to the active and vehicle groups. The randomization resulted in 101 patients in each of the two groups. Totals of 96 (95%) and 92 (91%) patients completed the study. Among the enrolled patients, 28 (28%) and 35 (35%) patients in the active and vehicle group, respectively, were confirmed with *Candida albicans* culture at baseline. The protocol included the following efficacy endpoints:

- a. Total rash score;
- b. Overall rating by investigator;
- c. Global clinical impression;
- d. Microbiological status (presence/absence of *Candida albicans*).

However, no primary efficacy endpoint was specified in the protocol.

Results of the efficacy endpoints on Day 7 are summarized from Statistical Review (dated 2/29/1999) and presented in Table 3 for patients with and without *Candida albicans* culture at baseline. For missing data handling, the last observation carried forward (LOCF) method was applied.

**Table 3: Number (%) of Patients for Efficacy Endpoints on Day 7 – Study 12966.37A**

Efficacy endpoint	Patients with <i>Candida albicans</i> at baseline			Patients without <i>Candida albicans</i> at baseline		
	Active (n = 28)	Vehicle (n = 35)	p-value <sup>b</sup>	Active (n = 73)	Vehicle (n = 66)	p-value <sup>b</sup>
<b>Total Rash Score = 0</b>	18 (64%)	2 (6%)	0.001	38 (52%)	28 (42%)	0.258
<b>Overall Rating by Investigator</b>			0.001			0.112
Cured	18 (64%)	4 (11%)		39 (53%)	29 (44%)	
Improved	4 (14%)	7 (20%)		15 (21%)	11 (17%)	
No change	0	8 (23%)		8 (11%)	10 (15%)	
Worse/recurred	6 (21%)	16 (46%)		11 (15%)	16 (24%)	
<b>Global Clinical Impression</b>			0.001			0.145
None	18 (64%)	3 (9%)		39 (53%)	29 (44%)	
Mild	7 (25%)	8 (23%)		28 (38%)	26 (39%)	
Moderate	2 (7%)	17 (49%)		5 (7%)	10 (15%)	
Severe	1 (4%)	7 (20%)		1 (1%)	1 (2%)	
<b>No <i>Candida albicans</i><sup>a</sup></b>	26 (93%)	6 (18%)	0.001	NA	NA	NA

Source: Data summary is based on the Statistical Review (dated 2/29/1999), Tables A.2.3, A.2.4, A.2.8, A.2.9, A.2.11, A.2.12 and A.2.12.  
<sup>a</sup> One patient in vehicle group did not have data on *Candida* culture.  
<sup>b</sup> p values were from Mantel-Haenszel chi-square test.

Summary of Table 3 is:

- For the proportion of patients with total rash score of 0, Miconazole is superior to vehicle for patients who had *Candida albicans* culture at baseline. The response rates are 64% vs. 6% for miconazole vs. vehicle with p = 0.001. However, the superiority of miconazole to vehicle is not demonstrated for patients without *Candida albicans* at baseline (52% vs. 42% with p = 0.258).

- Miconazole treatment has a better overall rating by investigator than vehicle group for patients who had *Candida albicans* culture at baseline ( $p = 0.001$ ). Two treatment groups are not significantly different for patients without *Candida albicans* at baseline ( $p = 0.112$ ).
- Miconazole group has a better global clinical impression than vehicle arm for patients who had *Candida albicans* at baseline ( $p = 0.001$ ). However, the difference is not significant between the two groups for patients without *Candida albicans* at baseline ( $p = 0.145$ ).
- For patients with *Candida albicans* at baseline, miconazole is superior to vehicle with respect to the proportion of patients without *Candida albicans* on Day 7. The negative culture rates are 93% vs. 17% for miconazole vs. vehicle with  $p = 0.001$ .

### 3.1.3 Study 12966.37B

The study was designed as double-blind, vehicle-controlled and randomized conducted at a single center in Australia during December 1988 and November 1989. The study objective was to evaluate the comparative efficacy of miconazole vs. vehicle in the treatment of acute diaper dermatitis in infants and in the prevention of the onset of severe diaper dermatitis. The treatment duration was 7-day. Clinical measures were assessed on Days 1, 3, 5 and 7.

A total of 196 patients were enrolled and randomized equally to receive miconazole and vehicle. This resulted in 98 patients in each of the two treatment groups. Totals of 95 (97%) and 87 (89%) patients in the respective group completed the study. It should be noted that no *Candida* culture was done in this study. Consequently, there was no information whether patients' baseline *Candida* culture were positive. The protocol included three efficacy endpoints:

- Total rash score;
- Overall rating by investigator;
- Global clinical impression.

No primary efficacy endpoint was specified in the protocol.

Overall results of the efficacy endpoints on Day 7 are summarized from Statistical Review (dated 2/29/1999) and presented in Table 4 for all patients. For missing data handling, the last observation carried forward (LOCF) method was applied.

Miconazole is superior to vehicle with respect to

- The proportion of patients with total rash score of 0 on Day 7. The response rates were 61% vs. 27% for miconazole vs. vehicle with  $p = 0.001$ .
- Percentage of patients with better overall rating by investigators ( $p = 0.001$ ).
- Percentage of patients with better global clinical impression ( $p = 0.001$ ).

Appears This Way  
On Original

**Table 4: Number (%) of Patients for Efficacy Endpoints on Day 7  
 Study 12966.37B**

Efficacy endpoints	All Patients		p-value*
	Active (n = 98)	Vehicle (n = 98)	
<b>Total Rash Score = 0</b>	60 (61%)	26 (27%)	0.001
<b>Overall Rating by Investigators</b>			0.001
Cured	62 (63%)	26 (27%)	
Improved	17 (17%)	21 (21%)	
No change	9 (9%)	26 (27%)	
Worse/recurred	10 (10%)	24 (24%)	
Missing	0	1 (1%)	
<b>Global Clinical Impression</b>			0.001
None	62 (63%)	26 (27%)	
Mild	30 (31%)	38 (39%)	
Moderate	6 (6%)	30 (31%)	
Severe	0	4 (4%)	
<b>Source:</b> Statistical Review (dated 2/29/1999), Tables A.3.1, A.3.3 and A.3.4. * p values were from Mantel-Haenszel chi-square test.			

### 3.1.4 Summary of Studies 10833/10842.33, 12966.37A and 12966.37B

As culture was not done in Study 12966.37B, it is impossible to evaluate the drug efficacy for patients who had diaper dermatitis associated with *Candida albicans*. For Studies 10833/10842.33, totals of 23 patients in each group had positive *Candida albicans* culture at baseline. The study demonstrated that miconazole group had a better overall investigator's rating statistically as compared to vehicle group (p = 0.014). However, it did not demonstrate statistical significance in the proportion of patients with 0 rash score on Day 7 (i.e., 35% vs. 13% with p = 0.087), and the proportion of patients with negative *Candida albicans* culture on Day 7 (i.e., 52% vs. 13% with p = 0.064).

On the other hand, Study 12966.37A had totals of 28 and 35 patients in the respective group with positive baseline culture. The study demonstrated statistical significance with respect to the proportion of patients with 0 rash score on Day 7 (i.e., 64% vs. 6% with p = 0.001), proportion of patients with negative culture on Day 7 (i.e., 93% vs. 17% with p = 0.001), and overall investigator's rating. It should be noted that results of the efficacy endpoints for miconazole group in studies 10833/10842.33 and 12966.37A are quite different. The response rates in Study 12966.37A are about two times of those in Study 10833/10842.33. This might be attributed to the number of study sites participated (1 site vs. 2 sites) and different clinical practice/evaluation (Australia vs. U.S.).

### 3.1.5 Study BT100

On the second non-approvable letter (dated 7/24/2000), the Agency cited a need for an adequate and well-controlled clinical trial to establish the safety and efficacy where the severity of the disease is adequately defined and *Candida albicans* involvement is proven. To support the

proposed efficacy claims, the sponsor conducted study BT100 which is the subject of the current NDA resubmission.

### 3.1.5.1 Study Design

According to the protocol of study BT100 (refer to IND21,542/SN-021 with stamp date of 11/14/2002), it was designed as double-blind, vehicle-controlled, multicenter and randomized. The original targeted location was 15 study sites in the U.S. The study objective was to evaluate the efficacy and tolerability of miconazole nitrate vs. vehicle in the treatment of cutaneous *Candidiasis* complicating diaper dermatitis. It turned out that the final study was conducted at 20 sites in the U.S., Latin America, and South America during April 2004 and June 2004. It should be noted that such a change of study location was documented in the sponsor's protocol amendment IV (dated 4/14/2004) and the Agency was not aware of it until at the Pre-NDA meeting (dated 7/27/2004). The Agency had requested the sponsor to address the issue of efficacy result extrapolation from foreign countries to the U.S., and to include a description of the clinical practices at non-U.S. sites, e.g., types of diapers, and frequency of changes.

The treatment duration was 7-day followed by a 3-week follow-up period. The study was planned to enroll at least 300 patients from 15 sites to derive at least 260 subjects having positive baseline KOH and culture for *Candida species*. With equal allocation to each treatment group, sponsor's sample size/power calculations, 130 per arm, yielded a power of 90% at a two-sided significance level of 0.05 assuming a treatment effect of 25%. The actual study enrollment was 330 patients from 20 study sites and resulted in 236 patients having positive baseline KOH and culture for *Candida species*. The study entry criteria included neonates, infants, and children 2-4 years of age and wearing commercially available diapers day/night.

### Reviewer's Comments:

*Sponsor's sample size/power calculation was based on a treatment effect of 25% between the active and vehicle arms. No response rates at Day 14 for each individual treatment were assumed in the protocol, as previous trials included only Day 7 response rates. It should be noted that, with a power of 90% at a two-sided level of 0.05, the range of miconazole response rates that reach the maximum sample size per arm of 90 are between 58% and 67% (i.e., 33%-42% in vehicle group). With equal treatment allocation, the planned sample size of 130 per arm takes into account patient dropouts. Though not explicitly, sponsor's sample size calculations assume an approximate similar dropout rates and a treatment effect of 25%.*

The enrolled patients were randomly assigned equally to miconazole and vehicle groups. The randomization resulted in 166 and 164 patients in the respective group. KOH and culture were taken from each patient at baseline to determine the presence of *Candidiasis*. Totals of 112 and 124 patients in the respective group were confirmed with *Candidiasis* and continued the study. Patients without the presence of *Candidiasis* at baseline were withdrawn from the study. Clinical measures were evaluated on Days 3, 5, 7, 14 and 28, with Day 14 as the primary time point for efficacy assessment.

Sponsor's randomization procedure was computer-generated. The patient randomization was study site basis. Following examining the sponsor's randomization list, the treatment assignments of 7 patients in study site 9 (John Fling – Fort Worth, Texas) were out of sequence. However, this is not expected to have an impact on the efficacy results.

The study was conducted in a double blind manner. At the conclusion of baseline visit, subjects were assigned with random study numbers that did not identify the treatment. The study packaging and the two treatments were indistinguishable in appearance. Additionally, study drug was dispensed by staffs that were neither performing clinical evaluations nor obtaining mycological samples, or performing the microscopy.

The primary efficacy endpoint pre-specified in the protocol and agreed upon with the Division was the overall cure rate on Day 14, where overall cure was defined as clinical cure (i.e., resolution of all signs/symptoms – diaper dermatitis severity index score of 0) plus mycological cure (i.e., negative KOH and culture). Sponsor's secondary efficacy endpoints included overall cure rate on Day 7, clinical cure rate and mycological cure rate on Days 7 and 14.

The evaluation of clinical signs/symptoms of diaper dermatitis was based on a 2 to 5-point scale for each of the three parameters listed below in diaper-covered area. The diaper dermatitis severity index score was then calculated as the sum of severity grades for each parameter evaluated (i.e. erythema, papules/pustules, and erosions). The maximum score possible for the diaper dermatitis severity index is 8.

Scale	Erythema	Papules/pustules	Erosions
0	None (to trace)	None to trace (0-5)	Absent
1	Mild (pink)	Few (6-10)	Present
2	Moderate (red)	Multiple (11-20)	--
3	Severe (beefy red)	Many (21-40)	--
4	--	Abundant (> 40)	--

The modified intent-to-treat (MITT) and per-protocol (PP) populations were analyzed for efficacy, with the MITT analyses as the primary. The MITT population included all subjects who were randomized and dispensed study drug and who had positive KOH and culture at baseline. The PP population was defined as all patients with confirmed *Candida species*, who met entry criteria, were dispensed study medication, and who completed the study with no noteworthy protocol violations, or who discontinued early due to treatment failure or treatment-related adverse events. Protocol violation included

- a. Failure to meet all inclusion/exclusion criteria;
- b. Non-compliance with treatment regimen;
- c. Use of disallowed medication at any time during the entire study period;
- d. Missing test-of-cure visit or a late test-of-cure visit (before Day 13 or after Day 16).

Sponsor's safety population included all randomized patients.

#### 3.1.5.2 Statistical Methods

Sponsor's statistical analysis plan in the protocol and submission included:

- For comparability of treatment groups at baseline, analysis of variance (ANOVA) was used to analyze continuous data and Cochran-Mantel-Haenszel (CMH) test, stratified by study site, for categorical data.
- Overall cure rate, clinical cure rate and mycological cure rate each was analyzed using CMH test stratified by study site. Breslow-Day test was used to assess the homogeneity of response rates across sites.

