American Academy of Dermatology
64th Annual Meeting
The Moscone Center
San Francisco, CA
March 3–7, 2006
Poster #P2533

TREATMENT OF DIAPER DERMATITIS COMPLICATED BY CANDIDIASIS: RESULTS OF A CLINICAL TRIAL INVOLVING COMBINATION MICONAZOLE NITRATE/ZINC OXIDE/PETROLATUM OINTMENT

SA Trinidad,[1] M Briones,[2] Z de Espinosa[3]

1. International Dermatology Research, Inc., Miami, FL, USA; 2. XXXXX; 3. Department of Dermatology, Clinica Metropolis II, Panama City, Panama.

Silvia A. Trinidad, BA
President/Research Director
International Dermatology Research, Inc.
8370 West Flagler St., Suite 200
Miami, FL 33144 USA
strinidad@intldermresearch.com

ABSTRACT

OBJECTIVES: To evaluate the efficacy and safety of a low concentration (0.25%) of miconazole nitrate in a 15% zinc oxide/83% white petrolatum ointment for the treatment of diaper dermatitis (DD) complicated by candidiasis. This formulation, with a lower concentration of miconazole nitrate than currently available topical antifungals, is designed for pediatric use in the treatment of DD.

METHODS: Double blind, vehicle controlled, randomized, parallel-group, multicenter study. Twenty sites in the US and Latin America from April 2003 to June 2004. Neonates as young as 4 weeks through children aged 4 years who had DD with a severity score of ≥3 and a positive baseline KOH preparation were eligible for inclusion. Eligible subjects received a baseline culture and were randomized to miconazole nitrate or zinc oxide/petrolatum vehicle control, which was applied to all clinically affected areas for 7 days at each diaper change and after bathing. Patients with a negative culture result for candidiasis at baseline were discontinued from the study.

ENDPOINTS: Clinical cure (DD severity index score of 0), microbiologic cure (no growth of *Candida* spp.), and combined clinical/microbiologic cure (overall cure, the primary outcome measure) assessed on study day 14 (7 days after the end of treatment).

RESULTS: Of the 330 subjects enrolled in the study, 236 (72%) had confirmed *Candida* spp. and were included in the modified intent to treat (MITT) population, the primary population for efficacy analysis reported here. The clinical cure rate was 38% (43/112) for miconazole nitrate and 11% (14/124) for vehicle control ($P<.001$). The microbiologic cure rate was 50% (56/112) for miconazole nitrate and 23% (29/124) for vehicle control, and the overall cure rate was 23% (26/112) for miconazole nitrate and 10% (12/124) for vehicle control ($P=.005$). All adverse events were assessed as unrelated to study medication.

CONCLUSION: Low dose (0.25%) miconazole nitrate in a zinc oxide/petrolatum ointment was well tolerated and significantly more effective than the zinc oxide/petrolatum vehicle control for the treatment of DD complicated by candidiasis.

INTRODUCTION

Diaper dermatitis (DD) is the most common dermatologic disorder of infancy,[1] and infection with *Candida albicans* is frequently associated with DD.[2] Topical antifungal therapy is warranted when DD complicated by candidiasis (DDCC) is suspected or confirmed.[3] Treatment for DDCC has typically involved various topical antifungals formulated for adults, including miconazole 2%. However, there is little data to substantiate the efficacy, tolerability, and safety with these products in infants. There are no antifungals currently approved by the FDA for use in DDCC. In addition, combination topical formulations containing an antifungal and a high potency corticosteroid (eg, clotrimazole) are inappropriate for use in intertriginous areas[4] and are contraindicated for use in the pediatric population.[5]

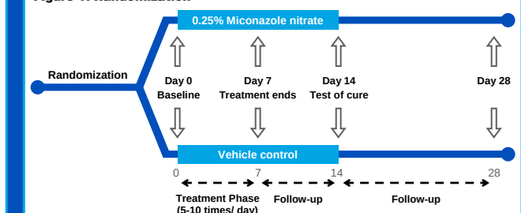
A pediatric formulation of a low concentration (0.25%) of miconazole nitrate in a zinc oxide/petrolatum ointment (Vusion, Barrier Pharmaceuticals, Princeton, NJ) has been shown to be effective and well tolerated in DDCC.[3] The rationale for this formulation is to provide effective antifungal activity in a steroid free treatment specifically designed for pediatric use. A concentration of 0.25% miconazole nitrate has been demonstrated to provide more than 50 times the minimal fungicidal concentration (MFC) required to eradicate *C albicans*.[6]

Here we present the efficacy and safety results of a double blind, vehicle controlled, randomized, multicenter, phase III study to evaluate 0.25% miconazole nitrate ointment versus vehicle control in the treatment of DDCC.

