

ABSTRACT

Background: Current topical therapies for the treatment of distal subungual onychomycosis (DSO) are largely ineffective and oral therapies carry significant safety risks. NB-002 is an oil-in-water emulsion made with pharmaceutically approved ingredients to produce droplets with an average diameter of 180 nm. The size and composition of these droplets allows selective uptake into the epidermis and dermis via hair follicles and skin pores without skin irritation. The nanoemulsion is applied to the skin surrounding the nail and the droplets then penetrate into the skin and diffuse laterally to the site of infection in the nail bed where they physically disrupt and kill dermatophytes. We assessed the safety and tolerability of a 42 week treatment regimen of NB-002 compared to vehicle.

Method: 443 subjects aged 18 to 75 with a clinical diagnosis of mild-to-moderate DSO of the toenails were randomized to receive NB-002 (0.25% BID, 0.5% QD, 0.5% BID) or vehicle (BID or QD). Two mL treatments were applied to all 10 toenails and 5 mm of adjacent skin for 42 weeks. Safety including dermal irritation was evaluated by AE query at weeks 1, 3, 6, 12, 18, 24, 32, 42, 46 and 50.

Results: 443 subjects started treatment and were included in the safety population. The mean age was 52 years and subjects were generally white (94%) and male (84%) with 49% mean nail involvement of the target great toenail at baseline. In the three NB-002 treatment groups, the reported AEs were generally mild to moderate in severity and as expected for this population. There were no treatment-related serious AEs and no subjects withdrew from the study due to treatment-related AEs in any of the 3 NB-002 groups. The most commonly reported treatment-related AE was nail discoloration (5 subjects in the 0.25% BID group, 2 subjects in the 0.5% QD group, and 3 subjects in the 0.5% BID group); all of these cases were mild and the majority resolved prior to the last study observation. Overall, the active treatments were well tolerated with 7 treatment-related application site reactions (one case of paraesthesia in each group; one case of anaesthesia, dermatitis and pain in the 0.25% BID group; and one case of irritation in the 0.5% QD group).

Conclusions: Topical application of NB-002 for 42 weeks was safe and well-tolerated in subjects with DSO. The safety and novel mechanism of antifungal action make NB-002 a candidate for further investigation in the treatment of onychomycosis.

BACKGROUND

Onychomycosis is a chronic persistent infection of the nail bed affecting 3% -14% of adults, leading to pain, disfigurement, and social embarrassment.

Although oral (systemic) antifungal agents are somewhat effective, they have a high relapse rate and safety risks that limit their use in older individuals and those with co-existing medical conditions.

NB-002 is a novel topical nanoemulsion composed of high energy nanometer-sized droplets (Figure 1) with fungicidal and sporocidal activity that reach the nail plate by lateral diffusion from the periungual skin and hyponichium (Figure 2).

In vitro skin permeation studies indicate that the levels of NB-002 in the nail bed following lateral diffusion can be as high as 50 times the minimal fungicidal concentration (MFC=4 µg/ml)¹.

The size of the nanoemulsion droplets (180 nm) precludes them from entering the tight junctions of stratum corneum and a previous clinical pharmacology study in subjects with onycholysis demonstrated no systemic absorption.

Based on these findings we expected minimal dermal irritation or systemic side effects with long term administration of NB-002 in subjects with distal subungual onychomycosis of the great toe nail.

¹Ciotti et al. Abstr. M-2135, 48th Intersci. Conf. Antimicrob. Agents Chemother.

MECHANISM OF ACTION NB-002

Figure 1: Nanoemulsion droplet

- Cetylpyridinium chloride
- Polysorbate
- Oil

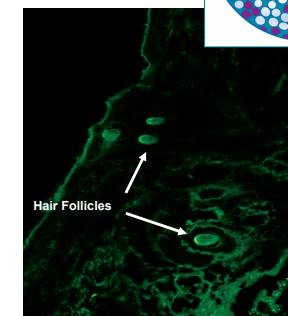
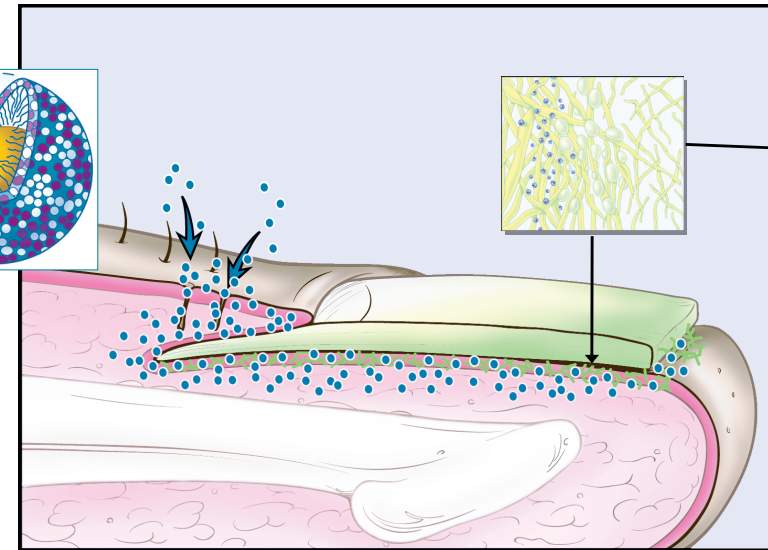


Figure 2. Accumulation of fluorescein-labeled NB-002 in hair follicles and diffusion to skin tissues.