- For handling missing data on Day 14, the last observation carried forward (LOCF) method was used for signs/symptoms of diaper dermatitis. For subjects who did not have Day 14 culture results, sponsor imputed them as failures. The Agency requested that results based on the LOCF method for missing culture on Day 14 be submitted for review.
- According to the sponsor's protocol, 15 sites were planned to enroll at least 300 patients. A minimum of 10 culture positive subjects per arm per site was planned. For study sites that did not meet the criteria, sponsor's pre-specified site-pooling method was to start combining from the smallest enrollment site and proceeded to involve the next largest enrollment site. If pooling of site provided a minimum of 10 culture-positive subjects per arm, no additional sites were added. Based on this algorithm, sponsor pooled the 20 study sites into 8 grouped study centers which were used in the efficacy analyses. They are presented in the following:

Grouped center	Site ID	# of MITT pts in Miconazole	# of MITT pts in Vehicle
Group 1	2, 6, 8, 20	9	14
Group 2	3, 15, 16, 17, 21	10	10
Group 3	4, 5, 7, 11	11	15
Group 4	9	15	15
Group 5	18	21	23
Group 6	19	18	17
Group 7	22	12	15
Group 8	24	16	15
Total	All sites	112	124

- Two-sided Fisher's exact test was used to compare adverse event incidence rates between treatment groups.

### 3.1.5.3 Patient Disposition and Baseline Characteristics

To evaluate the comparability between treatments for study BT100, Table 5 presents results of the patient disposition. For patients who had positive culture at baseline, the enrollment with respect to study site is in Table A.1 of the Appendix. Their demographics and baseline characteristics are presented in Tables A.2-A.3 of the Appendix.

**Table 5: Patient Disposition – Study BT100**

Variable	Miconazole	Vehicle	Total
Number of patients enrolled	166	164	330
Safety population	166	164	330
MITT population	112	124	236
PP population	88 (79%)	105 (85%)	193 (82%)
Subjects excluded from PP population	24 (21%)	19 (15%)	43 (18%)
Failure to meet inclusion/exclusion	1 (0.9%)	0	1 (0.4%)
Non-compliance with treatment regimen	11 (10%)	9 (7%)	20 (8%)
Use of disallowed medication	3 (3%)	1 (0.8%)	4 (2%)
Early test-of-cure visit <sup>a</sup>	0	1 (0.8%)	1 (0.4%)
Late test-of-cure visit	1 (0.9%)	3 (2%)	4 (2%)
Missing test-of-cure visit	8 (7%)	5 (4%)	13 (6%)
<b>Source:</b> Sponsor's NDA submission (page 008 00112).			
<sup>a</sup> Test-of-cure visit = Day 14.			

About 67% and 76% of the enrolled patients were confirmed with positive culture in miconazole and vehicle group, respectively. These patients defined the MITT population and were evaluated for efficacy. Among the MITT population, about 79% and 85% of the patients in the respective group were included in the PP population.

Four non-U.S. sites (i.e., Site #18, 19, 22 and 24) included totals of 67 and 70 MITT patients in miconazole and vehicle group, respectively (Table A.1). This constitutes 60% and 56% of the MITT population in the respective group. For the treatment distribution by demographic and baseline characteristics in the MITT population, results in Tables A.2-A.3 generally show non-significant differences between treatment groups except the mean age (p-value = 0.019, Table A.2). Miconazole group appeared to have a lower mean age as compared to vehicle group (7.67 vs. 9.57 months). Subgroup results by age are examined in the section of special/subgroup populations. Note that more than 60% of patients in the MITT population are Hispanic/Latino origin, and only about 24.6% of patients are White origin. Subgroup results are examined in the section of special/subgroup populations.

The enrolled patients had a minimum of 3 in the Diaper Dermatitis Severity Index Score (out of the maximum of 8). Based on the sponsor's severity definition of diaper rash, about 64% and 62% of patients in the MITT population were severe in severity for miconazole and vehicle group, respectively (Table A.3). Among the MITT population, mycological culture was confirmed to be *Candida albicans* in about 97% and 98% of patients in the respective group. The remaining patients had cultures of other *Candida species* (Table A.3).

#### 3.1.5.4 Primary Efficacy Endpoint

The primary efficacy endpoint is the overall cure rate on Day 14, where overall cure is defined as clinical cure (i.e., resolution of all signs/symptoms) plus mycological cure (i.e., negative culture and KOH). For missing data handling, sponsor's pre-specified methods were LOCF for sign/symptom scores and imputing missing as failure for mycological endpoint.

Sponsor's results of the primary efficacy endpoint based on the MITT and PP populations are presented in Table 6. The summary is:

- Results based on the MITT and PP populations are consistent.
- Both analyses show that miconazole is superior to vehicle in the overall cure rate on Day 14. The cure rates are 23% vs. 10% with  $p = 0.005$  based on the MITT analysis; while they are 26% vs. 7% with  $p < 0.001$  based on the PP analysis.

**Table 6: Comparison of Overall Cure Rate on Day 14 (Sponsor's Results)  
Study BT100**

Population	Miconazole	Vehicle	Comparison <sup>a</sup>
MITT	26/112 (23%)	12/124 (10%)	0.005
PP	23/88 (26%)	7/105 (7%)	< 0.001

Source: Sponsor's NDA submission (page 008 00118).  
<sup>a</sup> p-value from Cochran-Mantel-Haenszel test stratifying for grouped center.

### 3.1.5.5 Missing Data Handling and Sensitivity Analyses

The LOCF method was the pre-specified imputation method for sign/symptom score. The sponsor specified the method of “failure” for imputing missing culture. To be consistent with the methods used, the Agency had asked the sponsor to impute missing cultures based on the LOCF method. The sponsor conducted analyses by imputing missing cultures using the LOCF method. Results are identical to those based on the treatment failures for missing cultures. To examine the robustness of the imputation methods on the primary efficacy results, missing data rate over visit is examined (both sign/symptom and culture data). They are presented in Table 7.

It should be noted that missing data rates for the two treatment groups were comparable on Day 7, however, not on Day 14. Vehicle group appeared to have a higher missing data rate as compared to miconazole arm (52% vs. 13% with  $p < 0.001$ , based on Fisher’s exact test). Imputing missing cultures as treatment failures would be in favor of miconazole group. To examine if any study sites had in particular higher missing data rates, results of missing data rate along with the overall cure rate by investigational site are presented in Table A.4 of the Appendix.

**Table 7: Missing Data Rate over Visit (MITT) – Study BT100**

Visit	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>a</sup>
Baseline	0	0	1.000
Day 7	7 (6%)	10 <sup>b</sup> (8%)	0.591
Day 14	14 (13%)	65 <sup>c</sup> (52%)	< 0.001

**Source:** Sponsor’s electronic data at \\cdsesub\21026\N\_000\Hpbio\NDA\_21-026\BT100-USA-001.

<sup>a</sup> p-value from Fisher’s exact test.

<sup>b</sup> Based on the sponsor’s data sets. Sponsor’s submission listed as 11 (9%).

<sup>c</sup> Based on the sponsor’s data sets. The culture on Day 14 for Patient 411 was not done. Therefore, the culture of Patient 411 should be missing. Sponsor’s submission listed as 64 (52%).

Despite the majority patients were enrolled from the non-U.S. sites (i.e., 67 and 70 patients in miconazole and vehicle, respectively), it should be noted that missing data rates at the U.S. sites were 22% (= 10/45) and 70% (= 38/54) in miconazole and vehicle group, respectively, which are higher than those at the non-U.S. sites of 6% (= 4/67) vs. 39% (= 27/70).

To check the robustness of the efficacy results, sensitivity analyses based on the following are performed:

- a. Comparison of treatments based on the patients who had data on Day 14.
- b. Impute missing based on the response rate of patients having data in the respective group.

Results are:

- a. Totals of 98 (87.5%) and 59 (47.6%) MITT patients in miconazole and vehicle group, respectively, had data on Day 14. Totals of 26 and 12 MITT patients had overall cure of the disease. This resulted in the overall cure rates of 26.5% vs. 20.3% for miconazole vs. vehicle based on the patients who had data. The comparison yields a p value of 0.406. Such a non-significant result is due to the reduced sample sizes and a smaller treatment effect (i.e., 6.2%).

- b. Assuming the patients who had missing data had the same overall cure rate as others in the respective group, i.e., 26.5% vs. 20.3% for miconazole vs. vehicle based on sample size of 112 vs. 124, the resulted p values based on chi-square, CMH chi-square, and Fisher's exact test are 0.229, 0.230 and 0.281, respectively. The superiority of miconazole to its vehicle is not established. Alternatively, a simulation is performed by imputing missing with the overall cure rates of 26.5% and 20.3% for the respective group. Due to the variation of simulated data, a total of 10,000 simulated trials are evaluated instead of reporting results from only one simulated trial. The probability that miconazole is superior to vehicle would be only about 8%, if the trial had been repeated 10,000 times.

In summary, vehicle arm had a significantly higher missing data rate of 52% on Day 14 as compared to 13% in miconazole group ( $p < 0.001$ ). Such an imbalanced missing data rate has a great impact on the imputation methods used. By imputing missing as failures, the overall cure rates on Day 14 would be in favor of miconazole group. Sensitivity analyses based on the completed cases and imputing missing based on the response rate of the patients who had data in the respective group are performed. The superiority of miconazole to vehicle is not established based on the completed cases. The overall cure rates are 26.5% vs. 20.3% for miconazole vs. vehicle with  $p = 0.406$  based on Cochran-Mantel-Haenszel test adjusting for grouped center. Assuming missing-data patients had the same overall cure rate as others in the respective group, the superiority of miconazole to its vehicle is not established because of  $p = 0.281$  based on Fisher's exact test. Furthermore, a simulation study based on 10,000 trials gives a small probability of 8% that miconazole is superior to vehicle, when missing were imputed using the response rates of the patients who had data in the respective group.

It should be noted that, at the protocol stage, the sponsor's sample size/power calculations assumed a treatment effect of 25% (IND 21,542/SN-021). Accounting for similar dropouts, totals of 130 patients per arm with confirmed KOH and culture were planned. The current trial resulted in a treatment effect of 6.2% based on the completed cases which is smaller than the assumed treatment effect of 25%. The dropout rate in vehicle arm was 4-fold of that of miconazole group. Such a dramatic difference between groups in dropouts has a great impact on the efficacy conclusions as stated in the previous paragraph. Consequently, the efficacy results in Study BT100 are not robust to the imputation methods used.

Another note is that, according to the sponsor's submission, 4 and 58 patients in miconazole and vehicle group, respectively, withdrew from the study (i.e., had missing data) due to clinical failure/worsening/lack of improvement (page 008 00111). It should be a clinical judgment to evaluate the case report forms of these patients for verification of study withdrawal.

#### 3.1.5.6 Secondary Efficacy Endpoint

Sponsor's secondary efficacy endpoints included:

- Overall cure rate on Day 7
- Clinical cure rates on Days 7 and 14
- Mycological cure rates on Days 7 and 14.

Results of the secondary efficacy endpoints are presented in Tables A.5-A.7 of the Appendix, respectively. Missing data are imputed based on the LOCF method as the dropouts are

comparable between treatments on Day 7. Comments about results in clinical cure rate on Day 14 based on the LOCF method for handling missing data are provided in the section. The summary is:

- Miconazole is better than vehicle on Day 7 for the overall cure rate ( $p = 0.010$ , Table A.5).
- Miconazole is superior to vehicle with respect to the clinical cure rate on Days 7 and 14 ( $p < 0.001$  on both days, Table A.6).
- For mycological response, miconazole is better than vehicle on Days 7 and 14 ( $p = 0.001$  and  $< 0.001$ , respectively, Table A.7).

Per the previous section, vehicle arm had a significantly higher missing data rate on Day 14 than miconazole group (i.e., 52% vs. 13%). The missing rates of sign/symptom score on Day 14 were 12% (13/112) vs. 51% (= 63/124) for miconazole vs. vehicle. Patient 266 in miconazole group had sign/symptom score, but culture specimen was never received by lab. Patients 411 and 415 in vehicle group had sign/symptom scores, but cultures were not done.

As results of the primary efficacy endpoint are sensitive to the different imputation methods used, to examine the robustness of results of clinical cure rate on Day 14, sensitivity analyses based on the following are done:

- a. Comparison of treatments based on the patients who had sign/symptom score data on Day 14.
- b. Impute missing based on the response rate of patients having data in the respective group.

Results of the sensitivity analyses for clinical cure rate on Day 14 are summarized:

- a. Totals of 99 (88%) and 61 (49%) MITT patients in miconazole and vehicle group, respectively, had sign/symptom score data on Day 14. Totals of 43 and 14 MITT patients were clinical cure (i.e., sum of all sign/symptom scores of 0). This resulted in the clinical cure rates of 43.43% vs. 22.95% for miconazole vs. vehicle based on the patients who had data. The comparison yields  $p = 0.013$  based on Cochran-Mantel-Haenszel test adjusting for grouped center; and  $p = 0.011$  based on Fisher's exact test.
- b. A simulation is performed by imputing missing with the clinical cure rates of 43.43% and 22.95% for the respective group in a similar manner as the primary efficacy endpoint. A total of 10,000 simulated trials are evaluated. The probability that miconazole is superior to vehicle among the 10,000 simulated trials is about 99%.

In summary, miconazole treatment is found to be more effective than its vehicle with respect to the clinical cure rate on Day 14. This can be observed from analyses by imputing missing with the LOCF and failures ( $p < 0.001$ ). In addition, the superiority of miconazole to vehicle is also supported for the completed cases ( $p = 0.013$ ). Furthermore, a simulation study based on 10,000 trials gives a probability of 99% that miconazole is superior to vehicle, when missing were imputed using the response rates of the patients who had data in the respective group.