STUDY DESIGN

- Double blind, vehicle controlled, randomized, multicenter, phase III study to evaluate 0.25% miconazole nitrate ointment versus vehicle control in the treatment of DDCC

Figure 1. Randomization



- Evaluations took place on day 0, day 3, day 5 (optional), day 7, day 14, and day 28 (via telephone)
- KOH and culture preparations obtained at baseline (day 0), day 7, and day 14, and when discontinuations occurred

METHODS

INCLUSION CRITERIA

- Male and female pediatric patients aged 4 weeks through 4 years with Fitzpatrick Skin Type I - VI
- A positive KOH result for pseudohyphae and/or budding yeast at baseline (study day 0)
  - Positive culture result for *Candida* spp. as determined at day 3
- Clinical signs of DD: Overall Diaper Dermatitis Severity Index score of 3 to 8 at baseline visit; this score must have included an overall clinical grade of ≥2 for erythema
- Wearing commercially available diapers (day and night) for at least 7 days prior to enrollment on study day 0 and during the course of the study

EXCLUSION CRITERIA

- Any skin conditions (ie, atopic dermatitis, seborrheic dermatitis, psoriasis, and acrodermatitis enteropathica) other than DD that may have required concurrent therapy or confounded the evaluation
- Known sensitivity to skin care toiletry products, diapers, or the formulation components
- Chronic illnesses requiring systemic medication (ie, antihistamines, corticosteroids, and insulin)
  - Chronic antibiotic therapy did not exclude a child from this study
- Patients who had been treated with a prescription product (eg, corticosteroids) for diaper dermatitis or any other skin condition 7 days prior to enrollment

ENDPOINTS

- Primary outcome:
  - Overall cure: Patients who were both clinically cured (defined as a DD Severity Index score of 0) and microbiologically cured (defined as no growth of *Candida* spp.) on day 14. All others were considered a treatment failure
- Secondary outcomes:
  - Clinical cure on day 14
  - Microbiologic eradication on day 14

PATIENT POPULATION

Table 1: Summary of Patient Enrollment, Evaluability, and Demographics

	0.25% MICONAZOLE NITRATE OINTMENT	VEHICLE CONTROL	TOTAL
Number of Subjects Randomized	166	164	330
Number of Subjects in MITT Population, n (%)*	112 (67)	124 (76)	236 (72)
Patients Included in the PP Population, n (%)†	88 (79)	105 (85)	193 (82)
Patient Characteristics (MITT)			
Mean Age, Months (± SD)	7.67 (±4.87)	9.59 (±6.89)‡	
Sex, n (%)			
Male	51 (46)	57 (46)	
Female	61 (54)	67 (54)	
Race, n (%)			
White	24 (21)	34 (27)	
Non-White	88 (79)	90 (73)	
Diaper Dermatitis Severity Index Score, Mean (± SD)	5.05 (±1.25)	4.98 (±1.28)	
Severity of Diaper Rash at Baseline, n (%)			
Moderate	40 (36)	47 (38)	
Severe	72 (64)	77 (62)	

* MITT=modified intent-to-treat, all patients with confirmed *Candida* spp. who were dispensed study medication (active or vehicle control).

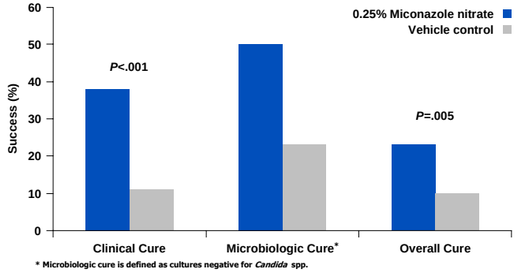
† PP=per protocol, all patients in the MITT population who completed the study with no noteworthy protocol violations, or who did not discontinue early due to treatment failure or treatment-related adverse events.

‡ $P=.019$.

- Baseline cultures in the MITT population were positive for *C albicans* in ≥97% of patients, with the remaining cultures positive for other *Candida* spp.
- The MITT population had a lower number of miconazole treated patients who discontinued for clinical failure than the vehicle control group (4/112 [4%] vs 58/124 [47%])

RESULTS: SUMMARY OF RESPONSE

Figure 2: Summary of Clinical and Microbiologic Efficacy at Day 14 (MITT)

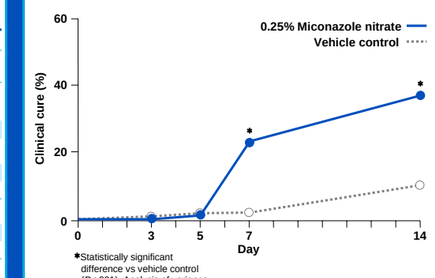


* Microbiologic cure is defined as cultures negative for *Candida* spp.