Illustrations by Holly R. Fischer, MFA

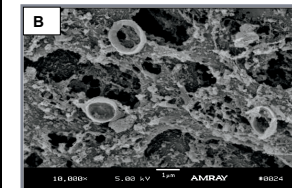
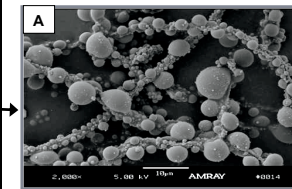


Figure 3. Scanning electron micrographs of *T. rubrum* (2,000 x) after treatment with NB-002 for 1 hour at room temperature. (A) mycelia and (B) conidia (spores)

RESULTS

SAFETY AND TOLERABILITY

- Adverse events were generally mild to moderate in severity and as expected for this population.
- No treatment-related serious adverse events and no subjects withdrew from the study due to treatment-related adverse events in any of the 3 NB-002 groups.
- Most commonly reported treatment-related adverse event was nail discoloration; all these events were mild and the majority resolved prior to the last study observation.
- Overall, the active treatment was well tolerated and with few application site reactions that occurred in both vehicle and active groups (see Table 3).

TABLE 1. Summary of adverse events

	Vehicle N=112	NB-002		
		0.25% BID N=110	0.5% QD N=114	0.5% BID N=107
Subjects with Severe AEs	5(4.5%)	4 (3.6%)	4 (3.5%)	5 (4.7%)
Subjects with Serious AEs	6 (5.4%)	4 (3.6%)	4 (3.5%)	5 (4.7%)
Subjects with AEs Leading to Discontinuation of Treatment	1 (0.9%)	2 (1.8%)	0 (0.0%)	3 (2.8%)
Subjects with Treatment-Related AEs	8 (7.1%)	8 (7.3%)	9 (7.9%)	9 (8.4%)

TABLE 2. Treatment-related adverse events experienced by ≥4% of subjects

Preferred Term	Vehicle N=112	NB-002		
		0.25% BID N=110	0.5% QD N=114	0.5% BID N=107
Upper Respiratory Tract Infection	7(6.3%)	13 (11.8%)	7 (6.1%)	7(6.5%)
Nasopharyngitis	4 (3.6%)	6 (5.5%)	8 (7.0%)	2 (1.9%)
Tinea Pedis	5 (4.5%)	5 (4.5%)	3 (2.6%)	4 (3.7%)
Sinusitis	2 (1.8%)	5 (4.5%)	3 (2.6%)	4 (3.7%)
Nail Discoloration	1 (0.9%)	6 (5.5%)	3 (2.6%)	3 (2.8%)
Hypertension	3 (2.7%)	3 (2.7%)	5 (4.4%)	2 (1.9%)

TABLE 3. Most commonly reported application site reactions

Preferred Term	Vehicle N=112	NB-002		
		0.25% BID N=110	0.5% QD N=114	0.5% BID N=107
Application Site Paresthesia	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Application Site Anesthesia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Application Site Dermatitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Application Site Irritation	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Application Site Pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)

METHODS

443 subjects with mild to moderate DSO (25% to 67% nail involvement on target great toenail) were randomized to one of five treatment arms; vehicle (BID or QD) or NB-002 (0.25% BID, 0.5% BID or 0.5% QD). For the analysis, the vehicle treatment arms were combined into a single treatment arm (Table 4).

There were no differences in the baseline demographic parameters between the 4 treatment groups (Table 5).

Subjects applied 2 ml of study medication once or twice daily for a maximum of 42 weeks. Safety, including dermal irritation, was evaluated by AE query at clinic visits.

Overall mean duration of treatment was 275.9 days. There were no differences in treatment duration among the treatment groups (Table 6).

TABLE 4. Subject Disposition

	Vehicle	NB-002		
		0.25% BID	0.5% QD	0.5% BID
Randomized Population	112	110	114	107
Intent-to-Treat/Safety Population	112 (100%)	110 (100%)	114 (100%)	107 (100%)

TABLE 5. Subject Demographics

	Vehicle N=112	NB-002		
		0.25% BID N=110	0.5% QD N=114	0.5% BID N=107
Age				
Median	53.1	51.8	53.4	54.6
Min, Max	21.6, 75.6	25.9, 74.4	21.6, 75.5	24.7, 75.4
Sex				
Men	91 (81.3)	91 (82.7)	96 (84.2)	94 (87.9)
Women	21 (18.8)	19 (17.3)	18 (15.8)	13 (12.1)
Race				
White	107 (95.5)	101 (91.8)	105 (92.1)	102 (95.3)

TABLE 6. Subject Exposure

	Vehicle N=112	NB-002		
		0.25% BID N=110	0.5% QD N=114	0.5% BID N=107
N	101	100	109	101
Mean Duration of Treatment (days)	274.5	265.0	281.8	281.8

CONCLUSIONS

Topical application of NB-002 for 42 weeks was safe and well-tolerated in subjects with DSO.

The ability to safely deliver both fungicidal and sporocidal activity to the nail bed could be a major advance in the treatment of onychomycosis.