In conclusion, vehicle had a significantly higher missing data rate than miconazole group on Day 14 (i.e., 52% vs. 13%). Such different missing data rates had a great impact on the efficacy results for the primary efficacy endpoint (i.e., overall cure rate). However, it does not affect the conclusion for the clinical cure rate.

### 3.1.6 Results Comparison among Studies

Based on the results available and presented in this review, clinical cure rate (or zero rash score rate) and mycological cure rate on Day 7 for patients who were confirmed with positive *Candidiasis* may be compared across studies. Results are presented in Table A.8 of the Appendix. Missing data were imputed using the LOCF method. The summary is:

- For clinical cure rate (or zero rash score rate), all studies showed that miconazole is better than vehicle. Studies 10833/10842.33 and BT100 are quite consistent with respect to the clinical cure rate with a treatment effect of 22%. The non-significance outcome in study 10833/10842.33 is due to a smaller sample size. On the contrary, the zero rash score rate, 64%, in study 12966.37A for miconazole group is larger than those of other studies.
- For mycological cure, all studies showed that miconazole group is better than vehicle arm. The treatment effect is different from study to study and range from 19% to 76%.

### 3.2 Evaluation of Safety

Safety assessment based on the extent of drug exposure and the incidence rates of adverse events is summarized for Study BT100. Sponsor's safety population includes all randomized subjects. Totals of 166 and 164 patients were included in the safety population for miconazole and vehicle group, respectively. In addition, the extent of drug exposure for the MITT population is also summarized.

#### 3.2.1 Extent of Drug Exposure

Results of the extent of drug exposure are presented in Table 8 for both the safety and MITT populations.

**Table 8: Extent of Drug Exposure (Safety and MITT) – Study BT100**

Variable	Safety Population		MITT Population	
	Miconazole (n=166)	Vehicle (n=164)	Miconazole (n=112)	Vehicle (n=124)
<b>Number of Applications</b>				
N	156	159	105	122
Mean (s.d.)	49.49 (19.47)	48.08 (20.37)	54.68 (19.23)	49.70 (20.19)
Range	9.0 – 104.0	7.0 – 96.0	9.0 – 104.0	7.0 – 96.0
<b>Total Applications</b>				
N	156	159	105	122
1 – 27	16 (10%)	22 (14%)	3 (3%)	13 (11%)
28 – 56	90 (58%)	90 (57%)	59 (56%)	70 (57%)
57 – 84	39 (25%)	36 (23%)	32 (30%)	30 (25%)
> 84	11 (7%)	11 (7%)	11 (10%)	9 (7%)
<b>Study Medication Usage (in grams)</b>				
N	159	160	107	123
Mean (s.d.)	26.66 (14.81)	27.45 (14.50)	28.89 (15.36)	28.49 (14.07)
Range	1.7 – 56.1	2.9 – 55.8	1.7 – 56.1	2.9 – 55.8

Source: Sponsor's NDA submission (pages 008 00134-00135).

The following gives a summary:

- The two treatment groups were generally comparable with respect to the total applications and total amount of study medication usage based on safety population.

- For the MITT population, miconazole group had a numerically higher number of applications. However, the mean total amount of study medication usage is comparable between the two groups. They were 28.89 grams vs. 28.49 grams for miconazole vs. vehicle.

### 3.2.2 Incidence of Adverse Event

Results of adverse event incidence rate are presented in Table 9. P values are listed for reference purpose only as the study was not designed to detect significant safety parameters. The summary of Table 9 is:

- The overall incidence rates were 22% vs. 19% for miconazole vs. vehicle with  $p = 0.585$  (Fisher's exact test).
- The majority events were mild in severity and all events were judged to be unlikely or unrelated to the study drug.
- The most frequent adverse event was related to infections and infestations with the incidence rates of 12% vs. 10% for miconazole vs. vehicle with  $p = 0.728$ .

**Table 9: Number (%) of Patients with Adverse Events (Safety) – Study BT100**

Category	Miconazole (n = 166)	Vehicle (n = 164)
Number of subjects had at least one AE	36 (22%)	31 (19%)
Total number of AEs	53	47
Serious		
No	53	47
Yes	0	0
Severity of AE		
Mild	38	35
Moderate	15	11
Severe	0	1
Relationship to Study Drug		
Definite	0	0
Probable	0	0
Possible	0	0
Unlikely	2	0
Unrelated	51	47
Number of patients had AE by system organ		
Ear and labyrinth disorders	1 (1%)	1 (1%)
Gastrointestinal disorders	7 (4%)	7 (4%)
General disorders and administration site	6 (4%)	5 (3%)
Infection and infestations	20 (12%)	17 (10%)
Injury, poisoning and procedural complications	1 (1%)	4 (2%)
Respiratory, thoracic and mediastinal disorders	9 (5%)	4 (2%)
Skin and subcutaneous tissue disorders	1 (1%)	1 (1%)

Source: Sponsor's NDA submission (pages 008 00202-00204).

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup efficacy results on the primary efficacy endpoint by gender, race, age and baseline diaper rash severity are examined. The results are presented in Tables A.9-A.10 of the Appendix. As results of the primary efficacy endpoint are sensitive to the imputation methods, results presented in Tables A.9-A.10 are based on the observed cases. It should be noted that subgroup

results are intended to explore efficacy trend over subgroups. The studies were not designed to test efficacy within subgroups.

#### 4.1 Gender, Race and Age

The MITT population included a higher female participation. The enrollment rates were 54% vs. 46% for female vs. male. Generally, miconazole treatment had higher overall cure rates than vehicle group regardless of gender. Note that male patients had higher observed overall cure rates as compared to female patients regardless of treatment groups. The observed overall cure rate for male vs. female was 32.6% vs. 21.8% in miconazole arm; while it was 24.1% vs. 16.7% in vehicle group (Table A.9). The treatment effect was higher for male patients than female patients (i.e., 8.5% for males and 5.1% for females).

Subgroup efficacy results show that miconazole is better than vehicle regardless of race/ethnicity. About 62% of the MITT patients are Hispanic/Latino origin; while only 24.6% of patients are White origin. There maybe an issue if the study population represents the demographics of the U.S. population. The observed overall cure rates were 30% vs. 22.2% for miconazole vs. vehicle for White patients; while 24.6% vs. 21.7% for the respective group in Hispanic/Latino patients. Thus, the inclusion of Hispanic/Latino patients actually works in favor of vehicle rather than miconazole. For Black and Other race groups, miconazole treatment had higher observed overall cure rates than vehicle arm. They were 10% vs. 0% for Black; while they were 100% vs. 0% for Other race.

The mean age between two treatment groups was significantly different ( $p = 0.019$ , Table A.2). Patients in miconazole group had a lower mean age than that of vehicle group (7.67 vs. 9.59 months). The division of age into 6 groups (i.e., less than 3 months, 3 to 6 months, 6 to 12 months, 12 to 24 months, 24 to 36 months, and 36 months and older) showed that miconazole treatment had more patients in the younger age groups; while vehicle arm had more patients in the older age groups. Results of the overall cure rate over age groups are presented. Miconazole treatment is numerically better than vehicle for age groups of between 3 and 6 months (33.3% vs. 18.8%), and between 6 and 12 months (34.1% vs. 22.2%). For patients younger than 3 months old, vehicle arm is numerically better than miconazole. The observed overall cure rates were 20% vs. 14.3%.

#### 4.2 Other Special/Subgroup Populations

Subgroup efficacy results by location (U.S. vs. non-US sites), baseline Diaper Dermatitis Severity Index score, and type of baseline *Candida species* are presented in Table A.10 of the Appendix. The summary is:

- Miconazole treatment is better than vehicle regardless of the location of study sites (i.e., U.S. vs. non-U.S.) with respect to the observed overall cure rate. However, the non-U.S. sites had a relatively larger treatment effect (6.8% vs. 3.6%). The observed overall cure rates are 28.6% vs. 25% for miconazole vs. vehicle in the U.S. sites; while they are 25.4% vs. 18.6% in the non-U.S. sites.
- Miconazole treatment is better than vehicle for all baseline index score except score of 3, where the observed overall cure rates are 33.3% vs. 42.9% for miconazole vs. vehicle. The efficacy trend of miconazole generally can be observed.

- As about 97% and 98% of the MITT patients in miconazole and vehicle group, respectively, had *Candida albicans* at baseline, the efficacy of miconazole to vehicle for patients with *Candida albicans* at baseline is generally similar to the MITT analyses. It appears that both miconazole and vehicle does not have effect on *Candida species* other than *albicans*.

Per clinical request, subgroup efficacy results by type of diaper used during the trial are presented in Table A.10. It should be noted that all MITT patients at the U.S. sites wore solely disposable diapers; while the majority of MITT patients (about 66%) at the non-U.S. sites wore both disposable and cloth diapers. The summary is:

- The two treatment groups had similar observed overall cure rates for patients who wore disposable diapers. The observed overall cure rates are 21.1% (= 12/57) vs. 20% (= 6/30) for miconazole vs. vehicle. They are 28.6% vs. 25% in the U.S. sites; while 9.1% vs. 14.3% in the non-U.S. sites.
- On the other hand, miconazole group had a better cure rate than vehicle group for patients who wore disposable/cloth diapers. The observed overall cure rates are 34.1% vs. 20.7% for miconazole vs. vehicle.

As the observed overall cure rates in the two treatments are different between the U.S. and non-U.S. sites for patients who wore disposable diapers, results on the number of diaper change per day over treatment group, country, type of diaper used, and whether overall cure on Day 14 attained are summarized in Table A.11 of the Appendix. The summary is:

- For patients with no overall cure, the numbers of diaper change are comparable between treatment groups regardless of country and type of diaper used.
- For patients who wore disposable diapers, they were changed more often in the U.S. sites than the non-U.S. sites regardless of overall cure on Day 14 and treatment received.
- For patients who wore disposable diapers and had overall cure on Day 14, they were changed, on the average, more often in the U.S. sites than the non-U.S. sites (10.1 vs. 8.0 for miconazole vs. vehicle in the U.S. sites, as compared to 8.5 vs. 4.0 in the non-U.S. sites). This may explain higher observed cure rates in the U.S. sites than the non-U.S. sites.
- For patients who had overall cure on Day 14, patients wearing disposable/cloth diapers changed more often than those wearing disposable diapers. Higher cure rates in miconazole group for patients who wore disposable/cloth diapers as compared to disposable diapers are observed. The observed overall cure rates are 34.1% vs. 20.7% for miconazole vs. vehicle for patients who wore disposable/cloth diapers; while they are 21.1% vs. 20% for the respective group for patients who wore disposable diapers.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The primary efficacy endpoint in study BT100 is the overall cure rate on Day 14 which was agreed upon with the Division. It is defined as clinical cure (i.e., resolution of signs/symptoms) plus mycological cure (i.e., negative KOH and culture). The proposed missing data handling for the two components were the last observation carried forward (LOCF) for signs/symptoms and treatment failure for mycological endpoint. The Division had requested that missing mycological endpoint be imputed using the LOCF. The results are identical.

The critical statistical issue in the current application is the missing data handling in efficacy analyses. It should be noted that sponsor's sample size calculation for the study at the IND stage assumed a treatment effect of 25%. Patients were assigned to treatments with an equal allocation ratio. Accounting for similar dropouts, totals of 130 patients per arm with confirmed KOH and culture at baseline were planned. The two treatment groups were comparable in terms of missing data rate on Day 7. However, vehicle arm had a significantly higher missing data rate than miconazole group on Day 14 which is the primary time point for efficacy assessment for study BT100. The missing data rates on Day 14 were 52% vs. 13% for vehicle vs. miconazole. Several sensitivity analyses were conducted to evaluate the robustness of efficacy results due to different imputation methods. As a result, a great impact on the efficacy results for the primary efficacy endpoint, overall cure rate on Day 14, is observed.

## 5.2 Conclusions and Recommendations

The sponsor in this resubmission presented results for study BT100 in support of the efficacy and safety claim of Miconazole nitrate, 0.5% ointment for the treatment of diaper dermatitis complicated by *Candidiasis*. The dosing of miconazole nitrate, 0.5%, is applying to diaper area after each diaper change (about 5 to 12 times daily) for 7 days. Results of the primary efficacy endpoint (i.e., overall cure rate) based on the MITT population with the last observation carried forward (LOCF) method for handling missing data, as well as other sensitivity analyses are presented in Table E.1 for Study BT100.

Table E.1: Comparison of Overall Cure Rate on Day 14 – Study BT100

Imputation	Miconazole	Vehicle	Comparison
LOCF (or treatment failure)	26/112 (23%)	12/124 (10%)	0.005 <sup>a</sup>
Observed cases	26/98 (26.5%)	12/59 (20.3%)	0.406 <sup>a</sup>
Imputing missing based on the observed cure rate	30/112 (26.8%)	25/124 (20.2%)	0.281 <sup>b</sup>
<b>Source:</b> Table 6 in this review and sponsor's data sets at \\cdsesub\21026\21_000\Hpbio\NDA_21-026\BT100-USA-001. <sup>a</sup> p value from CMH test adjusting for investigational group. <sup>b</sup> p value from Fisher's exact test.			