- Results were similar for all outcomes in the PP population

RESULTS: CLINICAL CURE

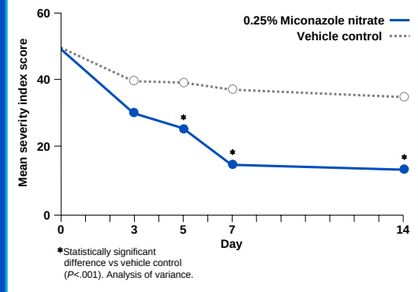
Figure 3. Analysis of Clinical Cure Through Day 14 (MITT)



- Beginning at day 7, the clinical cure rate in the miconazole nitrate group was significantly greater than that in the control group (27/112 [24%] vs 3/124 [2%]; $P<.001$)
  - This superior clinical response lasted through day 14 ($P<.001$)
  - Statistically significant results were also observed in the PP miconazole nitrate population at days 7 and 14

RESULTS: DD SEVERITY

Figure 4. Analysis of Diaper Dermatitis Severity Index Scores Through Day 14 (MITT)



- Mean DD Severity Index scores for patients in the miconazole nitrate group were significantly lower from day 3 through day 14 ($P<.001$)
  - The results in the PP population were also significantly better in the miconazole nitrate group from day 3 to day 14 ($P<.001$)
- At day 14, the mean DD Severity Index score had decreased 74% (5.05 to 1.3) from baseline for the miconazole nitrate group versus 29% (4.98 to 3.52) for the control group

RESULTS: SAFETY

Table 2. Adverse Events (All Patients)*

	0.25% MICONAZOLE NITRATE OINTMENT (n=166)	VEHICLE CONTROL (n=164)
Number of Events Reported	53 (32%)	47 (29%)
Number of Patients Reporting One or More Events	36 (22%)	31 (19%)
Severity of Event		
Mild	38 (72%)	35 (74%)
Moderate	15 (28%)	11 (23%)
Severe	0 (0%)	1 (2%)
Relationship to Study Drug		
Definite/Probable/Possible	0 (0%)	0 (0%)
Unlikely	2 (4%)	0 (0%)
Unrelated	51 (96%)	47 (100%)
System Organ Class (≥2%)		
Infections and infestations	20 (12%)	17 (10%)
Respiratory, thoracic, and mediastinal disorders	9 (5%)	4 (2%)
Gastrointestinal disorders	7 (4%)	7 (4%)
General disorders and administration site conditions	6 (4%)	5 (3%)
Injury, poisoning, and procedural complications	1 (1%)	4 (2%)

* Counts reflect number of subjects in each treatment group reporting one or more treatment events that map to the MedDRA system organ class. Subjects are only counted once and at each level of summarization.

- No serious adverse events (AEs) were observed in either arm
- There were no significant differences in AEs between groups
- No MITT patients in the miconazole nitrate group discontinued due to AEs
- The most common AE involved infections and infestations
- Only nasopharyngitis and upper respiratory tract infections occurred in ≥2% of the patients

SUMMARY

- The 0.25% miconazole nitrate antifungal ointment is significantly more effective than vehicle control for treatment of DDCC
  - 0.25% miconazole nitrate had significantly better overall cure, clinical cure, and microbiologic cure at day 14
- 0.25% miconazole nitrate rapidly improved DD severity, beginning at day 3 and continuing through day 14 (7 days after treatment ended)
- The adverse event profile of 0.25% miconazole nitrate was similar to that of vehicle control
- Only 4% of patients in the 0.25% miconazole nitrate group discontinued due to lack of efficacy versus 47% in the vehicle control group, suggesting that the active treatment was effective in maintaining subject participation from the onset of the study

REFERENCES

1. Ward DB, Fleischer AB Jr, Feldman SR, Krowchuk DP. *Arch Pediatr Adolesc Med.* 2000;154:943-946.
2. Ferrazzini G, Kaiser RR, Hirsig Cheng S-K, et al. *Dermatology.* 2003;206:136-141.
3. Spraker MK, Gisoldi EM, Siegfried EC, et al. *Cutis.* 2006;77:113-120.
4. Fleischer AB Jr, Feldman SR. *Clin Ther.* 1999;21:1725-1731.
5. Lotrisone Cream, Lotrisone Lotion [prescribing information]. Kenilworth, NJ: Schering Corporation; 2004.
6. Drouhet E, Dupont B. *Arzneimittelforschung.* 1992;42:705-710.

ACKNOWLEDGEMENTS:
The authors would like to thank John Quiring, PhD.

This poster exhibit was sponsored by Barrier Therapeutics, Inc., Princeton, NJ.