The following summarizes the results:

1. As vehicle arm had a significantly higher missing data rate on Day 14 than miconazole arm (i.e., 52% vs. 13% with  $p < 0.001$ ), efficacy results of the overall cure rate are sensitive to different imputation methods. This is evident from the summary stated in the following:
  - a. Imputing missing based on LOCF method or as treatment failure yielded superiority outcome of miconazole to vehicle. The overall cure rates are 23% vs. 10% for miconazole vs. vehicle with  $p = 0.005$ . It should be noted that imputing missing as treatment failures would be in favor of miconazole group, as vehicle arm had a significantly higher missing data rate than miconazole (52% vs. 13%).
  - b. However, the superiority of miconazole to vehicle is not established based on the observed cases. The observed overall cure rates are 26.5% vs. 20.3% for miconazole vs. vehicle with  $p = 0.406$ . The observed treatment effect is 6.2% which is smaller than the assumed 25% in the sample size calculation.
  - c. The superiority of miconazole to vehicle is not established by imputing missing based on the observed cure rate in the respective group. The resulted p value is 0.281 based on the

Fisher's exact test. Alternatively, a simulation based on 10,000 simulated trials is performed by imputing missing with the observed cure rate for the respective group. The probability (or power) that miconazole is superior to vehicle is found to be only about 8%.

2. Study BT100 enrolled more than 60% of MITT patients as Hispanic/Latino origin and only about 24.6% of White origin. It is a clinical judgment if the study population sufficiently represents the demographics of the U.S. population.

The summary with respect to the adverse event incidence is stated below. P values are listed for reference purpose only as the study was not designed for detecting significant safety parameters.

- The overall adverse event incidence rates were 22% vs. 19% for miconazole vs. vehicle with  $p = 0.585$  (Fisher's exact test).
- The majority events were mild in severity and all events were judged to be unlikely or unrelated to the study drug.
- The most frequent adverse event was related to infections and infestations with the incidence rates of 12% vs. 10% for miconazole vs. vehicle with  $p = 0.728$ .

**Appears This Way  
On Original**

## APPENDICES

### Additional Tables

**Table A.1: Patient Enrollment by Investigational Site – Study BT100**

Site ID	Investigator (Location)	# of patients enrolled	MITT	
			Miconazole	Vehicle
1		1	0	0
2		12	3	4
3		5	2	1
4		19	6	8
5		4	1	0
6		13	2	4
7		4	0	1
8		10	2	5
9	Fling (Fort Worth, TX)	39	15	15
11		18	4	6
12		2	0	0
15		13	3	4
16		13	3	5
17		2	1	0
18		52	21	23
19	Briones (Ecuador) <sup>a</sup>	41	18	17
20		4	2	1
21		1	1	0
22		39	12	15
24		38	16	15

**Source:** Sponsor's NDA submission (page 008 00142).  
<sup>a</sup>Non-U.S. sites.

b(4)

Appears This Way  
on Original

**Table A.2: Patient Demographics (MITT) – Study BT100**

Variable	Miconazole (n = 112)	Vehicle (n = 124)	comparison
Age (months)			
Mean (s.d.)	7.67 (4.87)	9.59 (6.89)	0.019 <sup>a</sup>
Median	7.46	7.72	
Range	0.4-24.5	0.6-30.5	
Age < 3	22 (20%)	17 (14%)	
3 ≤ Age < 6	21 (19%)	27 (22%)	
6 ≤ Age < 12	49 (44%)	46 (37%)	
12 ≤ Age < 24	19 (17%)	26 (21%)	
24 ≤ Age < 36	1 (1%)	8 (6%)	
36 or older	0	0	
Gender			
Male	51 (46%)	57 (46%)	0.813 <sup>b</sup>
Female	61 (54%)	67 (54%)	
Race			
White	24 (21%)	34 (27%)	0.384 <sup>b</sup>
Black	14 (13%)	8 (6%)	
Asian/Pacific Islander	0	0	
Hispanic/Latino	70 (63%)	76 (61%)	
American/Alaskan Native	0	1 (1%)	
Other	4 (4%)	5 (4%)	
Skin Type			
I	5 (4%)	7 (6%)	0.748 <sup>b</sup>
II	18 (16%)	13 (10%)	
III	18 (16%)	31 (25%)	
IV	49 (44%)	56 (45%)	
V	17 (15%)	11 (9%)	
VI	5 (4%)	6 (5%)	
Source: Sponsor's NDA submission (pages 008 00145 and 00150).			
<sup>a</sup> p-value from ANOVA with factors of treatment and grouped center.			
<sup>b</sup> p-value from CMH test stratifying by grouped center.			

Appears This Way  
 On Original

**Table A.3: Patient Baseline Characteristics (MITT) – Study BT100**

Variable	Miconazole (n = 112)	Vehicle (n = 124)	Comparison
<b>Erythema</b>			
0 – None	0	0	0.307 <sup>a</sup>
1 – Mild	0	0	
2 – Moderate	81 (72%)	96 (77%)	
3 – Severe	31 (28%)	28 (23%)	
<b>Papules/Pustules</b>			
0 – None	0	0	0.848 <sup>a</sup>
1 – Few (1-10)	20 (18%)	28 (23%)	
2 – Multiple (11-20)	53 (47%)	45 (36%)	
3 – Many (21-40)	30 (27%)	40 (32%)	
4 – Abundant (> 40)	9 (8%)	11 (9%)	
<b>Erosions</b>			
0 – Absent	53 (47%)	64 (52%)	0.560 <sup>a</sup>
1 – Present	59 (53%)	60 (48%)	
<b>Diaper Dermatitis Severity Index Score</b>			
3	9 (8%)	15 (12%)	0.660 <sup>a</sup>
4	31 (28%)	32 (26%)	
5	38 (34%)	38 (31%)	
6	18 (16%)	22 (18%)	
7	11 (10%)	13 (10%)	
8	5 (4%)	4 (3%)	
Mean (s.d.)	5.05 (1.25)	4.98 (1.28)	0.661 <sup>b</sup>
Range	3 – 8	3 – 8	
<b>Severity<sup>c</sup> of Diaper Rash</b>			
Moderate	40 (36%)	47 (38%)	0.681 <sup>a</sup>
Severe	72 (64%)	77 (62%)	
<b>Mycological Culture</b>			
<i>Candida albicans</i>	109 (97%)	121 (98%)	0.788 <sup>a</sup>
Other <i>Candida spp.</i>	3 (3%)	3 (2%)	
Both cultures negative	0	0	
Not reported	0	0	
<b>Source:</b> Sponsor's NDA submission (pages 008 00150 – 00152).			
<sup>a</sup> p-value from CMH test for row mean scores, stratified by grouped center.			
<sup>b</sup> p-value from ANOVA with factors of treatment and grouped center.			
<sup>c</sup> Severity of diaper rash at baseline was defined by the Diaper Dermatitis Severity Index Score: 3 – 4 = moderate; 5 – 8 = severe.			

Appears This Way  
 On Original

**Table A.4: Missing Data Rate and Overall Cure<sup>a</sup> Rate on Day 14 by Investigational Site – Study BT100**

Site ID	Investigator (Location)	# of patients enrolled	MITT Population		Missing Rate		Overall Cure Rate	
			Miconazole	Vehicle	Miconazole	Vehicle	Miconazole	Vehicle
1		1	0	0	0/0	0/0	0/0	0/0
2		12	3	4	0/3	1/4 (25%)	1/3 (33%)	1/4 (25%)
3		5	2	1	0/2	1/1 (100%)	0/2	0/1
4		19	6	8	2/6 (33%)	6/8 (75%)	2/6 (33%)	0/8
5		4	1	0	0/1	0/0	0/1	0/0
6		13	2	4	2/2 (100%)	2/4 (50%)	0/2	0/4
7		4	0	1	0/0	0/1	0/0	1/1 (100%)
8		10	2	5	0/2	5/5 (100%)	2/2 (100%)	0/5
9	Fling (Fort Worth, TX)	39	15	15	4/15 (27%)	12/15 (80%)	4/15 (27%)	1/15 (7%)
11		18	4	6	1/4 (25%)	2/6 (33%)	0/4	0/6
12		2	0	0	0/0	0/0	0/0	0/0
15		13	3	4	0/3	4/4 (100%)	0/3	0/4
16		13	3	5	0/3	4/5 (80%)	0/3	1/5 (20%)
17		2	1	0	0/1	0/0	0/1	0/0
18		52	21	23	2/21 (10%)	6/23 (26%)	5/21 (24%)	4/23 (17%)
19	Briones (Ecuador) <sup>b</sup>	41	18	17	0/18	8/17 (47%)	6/18 (33%)	0/17
2		4	2	1	0/2	1/1 (100%)	1/2 (50%)	0/1
2		1	1	0	1/1 (100%)	0/0	0/1	0/0
2		39	12	15	1/12 (8%)	4/15 (27%)	1/12 (8%)	2/15 (13%)
2		38	16	15	1/16 (6%)	9/15 (60%)	4/16 (25%)	2/15 (13%)
Total	All Location	330	112	124	14/112 (13%)	65/124 (52%)	26/112 (23.2%)	12/124 (9.7%)

<sup>a</sup> Source: Sponsor's electronic data at \\cdsesub\h21026\h\_000\Hpbio\NDA\_21-026\BT100-USA-001.

<sup>b</sup> Results of overall cure rate are based on LOCF for handling missing data.

<sup>c</sup> Non-U.S. sites.

Appears This Way  
 On Original

**Table A.5: Overall Cure<sup>a</sup> Rate by Visit (MITT) – Study BT100**

Visit	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>b</sup>
Baseline	0	0	--
Day 7	8 (7%)	1 (0.8%)	0.010
Day 14	26 (23%)	12 (10%)	0.005

**Source:** Sponsor's NDA submission (pages 008 00159-00160) and electronic data at \\cdsesub\21026\21000\Hpbio\NDA\_21-026\BT100-USA-001.  
<sup>a</sup> Overall cure is defined as clinical cure (i.e., all sign/symptom scores of 0) plus mycological cure (i.e., negative culture). Missing is based on LOCF.  
<sup>b</sup> p value from CMH test adjusting for investigational group.

**Table A.6: Clinical Cure<sup>a</sup> Rate by Visit (MITT) – Study BT100**

Visit	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>b</sup>
Baseline	0	0	--
Day 3	0	1 (1%)	--
Day 5	2 (2%)	1 (1%)	--
Day 7	27 (24%)	3 (2%)	< 0.001
Day 14	43 (38%)	14 (11%)	< 0.001

**Source:** Sponsor's NDA submission (page 008 00189).  
<sup>a</sup> Clinical cure is defined as the resolution of all sign/symptom (i.e., sum of sign/symptom scores of 0). Missing is imputed based on LOCF.  
<sup>b</sup> p value from CMH test adjusting for investigational group.

Appears This Way  
 On Original

**Table A.7: Mycological Response by Visit (MITT) – Study BT100**

Visit	Response	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>c</sup>
Baseline	<i>Candida albicans</i>	109 (97%)	121 (98%)	0.788
	Other <i>Candida spp.</i>	3 (3%)	3 (2%)	
	Both cultures negative	0	0	
	Missing	0	0	
Day 7	<i>Candida albicans</i>	57 (51%)	88 (71%)	0.004
	Other <i>Candida spp.</i>	5 (4%)	2 (2%)	
	Both cultures negative	43 (38%)	24 (19%)	
	Missing	7 (6%)	10 <sup>a</sup> (8%)	
	Mycological Cure Rate (LOCF)	43 (38%)	24 (19%)	
Day 14	<i>Candida albicans</i>	39 (35%)	29 (23%)	< 0.001
	Other <i>Candida spp.</i>	3 (3%)	1 (<1%)	
	Both cultures negative	56 (50%)	29 (23%)	
	Missing	14 (13%)	65 <sup>b</sup> (52%)	
	Mycological Cure Rate (LOCF)	58 (52%)	36 (29%)	
<p><b>Source:</b> Sponsor's NDA submission (pages 008 00152, 00159, and 00160) and electronic data set at \\cdsesub\n21026\n_000\Hpbio\NDA_21-026\BT100-USA-001.</p> <p><sup>a</sup>Based on the sponsor's data sets. Sponsor's submission listed as 11 (9%).</p> <p><sup>b</sup>Based on the sponsor's data sets. The culture on Day 14 for Patient 411 in vehicle arm was not done. Therefore, the culture of Patient 411 should be missing. Sponsor's submission listed as 64 (52%).</p> <p><sup>c</sup>Comparison of distribution of data in various categories. For comparison of mycological cure rate based on the LOCF method for missing data, p value is from CMH test adjusting for investigational group.</p>				

Appears This Way  
 On Original

**Table A.8: Results Comparison on Day 7 among Studies 10833/10842.33,  
12966.37A and BT100**

Study	Clinical Cure Rate			Mycological Cure Rate		
	Miconazole	Vehicle	Comparison	Miconazole	Vehicle	Comparison
10833/10842.33	8/23 (35%)	3/23 (13%)	0.087	12/23 (52%)	3/23 (13%)	0.064
12966.37A	18/28 (64%)	2/35 (6%)	0.001	26/28 (93%)	6/35 (17%)	0.001
BT100	27/112 (24%)	3/124 (2%)	< 0.001	43/112 (38%)	24/124 (19%)	0.001

Source: Tables 2-3 and Tables A.6 and A.7 of the Appendix in this review.

Appears This Way  
On Original

**Table A.9: Subgroup Results of Observed Overall Cure Rate on Day 14  
 by Demographics (MITT) – Study BT100**

Subgroup (Observed results)	Miconazole (n = 112)	Vehicle (n = 124)	Missing (Micon., Vehicle)
Overall	26/98 (26.5%)	12/59 (20.3%)	(14, 65)
Gender			
Male	14/43 (32.6%)	7/29 (24.1%)	(8, 28)
Female	12/55 (21.8%)	5/30 (16.7%)	(6, 37)
Race			
White	6/20 (30%)	2/9 (22.2%)	(4, 25)
Black	1/10 (10%)	0/2 (0%)	(4, 6)
Hispanic/Latino	16/65 (24.6%)	10/46 (21.7%)	(5, 30)
Asian/Pacific Islander	NA	NA	NA
American/Alaska Native	0	0/1 (0%)	(0, 0)
Other	3/3 (100%)	0/1 (0%)	(1, 4)
Age			
Age < 3 months	3/21 (14.3%)	2/10 (20%)	(1, 7)
3 ≤ age < 6 months	6/18 (33.3%)	3/16 (18.8%)	(3, 11)
6 ≤ age < 12 months	14/41 (34.1%)	4/18 (22.2%)	(8, 28)
12 ≤ age < 24 months	3/18 (16.7%)	2/12 (16.7%)	(1, 14)
24 ≤ age < 36 months	NA	1/3 (33.3%)	(1, 5)
age ≥ 36 months	NA	NA	NA
<b>Source:</b> Sponsor's electronic data sets at \\cdsesub\21026\000\Hpbio\NDA_21-026\BT100-USA-001.			

Appears This Way  
 On Original

**Table A.10: Subgroup Results of Observed Overall Cure Rate on Day 14  
 by Baseline Characteristics (MITT) – Study BT100**

Subgroup (observed results)	Miconazole (n = 112)	Vehicle (n = 124)	Missing (Micon., Vehicle)
<b>Overall</b>	26/98 (26.5%)	12/59 (20.3%)	(14, 65)
<b>Location</b>			
U.S. Sites	10/35 (28.6%)	4/16 (25%)	(10, 38)
Non-US sites	16/63 (25.4%)	8/43 (18.6%)	(4, 27)
<b>Diaper Dermatitis Severity Index Score</b>			
3	2/6 (33.3%)	3/7 (42.9%)	(3, 8)
4	10/30 (33.3%)	3/17 (17.6%)	(1, 15)
5	11/31 (35.5%)	5/22 (22.7%)	(7, 16)
6	2/16 (12.5%)	1/9 (11.1%)	(2, 13)
7	1/10 (10%)	0/4 (0%)	(1, 9)
8	0/5 (0%)	NA	(0, 4)
<b>Baseline Severity of Diaper Rash</b>			
Mild (score 3-4)	12/36 (33.3%)	6/24 (25%)	(4, 23)
Moderate (score 5-8)	14/62 (22.6%)	6/35 (17.1%)	(10, 42)
<b>Baseline <i>Candida</i> Positive</b>			
<i>Albicans</i>	26/95 (27.4%)	12/57 (21.1%)	(14, 64)
Species other than <i>albicans</i>	0/3 (0%)	0/2 (0%)	(0, 1)
<b>Type of Diaper Used</b>			
U.S. – disposable	10/35 (28.6%)	4/16 (25%)	(10, 38)
Non-U.S.			
Disposable	2/22 (9.1%)	2/14 (14.3%)	(1, 10)
Disposable/Cloth	14/41 (34.1%)	6/29 (20.7%)	(3, 17)
<b>Source:</b> Sponsor's electronic data sets at \\cdsesub\n21026\n_000\Hpbio\NDA_21-026\BT100-USA-001.			

Appears This Way  
 On Original

**Table A.11: Mean Number of Diaper Changes Per Day – Study BT100**

Country	Type of Diaper	Overall Cure <sup>a</sup> on Day 14?	Miconazole		Vehicle	
			n	Mean (s.d.) range	n	Mean (s.d.) range
U.S.	Disposable	Yes	10	10.1 (4.3) 6 – 20	4	8.0 (2.8) 6 – 12
		No	25	7.5 (2.5) 4 – 15	12	8.0 (2.6) 6 – 15
Non-U.S.	Disposable	Yes	2	8.5 (2.1) 7 – 10	2	4.0 (0) 4 – 4
		No	20	5.6 (2.4) 3 – 12	12	6.2 (1.9) 4 – 10
	Disposable/Cloth	Yes	14	11.9 (5.0) 6 – 20	6	19.0 (7.0) 12 – 30
		No	27	14.3 (6.7) 5 – 30	23	14.5 (9.0) 4 – 36

Source: Sponsor's electronic data sets at \\cdsesub\21026\000\Hpbio\NDA\_21-026\BT100-USA-001.  
<sup>a</sup>Patients with observed overall cure data on Day 14.

Appears This Way  
 On Original

## **SIGNATURES/DISTRIBUTION LIST PAGE**

Primary Statistical Reviewer:

Shiowjen Lee, Ph.D., Biometrics III

Date:

April 1, 2005

Concurring Reviewer/  
Statistical Team Leader:

Mohamed Alosh, Ph.D., Biometrics III

cc:

HFD-540/Div. File  
HFD-540/Ms. Wright  
HFD-540/Dr. Carr  
HFD-540/Dr. Luke  
HFD-540/Dr. Wilkin  
HFD-725/Dr. Lee  
HFD-725/Dr. Alosh  
HFD-725/Dr. Lin  
HFD-725/Dr. Huque  
HFD-710/Dr. Anello

This statistical review contains 35 pages (24 pages of text, 10 pages of Appendix and one page of distribution list).

Appears This Way  
On Original

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

/s/  
-----

Mohamed Alesh  
4/15/05 12:26:35 PM  
BIOMETRICS  
Signing for Shiojjen Lee, Ph.D.

Mohamed Alesh  
4/15/05 03:31:42 PM  
BIOMETRICS

**STATISTICAL REVIEW AND EVALUATION**

**NDA:** 21-026/3S  
**Applicant:** Johnson & Johnson Consumer Co. Inc.  
**Name of Drug:** PEDIASTAT™(0.25% miconazole nitrate)  
**Route of Administration:** Topical  
**Documents Reviewed:** NDA 21-026: Vol. 1.1 , 1.23-1.27(Total Vol. : 1.1- 1.30) (submitted Aug. 24, 1999)  
**Indication:** Treatment of moderate-to-severe diaper dermatitis where *Candida albicans* may be a contributing factor  
**Related INDs:** IND No. 21,542 IND  
**Related NDAs:** NDA 17-494, , NDA 18-040, NDA 17-450, NDA 18-520 **b(4)**  
**Medical Officer:** Hon-Sum Ko, M. D. (HFD-540)

**Table of Contents:**

Introduction ..... 1  
Study 10833/10842.33. ....1  
Study 12966.37A.. .....3  
Study 12966.37B.. .....6  
Summary and Conclusions.....8  
Appendix.....10

**Introduction :** Miconazole is one of the oldest topical imidazoles for the treatment of superficial fungal infections. It has *in vitro* antifungal activity against most pathogenic fungi and yeast, some gram-positive bacilli and cocci, and some gram-negative organisms. This activity is based on the inhibition of the ergosterol biosynthesis in the cell membrane of the pathogenic microorganism.

The sponsor submitted this NDA for the indication of the treatment of moderate-to-severe diaper dermatitis where *Candida albicans* may be a contributing factor. The submission included two pivotal phase III trials, (12966.37A and 12966.37B) which were conducted in Australia, and a supportive, U.S. double blind, placebo-controlled trial (10833/10842.33, which was submitted to FDA in 1985), to support the efficacy claim. **b(4)**

**Results:**

**Study 10833/10842.33:**

**Study Design and objectives:**

*Design:* Controlled, randomized, double blind parallel study. Subjects were randomly assigned to the following two treatment groups:

- BPC formula No. 610-58
- Ointment base

*Duration:* 7 days.

**Objective:** To evaluate the comparative efficacy of BPC formula No. 610-58 versus the ointment base in the treatment of acute infantile diaper dermatitis and in the prevention of the onset of severe diaper dermatitis due to *Candida albicans*.

**Primary Efficacy Variables:** This protocol was written in 1983. No primary effectiveness parameter was specified.

**Efficacy Variables:** include

1. Total rash score;
2. Overall rating by investigator;
3. Microbiological status (presence/absence of *Candida Albican*).

Table 1 Patient disposition- -study 10883/10842.33

	Number of patients		
	active	base	overall
All randomized subjects	53	54	107
Number of subjects who completed the therapy	51	48	99
Number of subjects excluded from analysis	3	4	
Number of subjects prematurely discontinued from therapy	2	6	
Reasons for premature discontinuation:			
Parental request	0	1	
Subject did not meet protocol criteria	1	0	
other	1	5	

The proportion of all patients with rash score=0 was calculated at days 0,1,3,5, and 7 (Table A.1.1). No statistically significant differences among the treatment groups were found ( $p>0.298$ ). The difference was also not statistically significantly different at the last observed value (LOCF,  $p=0.212$ . Table A.1.1). The mean rash score for the active group and the base group were statistically significantly different on days 3, 5,7, and LOCF ( $p<0.05$ . Table A.1.2).

The proportion of patients with rash score=0 was calculated at days 0,1,3,5, and 7 for those who had *Candida Albican* at baseline (Table A.1.3). No statistically significant differences among the treatment groups were found ( $p>0.08$ ). The difference was also not statistically significantly different at the last observed value (LOCF,  $p=0.087$ ). The mean rash score for the active group and the base group were statistically significantly different on days 3, 5,7, and LOCF ( $p<0.05$ , Table A.1.5).

The proportion of patients with rash score=0 was calculated at days 0,1,3,5, and 7 for those who did not have *Candida Albican* at baseline (Table A.1.4). No statistically significant differences among the treatment groups were found ( $p>0.597$ ). The difference was also not statistically significantly different at the last observed value (LOCF,  $p=0.665$ ). The mean rash score for the active group and the base group were not statistically significantly different on days 0,1, 3, 5,7, and LOCF ( $p>0.12$ . Table A.1.6).

There were no statistically significant differences in the proportion of patients being rated cured/improved/no change in the overall rating by the investigators for the active and base treatment

groups ( $p > 0.122$ . Table A.1.7). For the sub-population of patients who had Candida Albican at baseline, the proportion of patients being rated cured/improved/no change in the overall rating by the investigators were statistically significantly different for the active and base treatment groups on day 7 and LOCF ( $p < 0.05$ . Table A.1.8). For the sub-population of patients who did not have Candida Albican at baseline, the proportion of patients being rated cured/improved/no change in the overall rating by the investigators were not statistically significantly different for the active and base treatment groups at any time point ( $p > 0.26$ . Table A.1.9).

Among the patients who had Candida Albican at baseline, the proportion of patients without Candida Albican at end of study (LOCF) was not statistically significantly different ( $P > 0.05$ . Table A.1.10).

**Safety:** The sponsor stated that “no adverse experience reported”.

**Reviewer’s comments :**

For study 10883/10842.33, there were no statistically significant differences in:

- Proportion of patients with rash score=0 (all patients, patients with Candida Albican and without Candida Albican at baseline);
- The proportion of patients being rated cured/improved/no change in the overall rating by the investigators (all patients, patients without Candida Albican at baseline);
- The mean rash score for patients without Candida Albican at baseline;
- the proportion of patients without Candida Albican at end of study (LOCF, patients with Candida Albican Candida Albican at baseline)

There were statistically significant differences in:

- The proportion of patients being rated cured/improved/no change in the overall rating by the investigators (patients with Candida Albican at baseline);
- The mean rash score (all patients, patients with Candida Albican at baseline);

**Study 12966.37A:**

**Study Design and objectives:**

*Design:* Controlled, randomized, double blind parallel study. Subjects were randomly assigned to the following two treatment groups:

- BPC formula No. 610-73
- Zinc oxide ointment base Formula No. 610-115

*Duration:* 7 days.

*Objective:* To evaluate the comparative efficacy of BPC formula No. 610-73 versus the ointment base in the treatment of acute diaper dermatitis in infants and in the prevention of the onset of severe diaper dermatitis and to assess the role of Candida.

Table 2 Patient disposition- 12966.37A

	Number of patients		
	active	base	overall
All randomized subjects	101	101	202
Number of subjects who completed the therapy	96	92	188
Number of subjects excluded from analysis	2	0	2
Number of subjects prematurely discontinued from therapy	5	9	14
Reasons for premature discontinuation:			
Parental request/lack of efficacy	2	6	8
Lack of efficacy/other	0	1	1
Subject did not meet protocol criteria	2	0	2
Unrelated intercurrent illness	0	1	1
Adverse experience	0	0	0
other	1	1	2

**Results:****Efficacy Analysis**

**Primary Efficacy Variables:** This protocol was written in 1988. No primary effectiveness parameter was specified.

**Efficacy Variables:** include

1. Total rash score;
2. Overall rating by investigator;
3. Global clinical impression ;
4. Microbiological status (presence/absence of candida albican).

The proportion of all patients with rash score=0 was calculated at days 0,1,3,5, and 7 (Table A.2.1). The difference between the active and the base groups were statistically significant on day 7 and LOCF (p=0.001). The mean rash score for the active group and the base group were statistically significantly different on days 5,7, and LOCF (p<0.05. Table A.2.2).

The proportion of patients with rash score=0 was calculated at days 0,1,3,5, and 7 for those who had Candida Albican at baseline (Table A.2.3). The difference between the active and the base groups were statistically significant on day 7 and LOCF (p=0.001). The mean rash score for the active group and the base group were statistically significantly different on days 3, 5,7, and LOCF (p<0.05, Table A.2.5).

The proportion of patients with rash score=0 was calculated at days 0,1,3,5, and 7 for those who did not have Candida Albican at baseline (Table A.2.4). No statistically significant differences among the treatment groups were found (p>0.22). The difference was also not statistically significantly different at the last observed value (LOCF, p=0.258). The mean rash score for the active group and the base group were not statistically significantly different on days 0,1, 3, 5,7, and LOCF (p>0.09. Table A.2.6).

The difference was statistically significant in the proportion of patients being rated cured/improved/no change in the overall rating by the investigators for the active and base treatment groups on days 3 through 7 and LOCF ( $p < 0.05$ . Table A.2.7). For the sub-population of patients who had Candida Albican at baseline, the proportion of patients being rated cured/improved/no change in the overall rating by the investigators was statistically significantly different for the active and base treatment groups on days 3 through 7 and LOCF ( $p < 0.05$ . Table A.2.8). For the sub-population of patients who did not have Candida Albican at baseline, the proportion of patients being rated cured/improved/no change in the overall rating by the investigators were not statistically significantly different for the active and base treatment groups on day 7 and LOCF ( $p > 0.11$ . Table A.2.9).

The difference was statistically significant in the proportion of patients being rated none/mild/moderate/severe in the global clinical impression by the investigators for the active and base treatment groups on days 5,7 and LOCF ( $p < 0.05$ . Table A.2.10). For the sub-population of patients who had Candida Albican at baseline, the proportion of patients being rated none/mild/moderate/severe in the global clinical impression by the investigators were statistically significantly different for the active and base treatment groups on days 3 through 7 and LOCF ( $p < 0.05$ . Table A.2.11). For the sub-population of patients who did not have Candida Albican at baseline, the proportion of patients being none/mild/moderate/severe in the global clinical impression by the investigators was not statistically significantly different for the active and base treatment groups on day 7 and LOCF ( $p > 0.14$ . Table A.2.12).

Among the patients who had Candida Albican at baseline, the proportion of patients without Candida Albican at end of study (LOCF) was statistically significantly different ( $P = 0.001$ . Table A.2.13).

#### Safety:

Table 3 Adverse experiences- All subjects - 12966.37A

Body system (Costart)	Active (N=101)	Base (N=101)
Skin and appendages		
Rash	1(1%)	0(0%)
Total No. of subjects with adverse events	1(1%)	0(0%)

Adverse experiences - 12966.37A

Subject No.	Study day onset	Costart	duration	severity	Due to test product	description	comments
Active							
420-010	2	Skin/derm/ery	>5 days	moderate	uncertain	Rash on face, neck & chin	Treated with hydrocortisone 1%

#### Reviewer's comments :

In study 12966.37A, for patients *without* Candida Albican at baseline, there were no statistically significant differences in all the efficacy measurements for the active and base groups:

- Proportion of patients with rash score=0 ;
- The proportion of patients being rated cured/improved/no change in the overall rating by the investigators ;
- The mean rash score;
- The proportion of patients being rated none/mild/moderate/severe in the global clinical impression by the investigators;

For all the patients as a group, and for patients *with* Candida Albican at baseline, there were statistically significant differences in:

- Proportion of patients with rash score=0 ;
- The proportion of patients being rated cured/improved/no change in the overall rating by the investigators ;
- The mean rash score;
- The proportion of patients being rated none/mild/moderate/severe in the global clinical impression by the investigators;
- The proportion of patients without Candida Albican at end of study (LOCF, patients with Candida Albican at baseline).

### Study 12966.37B:

#### Study Design and objectives:

*Design:* Controlled, randomized, double blind parallel study. Subjects were randomly assigned to the following two treatment groups:

- BPC formula No. 610-73
- Zinc oxide ointment base Formula No. 610-115

*Duration:* 7 days.

*Objective:* To evaluate the comparative efficacy of BPC formula No. 610-73 versus the ointment base in the treatment of acute diaper dermatitis in infants and in the prevention of the onset of severe diaper dermatitis.

Table 4 Patient disposition- 12966.37B

	Number of patients		
	active	base	overall
All randomized subjects	98	98	196
Number of subjects who completed the therapy	95	87	182
Number of subjects excluded from analysis	2	5	7
Number of subjects prematurely discontinued from therapy	3	11	14
Reasons for premature discontinuation:			
Parental request/lack of efficacy	2	8	10
Lack of efficacy/other	0	1	1
Subject did not meet protocol criteria	0	0	0
Unrelated intercurrent illness	0	1	1
Adverse experience	0	0	0
other	1	1	2

**Results:****Efficacy Analysis**

**Primary Efficacy Variables:** This protocol was written in 1988. No primary effectiveness parameter was specified.

**Efficacy Variables:** include

1. Total rash score;
2. Overall rating by investigator;
3. Global clinical impression ;

There was no Candida culture for this study.

The proportion of all patients with rash score=0 was calculated at days 0,1,3,5, and 7 (Table A.3.1). The difference between the active and the base groups was statistically on day 7 and LOCF (p=0.001). The mean rash score for the active group and the base group were statistically significantly different on days 5,7, and LOCF (p<0.05. Table A.3.2).

The differences were statistically significant in the proportion of patients being rated cured/improved/no change in the overall rating by the investigators for the active and base treatment groups on days 3 through 7 and LOCF (p<0.05. Table A.3.3).

The difference was statistically significant in the proportion of patients being rated none/mild/moderate/severe in the global clinical impression by the investigators for the active and base treatment groups on days 3 through 7 and LOCF (p<0.05. Table A.3.4).

**Safety:**

Table 5 Adverse experiences- All subjects- 12966.37B

Body system (Costart)	Active (N=98)	Base (N=98)
Skin and appendages		
Rash	0(0%)	2 (2%)
Total No. of subjects with adverse events	0(0%)	2 (2%)

Adverse experiences- - 12966.37B

Subject No.	Study day onset	Costart	duration	severity	Due to test product	description	comments
Base							
4038-013	2		Continuing	mild	uncertain	rash	Hx of mild seborrheic* intertrigo
4038-026	3	Skin/derm/ery	>3 days	severe	possible	Erythema multiforme	Has previously used zinc oxide cream

\* "Intertrigo" is incorrect-subject had seborrhea only

**Reviewer's comments :**

In study 12966.37B, there were statistically significant differences between the active and the base treatment groups in all the efficacy measurements.

**Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):****Summary:**

In study 10883/10842.33,

- No statistically significant efficacy was demonstrated for patients *without* Candida Albican at baseline.
- For patients *with* Candida Albican at baseline, the active treatment group *was* statistically superior to the base group
  - i) in the proportion of patients being rated cured/improved/no change in the overall rating by the investigators ;
  - ii) mean rash score;

*was not* statistically superior to the base group in

- i) The proportion of patients with rash score=0;
- ii) The proportion of patients without Candida Albican at end of study.

In study 12966.37A,

- No statistically significant efficacy was demonstrated for patients *without* Candida Albican at baseline.
- For patients *with* Candida Albican at baseline, the active treatment group was statistically superior to the base group in
  - i) The proportion of patients with rash score=0 ;
  - ii) The proportion of patients being rated cured/improved/no change in the overall rating by the investigators ;
  - iii) The mean rash score;
  - iv) The proportion of patients being rated none/mild/moderate/severe in the global clinical impression by the investigators;
  - v) The proportion of patients without Candida Albican at end of study (LOCF).

In study 12966.37B, there were statistically significant differences between the active and the base treatment groups in all the efficacy measurements. *However*, since there was no Candida culture for this study, no information can be obtained on the efficacy of the active treatment on patients with Candida Albican at baseline.

**Safety:** The sponsor reported only a few adverse events.

**Conclusion:** The submission did *not* include two pivotal trials, which demonstrate the efficacy of the active treatment on patients with Candida Albican at baseline in *all* of the following efficacy measurements:

- i) The proportion of patients with rash score=0;
- ii) The proportion of patients without Candida Albican at end of study.
- iii) The proportion of patients being rated cured/improved/no change in the overall rating by the investigators ;
- iii) Mean rash score;

Since the primary efficacy analysis was not specified in the protocol, the efficacy analysis performed in this review was requested by the reviewing medical officer. Clinical input is needed to determine whether sufficient efficacy has been demonstrated in this submission.

  
March 29, '99.

*Ping Gao* 03/29/99  
Ping Gao, Ph.D.  
Mathematical Statistician, DOB III

Concur: Rajagopalan Srinivasan, Ph.D.  
Team Leader, DOB III

- HFD 540
- NDA 21-026
- HFD-540/Dr. Wilkin
- HFD-540/Dr. Walker
- HFD-540/Dr. Ko
- HFD-540/Ms. Wright
- HFD-725/Dr. Huque
- HFD-725/Dr. Srinivasan
- HFD-725/Dr. Gao
- HFD-344/Dr. Carreras
- HFD-725 Chron.

This review contains 25 pages.

MS word/d: \nda\21-026\21-026.doc\Mar. 29, '99; Ping Gao /(301)-827-2083

**Appears This Way  
On Original**

**Appendix :** Efficacy analysis tables

**1. Study 10883/10842.33**

Table A.1.1 Proportion of patients with rash score=0 –All patients in ITT-study 10883/10842.33

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	53 (100%)	54 (100%)	
	Total patients	53	54	
1	Score=0	1 (1.9%)	1 (1.9%)	0.989
	Score>0	51 (98.1%)	52 (98.1%)	
	Total patients	52	53	
3	Score=0	10 (19.2%)	6 (11.8%)	0.298
	Score>0	42 (80.8%)	45 (88.2%)	
	Total patients	52	51	
5	Score=0	15 (29.4%)	15 (30.6%)	0.896
	Score>0	36 (70.6%)	34 (69.4%)	
	Total patients	51	49	
7	Score=0	28 (54.9%)	22 (45.8%)	0.370
	Score>0	23 (45.1%)	26 (54.2%)	
	Total patients	51	48	
Final day (LOCF)	Score=0	28 (52.8%)	22 (40.7%)	0.212
	Score>0	25 (47.2%)	32 (59.3%)	
	Total patients	53	54	

Table A.1.2 Mean rash score –All patients in ITT-study 10883/10842.33

Day	Treatment groups		p-value
	Active Mean score (N)	Base Mean score (N)	
0	4.92 (53)	5.37 (54)	0.4872
1	3.12 (52)	3.85 (53)	0.2109
3	2.02 (52)	3.29 (51)	0.0277
5	1.29 (51)	2.53 (49)	0.0178
7	1.20 (51)	2.42 (48)	0.0226
Final day (LOCF)	1.28 (53)	3.09 (54)	0.0041

Appears This Way  
On Original

Table A.1.3 Proportion of patients with rash score=0 –Patients with Candida albican at baseline  
-study 10883/10842.33

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	23 (100%)	23 (100%)	
	Total patients	23	23	
1	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	23 (100%)	23 (100%)	
	Total patients	23	23	
3	Score=0	3 (13%)	0 (0%)	0.083
	Score>0	20 (87%)	22 (100%)	
	Total patients	23	22	
5	Score=0	4 (18.2%)	2 (10%)	0.455
	Score>0	18 (81.8%)	18 (90%)	
	Total patients	22	20	
7	Score=0	8 (36.4%)	3 (15.8%)	0.143
	Score>0	14 (63.6%)	16 (84.2%)	
	Total patients	22	19	
Final day (LOCF)	Score=0	8 (34.8%)	3 (13%)	0.087
	Score>0	15 (65.2%)	20 (87%)	
	Total patients	23	23	

Table A.1.4 Proportion of patients with rash score=0 –Patients without Candida albican at baseline  
-study 10883/10842.33

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	30 (100%)	31 (100%)	
	Total patients	30	31	
1	Score=0	1 (3.45%)	1 (3.3%)	0.981
	Score>0	28 (96.55%)	29 (96.7%)	
	Total patients	29	30	
3	Score=0	7 (24.1%)	6 (20.7%)	0.755
	Score>0	22 (75.9%)	23 (79.3%)	
	Total patients	29	29	
5	Score=0	11 (37.9%)	13 (44.8%)	0.597
	Score>0	18 (62.1%)	16 (55.2%)	
	Total patients	29	29	
7	Score=0	20 (69%)	19 (65.5%)	0.782
	Score>0	9 (31%)	10 (34.5%)	
	Total patients	29	29	
Final day (LOCF)	Score=0	20 (66.7%)	19 (61.3%)	0.665
	Score>0	10 (33.3%)	12 (38.7%)	
	Total patients	30	31	

Table A.1.5 Mean rash score – Patients with Candida albican at baseline -study 10883/10842.33

Day	Treatment groups		p-value
	Active	Base	
0	Mean score (N) 5.83 (23)	Mean score (N) 6.22 (23)	0.6793
1	4.43(23)	4.96(23)	0.6011
3	2.57(23)	5.45(22)	0.0081
5	1.68(22)	4.45(20)	0.0087
7	1.82(22)	4.58(19)	0.0059
Final day (LOCF)	2.0(23)	5.70(23)	0.0017

Table A.1.6 Mean rash score – Patients without Candida albican at baseline -study 10883/10842.33

Day	Treatment groups		p-value
	Active	Base	
0	Mean score (N) 4.23(30)	Mean score (N) 4.74(31)	0.5486
1	2.07(29)	3.0(30)	0.1246
3	1.59(29)	1.66(29)	0.8646
5	1.0(29)	1.21(29)	0.5429
7	0.72(29)	1.0(29)	0.5177
Final day (LOCF)	0.73(30)	1.16(31)	0.3115

Table A.1.7 Overall rating by investigator —All patients in ITT-study 10883/10842.33

Day	N	Number of Patients (%)		p
		Active	base	
Day 1	N	52	53	0.464
	cured	1 (1.9%)	1 (1.9%)	
	Improved	38 (73.1%)	37 (69.8%)	
	No change	11 (21.2%)	10 (18.9%)	
	Worse/recured	2 (3.9%)	5 (9.4%)	
Day 3	N	52	51	0.136
	cured	10 (19.2%)	6 (11.8%)	
	Improved	33 (63.5%)	29 (56.9%)	
	No change	3 (5.8%)	8 (15.7%)	
	Worse/recured	6 (11.5%)	8 (15.7%)	
Day 5	N	51	49	0.434
	cured	14 (27.5%)	15 (30.6%)	
	Improved	31 (60.8%)	23 (46.9%)	
	No change	2 (3.9%)	4 (8.2%)	
	Worse/recured	4 (7.8%)	7 (14.3%)	
Day 7	N	51	48	0.263
	cured	28 (54.9%)	23 (47.9%)	
	Improved	14 (27.5%)	10 (20.8%)	
	No change	1 (2.0%)	5 (10.4%)	
	Worse/recured	8 (15.7%)	10 (20.8%)	
Final day (LOCF)	N	52	53	0.122
	cured	28 (53.9%)	23 (43.4%)	
	Improved	14 (26.9%)	11 (20.8%)	
	No change	1 (1.9%)	5 (9.4%)	
	Worse/recured	9 (17.3%)	14 (26.4%)	

\* p values were from the Mantel-Haenszel chi-square test.

Table A.1.8 Overall rating by investigator — Patients with Candida albican at baseline  
-study 10883/10842.33

		Number of Patients (%)		p
		Active	base	
Day 1	N	23	23	
	cured	0(0%)	0(0%)	1.0
	Improved	14 (60.9%)	17 (73.9%)	
	No change	8 (34.8%)	2 (8.7%)	
	Worse/recured	1 (4.4%)	4 (17.4%)	
Day 3	N	23	22	0.005
	cured	3 (13%)	0(0%)	
	Improved	17 (73.9%)	10 (45.5%)	
	No change	1 (4.4%)	6 (27.3%)	
	Worse/recured	2 (8.7%)	6 (27.3%)	
Day 5	N	22	20	
	cured	4 (18.2%)	2 (10%)	0.357
	Improved	13 (59.1%)	10 (50%)	
	No change	1 (4.6%)	4 (20%)	
	Worse/recured	4 (18.2%)	4 (20%)	
Day 7	N	22	19	0.04
	cured	8 (36.4%)	3 (15.8%)	
	Improved	9 (40.9%)	5 (26.3%)	
	No change	1 (4.6%)	4 (21.1%)	
	Worse/recured	4 (18.2%)	7 (36.8%)	
Final day (LOCF)	N	23	23	0.014
	cured	8 (34.8%)	3 (13%)	
	Improved	9 (39.1%)	5 (21.7%)	
	No change	1 (4.4%)	4 (17.4%)	
	Worse/recured	5 (21.7%)	11 (47.8%)	

\*p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

Table A.1.9 Overall rating by investigator — Patients without Candida albican at baseline  
-study 10883/10842.33

		Number of Patients (%)		*p
		Active	base	
Day 1	N	29	30	
	cured	1 (3.5%)	1 (3.3%)	0.266
	Improved	24 (82.8%)	20 (66.7%)	
	No change	3 (10.3%)	8 (26.7%)	
	Worse/recured	1 (3.5%)	1 (3.3%)	
Day 3	N	29	29	0.642
	cured	7 (24.1%)	6 (20.7%)	
	Improved	16 (55.2%)	19 (65.5%)	
	No change	2 (6.9%)	2 (6.9%)	
	Worse/recured	4 (13.8%)	2 (6.9%)	
Day 5	N	29	29	
	cured	10 (34.5%)	13 (44.8%)	0.724
	Improved	18 (62.1%)	13 (44.8%)	
	No change	1 (3.5%)	0(0%)	
	Worse/recured	0(0%)	3 (10.3%)	
Day 7	N	29	29	0.897
	cured	20 (69%)	20 (69%)	
	Improved	5 (17.2%)	5 (17.2%)	
	No change	0(0%)	1 (3.5%)	
	Worse/recured	4 (13.8%)	3 (10.3%)	
Final day (LOCF)	N	29	30	0.940
	cured	20 (69%)	20 (66.7%)	
	Improved	5 (17.2%)	6 (20%)	
	No change	0(0%)	1 (3.3%)	
	Worse/recured	4 (13.8%)	3 (10%)	

\*p values were from the Mantel-Haenszel chi-square test.

Table A.1.10 Proportion of patients without Candida albican at end of study (LOCF)  
---- for patients with Candida albican at baseline  
-study 10883/10842.33

	Number of Patients (%)		*p
	Active	base	
N	23	23	
No	12 (52.2%)	3(13%)	0.064
Yes	8 (34.8%)	17 (73.9%)	
No data	3(13%)	3(13%)	

Appears This Way  
On Original

**2. Study 12966.37A**

**Table A.2.1 Proportion of patients with rash score=0 –All patients in ITT- 12966.37A**

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	101 (100%)	101 (100%)	
	Total patients	101	101	
1	Score=0	1(1%)	1(1%)	1.0
	Score>0	100 (99%)	100 (99%)	
	Total patients	101	101	
3	Score=0	11 (11%)	13(13%)	0.683
	Score>0	88 (89%)	87(87%)	
	Total patients	99	100	
5	Score=0	31 (32%)	20 (20.4%)	0.067
	Score>0	66 (68%)	78 (79.6%)	
	Total patients	97	98	
7	Score=0	56 (57.7%)	30 (32.3%)	0.001
	Score>0	41(42.3%)	63(67.7%)	
	Total patients	97	93	
Final day (LOCF)	Score=0	56 (55.45%)	30 (29.7%)	0.001
	Score>0	45 (45.55%)	71 (70.3%)	

**Table A.2.2 Mean rash score –All patients in ITT- 12966.37A**

Day	Treatment groups		p-value
	Active Mean score (N)	Base Mean score (N)	
0	6.465 (101)	6.733 (101)	0.599
1	5.72 (101)	5.64 (101)	0.871
3	3.84 (99)	4.86 (100)	0.057
5	2.53 (97)	4.53 (98)	0.0004
7	1.79 (97)	4.06 (93)	0.0001
Final day (LOCF)	1.97 (101)	4.56 (101)	0.0001

Appears This Way  
On Original

Table A.2.3 Proportion of patients with rash score=0 –Patients with Candida Albican at baseline  
- 12966.37A

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	28(100%)	35 (100%)	
	Total patients	28	35	
1	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	28(100%)	35 (100%)	
	Total patients	28	35	
3	Score=0	1 (3.7%)	1(2.9%)	0.853
	Score>0	26 (96.3%)	34(97.1%)	
	Total patients	27	35	
5	Score=0	5 (19.2%)	2(5.9%)	0.113
	Score>0	21 (80.8%)	32 (94.1%)	
	Total patients	26	34	
7	Score=0	18 (66.7%)	2 (6.9%)	0.001
	Score>0	9(33.3%)	27(93.1%)	
	Total patients	27	29	
Final day (LOCF)	Score=0	18 (64.3%)	2 (5.7%)	0.001
	Score>0	10 (35.7%)	33 (94.3%)	

Table A.2.4 Proportion of patients with rash score=0 –Patients without Candida albican at baseline  
- 12966.37A

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	73(100%)	66 (100%)	
	Total patients	73	66	
1	Score=0	1 (1.4%)	1 (1.5%)	0.943
	Score>0	72(98.6%)	65 (98.5%)	
	Total patients	73	66	
3	Score=0	10 (13.9%)	12(18.5%)	0.468
	Score>0	62 (86.1%)	53(81.5%)	
	Total patients	72	65	
5	Score=0	26 (36.6%)	18(28.1%)	0.295
	Score>0	45 (63.4%)	46 (71.9%)	
	Total patients	71	64	
7	Score=0	38 (54.3%)	28 (43.8%)	0.225
	Score>0	32(45.7%)	36(56.3%)	
	Total patients	70	64	
Final day (LOCF)	Score=0	38 (52.05%)	28 (42.4%)	0.258
	Score>0	35 (47.95%)	38 (57.6%)	
	Total patients	73	66	

Table A.2.5 Mean rash score – Patients with Candida albican at baseline- 12966.37A

	Treatment groups		p-value
	Active	Base	
Day	Mean score (N)	Mean score (N)	
0	7.86 (28)	7.97 (35)	0.897
1	7.04(28)	6.97(35)	0.939
3	4.63 (27)	7.23 (35)	0.011
5	3.0 (26)	7.29 (34)	0.0004
7	1.96 (27)	7.52 (29)	0.0001
Final day (LOCF)	2.32 (28)	8.03 (35)	0.0001

Table A.2.6 Mean rash score – Patients without Candida albican at baseline- 12966.37A

	Treatment groups		p-value
	Active	Base	
Day	Mean score (N)	Mean score (N)	
0	5.93 (73)	6.08 (66)	0.810
1	5.22(73)	4.94 (66)	0.627
3	3.54 (72)	3.58 (65)	0.942
5	2.35 (71)	3.06 (64)	0.20
7	1.73 (70)	2.50 (64)	0.143
Final day (LOCF)	1.84 (73)	2.73 (66)	0.098

Table A.2.7 Overall rating by investigator —All patients in ITT- 12966.37A

		Number of Patients (%)		*p
		Active	base	
Day 1	N	101	101	
	cured	1 (1%)	1 (1%)	0.243
	Improved	51 (50.5%)	57 (56.4%)	
	No change	38 (37.2%)	37 (36.6%)	
	Worse/recured	11 (10.9%)	6 (5.9%)	
Day 3	N	99	100	0.005
	cured	11 (11.1%)	14 (14%)	
	Improved	70 (70.7%)	47 (47%)	
	No change	10 (10.1%)	19 (19%)	
	Worse/recured	8 (8.1%)	20 (20%)	
Day 5	N	97	97	
	cured	33 (34%)	20 (20.6%)	0.001
	Improved	39 (40.2%)	24 (24.7%)	
	No change	16 (16.5%)	35 (36.1%)	
	Worse/recured	9 (9.3%)	18 (18.6%)	
Day 7	N	97	93	0.001
	cured	57 (58.8%)	33 (35.5%)	
	Improved	17 (17.5%)	17 (18.3%)	
	No change	7 (7.2%)	17 (18.3%)	
	Worse/recured	16 (16.5%)	26 (28%)	
Final day (LOCF)	N	101	101	0.001
	cured	57 (56.4%)	33 (32.7%)	
	Improved	19 (18.8%)	18 (17.8%)	
	No change	8 (7.9%)	18 (17.8%)	
	Worse/recured	17 (16.8%)	32 (31.7%)	

\*p values were from the Mantel-Haenszel chi-square test.

Table A.2.8 Overall rating by investigator — Patients with Candida albican at baseline  
- 12966.37A

		Number of Patients (%)		p
		Active	base	
Day 1	N	28	35	
	cured	0 (0%)	0 (0%)	0.462
	Improved	15 (53.6%)	19 (54.3%)	
	No change	8 (28.6%)	14 (40%)	
	Worse/recured	5 (17.9%)	2 (5.7%)	
Day 3	N	27	35	0.005
	cured	1 (3.7%)	1 (2.9%)	
	Improved	22 (81.5%)	11 (31.4%)	
	No change	3 (11.1%)	9 (25.7%)	
	Worse/recured	1 (3.7%)	14 (40%)	
Day 5	N	26	34	
	cured	6 (23.1%)	2 (5.9%)	0.002
	Improved	15 (57.7%)	9 (26.5%)	
	No change	2 (7.7%)	15 (44.1%)	
	Worse/recured	3 (11.5%)	8 (23.5%)	
Day 7	N	27	29	0.001
	cured	18 (66.7%)	4 (13.8%)	
	Improved	4 (14.8%)	6 (20.7%)	
	No change	0 (0%)	7 (24.1%)	
	Worse/recured	5 (18.5%)	12 (41.4%)	
Final day (LOCF)	N	28	35	0.001
	cured	18 (64.3%)	4 (11.4%)	
	Improved	4 (14.3%)	7 (20%)	
	No change	0 (0%)	8 (22.9%)	
	Worse/recured	6 (21.4%)	16 (45.7%)	

\*p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

Table A.2.9 Overall rating by investigator — Patients without Candida albican at baseline  
- 12966.37A

		Number of Patients (%)		*p
		Active	base	
Day 1	N	73	66	
	cured	1 (1.4%)	1 (1.5%)	0.334
	Improved	36 (49.3%)	38 (57.6%)	
	No change	30 (41.1%)	23 (34.9%)	
	Worse/recured	6 (8.2%)	4 (6.1%)	
Day 3	N	72	65	0.918
	cured	10 (13.9%)	13 (20%)	
	Improved	48 (66.7%)	36 (55.4%)	
	No change	7 (9.7%)	10 (15.4%)	
	Worse/recured	7 (9.7%)	6 (9.2%)	
Day 5	N	71	63	
	cured	27 (38%)	18 (28.6%)	0.041
	Improved	24 (33.8%)	15 (23.8%)	
	No change	14 (19.7%)	20 (31.8%)	
	Worse/recured	6 (8.5%)	10 (15.9%)	
Day 7	N	70	64	0.165
	cured	39 (55.7%)	29 (45.3%)	
	Improved	13 (18.6%)	11 (17.2%)	
	No change	7 (10%)	10 (15.6%)	
	Worse/recured	11 (15.7%)	14 (21.9%)	
Final day (LOCF)	N	73	66	0.112
	cured	39 (53.4%)	29 (43.9%)	
	Improved	15 (20.6%)	11 (16.7%)	
	No change	8 (11%)	10 (15.2%)	
	Worse/recured	11 (15.1%)	16 (24.2%)	

\*p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

Table A.2.10 Global clinical impression by investigator —All patients in ITT  
- 12966.37A

		Number of Patients (%)		* p
		Active	base	
Day 0	N	101	101	
	none	0 (0%)	0 (0%)	0.823
	mild	53 (52.5%)	52 (51.5%)	
	moderate	41 (40.6%)	41 (40.6%)	
	severe	7 (6.9%)	8 (7.9%)	
Day 1	N	101	101	1.0
	none	1 (1%)	1 (1%)	
	mild	58 (57.4%)	59 (58.4%)	
	moderate	38 (37.6%)	36 (35.6%)	
	severe	4 (4%)	5 (5%)	
Day 3	N	99	100	
	none	11 (11.1%)	13 (13%)	0.117
	mild	69 (69.7%)	53 (53%)	
	moderate	17 (17.2%)	30 (30%)	
	severe	2 (2%)	4 (4%)	
Day 5	N	97	98	0.001
	none	32 (33%)	20 (20.4%)	
	mild	55 (56.7%)	43 (43.9%)	
	moderate	8 (8.3%)	29 (29.6%)	
	severe	2 (2.1%)	6 (6.1%)	
Day 7	N	97	93	0.001
	none	57 (58.8%)	32 (34.4%)	
	mild	33 (34%)	34 (36.6%)	
	moderate	5 (5.2%)	22 (23.7%)	
	severe	2 (2.1%)	5 (5.4%)	
Final day (LOCF)	N	99	100	0.001
	none	57 (56.4%)	32 (31.7%)	
	mild	35 (34.7%)	34 (33.7%)	
	moderate	7 (6.9%)	27 (26.7%)	
	severe	2 (2%)	8 (7.9%)	

\*p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

Table A.2.11 Global clinical impression by investigator — Patients with Candida Albican at baseline - 12966.37A

		Number of Patients (%)		* p
		Active	base	
Day 0	N	28	35	
	none	0 (0%)	0 (0%)	0.302
	mild	9 (32.1%)	9 (25.7%)	
	moderate	17 (60.7%)	20 (57.1%)	
	severe	2 (7.1%)	6 (17.1%)	
Day 1	N	28	35	
	none	0 (0%)	0 (0%)	0.365
	mild	12 (42.9%)	12 (34.3%)	
	moderate	15 (53.6%)	20 (57.1%)	
	severe	1 (3.6%)	3 (8.6%)	
Day 3	N	27	35	0.005
	none	1 (3.7%)	1 (2.9%)	
	mild	21 (77.8%)	13 (37.1%)	
	moderate	4 (14.8%)	17 (48.6%)	
	severe	1 (3.7%)	4 (11.4%)	
Day 5	N	26	34	
	none	5 (19.2%)	2 (5.9%)	0.001
	mild	19 (73.1%)	11 (32.4%)	
	moderate	1 (3.9%)	16 (47.1%)	
	severe	1 (3.9%)	5 (14.7%)	
Day 7	N	27	29	0.001
	none	18 (66.7%)	3 (10.3%)	
	mild	7 (25.9%)	8 (27.6%)	
	moderate	1 (3.7%)	13 (44.8%)	
	severe	1 (3.7%)	5 (17.2%)	
Final day (LOCF)	N	28	35	0.001
	none	18 (64.3%)	3 (8.6%)	
	mild	7 (25%)	8 (22.9%)	
	moderate	2 (7.1%)	17 (48.6%)	
	severe	1 (3.6%)	7 (20%)	

\* p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

Table A.2.12 Global clinical impression by investigator — Patients without Candida albican at baseline - 12966.37A

		Number of Patients (%)		* p
		Active	base	
Day 0	N	73	66	
	none	0 (0%)	0 (0%)	0.385
	mild	44 (60.3%)	43 (65.2%)	
	moderate	24 (32.9%)	21 (31.8%)	
	severe	5 (6.9%)	2 (3%)	
Day 1	N	73	66	
	none	1 (1.4%)	1 (1.5%)	0.324
	mild	46 (63%)	47 (71.2%)	
	moderate	23 (31.5%)	16 (24.2%)	
	severe	3 (4.1%)	2 (3%)	
Day 3	N	72	65	0.608
	none	10 (13.9%)	12 (18.5%)	
	mild	48 (66.7%)	40 (61.5%)	
	moderate	13 (18.1%)	13 (20%)	
	severe	1 (1.4%)	0 (0%)	
Day 5	N	71	64	
	none	27 (38%)	18 (28.1%)	0.097
	mild	36 (50.7%)	32 (50%)	
	moderate	7 (9.9%)	13 (20.3%)	
	severe	1 (1.4%)	1 (1.6%)	
Day 7	N	70	64	0.185
	none	39 (55.7%)	29 (45.3%)	
	mild	26 (37.1%)	26 (40.6%)	
	moderate	4 (5.7%)	9 (14.1%)	
	severe	1 (1.4%)	0 (0%)	
Final day (LOCF)	N	73	66	0.145
	none	39 (53.4%)	29 (43.9%)	
	mild	28 (38.4%)	26 (39.4%)	
	moderate	5 (6.9%)	10 (15.2%)	
	severe	1 (1.4%)	1 (1.5%)	

\* p values were from the Mantel-Haenszel chi-square test

Table A.2.13 Proportion of patients without Candida albican at end of study (LOCF) ---- for patients with Candida albican at baseline - 12966.37A

	Number of Patients (%)		* p
	Active	base	
N	28	34	
No	26 (92.9%)	6 (17.7%)	0.001
Yes	2 (7.1%)	27 (79.4%)	
No data	0 (0%)	1 (2.9%)	

Appears This Way  
On Original

3. Study 12966.37B

Table A.3.1 Proportion of patients with rash score=0 –ITT population - 12966.37B

Day	Rash score	Treatment groups		p-value
		Active N (%)	Base N(%)	
0	Score=0	0 (0%)	0 (0%)	1.0
	Score>0	98 (100%)	98 (100%)	
	Total patients	98	98	
1	Score=0	1(1%)	2(2.1%)	0.549
	Score>0	96 (99%)	93 (97.9%)	
	Total patients	97	95	
3	Score=0	17 (17.35%)	12(12.4%)	0.330
	Score>0	81 (82.65%)	85(87.6%)	
	Total patients	98	97	
5	Score=0	33 (34.4%)	20 (21.7%)	0.055
	Score>0	63 (65.6%)	72 (78.3%)	
	Total patients	96	92	
7	Score=0	60 (63.2%)	26 (29.9%)	0.001
	Score>0	35(36.8%)	61(71.1%)	
	Total patients	95	87	
Final day (LOCF)	Score=0	60 (61.2%)	26 (26.5%)	0.001
	Score>0	38 (38.8%)	72 (73.5%)	

Table A.3.2 Mean rash score –All patients in ITT- 12966.37B

Day	Treatment groups		p-value
	Active Mean score (N)	Base Mean score (N)	
0	7.44 (98)	6.77 (98)	0.303
1	5.90 (97)	4.96 (95)	0.111
3	3.35 (98)	4.25 (97)	0.064
5	1.90 (96)	3.89 (92)	0.0001
7	1.11 (95)	3.76 (87)	0.0001
Final day (LOCF)	1.31 (98)	4.02 (98)	0.0001

Appears This Way  
On Original

Table A.3.3 Overall rating by investigator —All patients in ITT- 12966.37B

		Number of Patients (%)		*p
		Active	base	
Day 1	N	97	95	
	cured	1(1%)	2(2.1%)	0.226
	Improved	65(67%)	70(73.7%)	
	No change	30(30.9%)	22(23.2%)	
	Worse/recured	1(1%)	1(1.1%)	
Day 3	N	98	96	0.001
	cured	18(18.4%)	12(12.5%)	
	Improved	62(63.3%)	38(39.6%)	
	No change	10(10.2%)	29(30.2%)	
	Worse/recured	8(8.2%)	17(17.7%)	
Day 5	N	96	92	
	cured	34(35.4%)	21(22.8%)	0.001
	Improved	41(42.7%)	20(21.7%)	
	No change	10(10.4%)	34(37%)	
	Worse/recured	11(11.5%)	17(18.5%)	
Day 7	N	95	87	0.001
	cured	62(65.3%)	26(29.9%)	
	Improved	16(16.8%)	20(23%)	
	No change	9(9.5%)	21(24.1%)	
	Worse/recured	8(8.4%)	20(23%)	
Final day (LOCF)	N	98	97	0.001
	cured	62(63.3%)	26(26.8%)	
	Improved	17(17.4%)	21(21.7%)	
	No change	9(9.2%)	26(26.8%)	
	Worse/recured	10(10.2%)	24(24.7%)	

\*p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

Table A.3.4 Global clinical impression by investigator —All patients in ITT- 12966.37B

		Number of Patients (%)		* p
		Active	base	
Day 0	N	98	98	
	none	0 (0%)	0 (0%)	0.828
	mild	48 (49%)	47 (48%)	
	moderate	39 (39.8%)	43 (43.9%)	
	severe	11 (11.2%)	8 (8.2%)	
Day 1	N	97	95	0.478
	none	1 (1%)	2 (2.1%)	
	mild	59(60.8%)	57 (60%)	
	moderate	29 (29.9%)	33 (34.7%)	
	severe	8(8.3%)	3 (3.2%)	
Day 3	N	98	97	
	none	17 (17.4%)	12 (12.4%)	0.019
	mild	64(65.3%)	54 (55.7%)	
	moderate	17 (17.4%)	29 (29.9%)	
	severe	0 (0%)	2 (2.1%)	
Day 5	N	96	92	0.001
	none	34(35.4%)	21 (22.8%)	
	mild	55 (57.3%)	43 (46.7%)	
	moderate	6 (6.3%)	26 (28.3%)	
	severe	1 (1%)	2 (2.2%)	
Day 7	N	95	87	0.001
	none	62 (65.3%)	26(29.9%)	
	mild	28 (29.5%)	34 (39.1%)	
	moderate	5 (5.3%)	24 (27.6%)	
	severe	0 (0%)	3 (3.5%)	
Final day (LOCF)	N	98	98	0.001
	none	62 (63.3%)	26(26.5%)	
	mild	30 (30.6%)	38 (38.8%)	
	moderate	6 (6.1%)	30 (30.6%)	
	severe	0 (0%)	4 (4.1%)	

\* p values were from the Mantel-Haenszel chi-square test.

Appears This Way  
On Original

OCT 13 1998

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW  
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 21-026

DRUG CLASS: 3S

NAME OF DRUG: PediaSTAT (miconazole nitrate)

APPLICANT: Johnson & Johnson Consumer Companies, INC.

SUBMISSION DATE: Aug. 24, 1998

INDICATION(S): Treatment of moderate-to-severe diaper dermatitis where *Candida albicans* may be a contributing factor.

NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES: 3, vehicle controlled.

STATISTICAL REVIEWER: Ping Gao

CLINICAL REVIEWER: Hon-sum Ko

PROJECT MANAGER: Mildred Wright

45 DAY MEETING DATE: 10/13/98

WAS THE NDA FILED: Yes

IF YES, DUE DATE: 04/99

USER FEE DATE: 06/24/1999

I. ORGANIZATION AND DATA PRESENTATION

YES NO N/A

- |  |              |             |             |
|--|--------------|-------------|-------------|
| *A. Is there a comprehensive table of contents with adequate indexing and pagination?    | <u>  X  </u> | <u>    </u> | <u>    </u> |
| *B. Are the original protocols, protocol amendments and proposed label provided?         | <u>  X  </u> | <u>    </u> | <u>    </u> |
| *C. Are the following tables/listings provided in each study report?                     |              |             |             |
| 1. Patient profile listings by center (includes <u>all</u> enrolled patients).           | <u>  X  </u> | <u>    </u> | <u>    </u> |
| 2. Lost subject tables by center which includes reason and time of loss.                 | <u>  X  </u> | <u>    </u> | <u>    </u> |
| 3. Intermediate analysis summary tables (gender, age, race/ethnic, etc.).                | <u>  X  </u> | <u>    </u> | <u>    </u> |
| *D. Adverse event listings by center and time of occurrence relative to enrollment date. | <u>  X  </u> | <u>    </u> | <u>    </u> |
| 1. Are adverse events from cited sources (foreign and domestic) provided?                | <u>  X  </u> | <u>    </u> | <u>    </u> |
| *E. Is a CANDAR or an electronic submission of the data necessary?                       | <u>  X  </u> | <u>    </u> | <u>    </u> |



\*E. Are there studies which are incomplete or ongoing?       X      

\*F. Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?       X      

**III. FILEABILITY CONCLUSIONS**

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes.

*Mr. [Signature]* *out 13.96*  
Ping Gao *Ping Gao 10/13/98*  
Biomedical Statistician, DOB IV

Concur: R. Srinivasan, Ph.D.  
TEAM LEADER, DOB IV

cc:

Arcgival:NDA 21-026  
HFD-540  
HFD-540/Dr.Wilkin  
HFD-540/Dr.Walker  
HFD-540/Dr.Ko  
HFD-540/Ms. Wright  
HFD-725/Dr.Huque  
HFD-725/Dr.Srinivasan  
HFD-725/Dr. Gao  
HFD-344/Dr. Carreras  
HFD-725/Chron.

\* These items, if not included or if incorrect, are justifiable reasons for not filing the NDA.

° These items, if not acceptable, are reason to consider not filing.

# It is the Agency's intent that all submissions be CANDARs or electronic in format in 1995. Clearly, we do not need CANDARs for every submission, but, just as clearly, we need data on disks if we are to do an expeditious review. Since the company, in all likelihood, used computers to do their evaluations, all data should be readily available to us on disk, at least, for our use in the review action.