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Safety, Tolerance, and Pharmacokinetics of Topical Nanoemulsion (NB-002) for the Treatment of Onychomycosis

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ABSTRACT

Background: NB-002 is a topical oil-in-water emulsion containing high-energy nanometer-sized droplets with a cationic agent at the oil-water interface. These nanodroplets have potent activity against the dermatophytes that cause onychomycosis, including activity against fungal spores. We examined the safety, tolerability (dermal irritation), and pharmacokinetics of NB-002 in subjects with distal subungual onychomycosis (DSO).

Methods: Twenty (20) subjects with advanced DSO of the toenails were randomized to 0.25% NB-002 or 0.5% NB-002 BID. The levels of NB-002 applied to the skin (0.25% and 0.5%) were 1250-2500-fold higher than the minimal fungicidal concentrations determined against dermatophytes (0.0002%). Treatments were applied twice daily to 10 toenails and 5 mm of adjacent skin for 28 days. Adverse event query, dermal irritation scoring, and pharmacokinetic sampling were performed on days 1, 3, 7, 14, 21, and 28 as well as a follow-up safety evaluation on day 58. Systemic drug absorption of cationic agent was determined by HPLC in plasma samples collected at 14 time points during the 28-day treatment period. Sixty (60) additional subjects with mild-to-moderate DSO were randomized to receive either vehicle or NB-002 (0.25% BID, 0.5% QD, or 0.5% BID). Adverse event query and dermal irritation scoring were performed at baseline and weeks 1, 3, 6, and 12.

Results: NB-002 was well tolerated with no safety or skin irritation concerns. There were no serious adverse events, no dropouts due to adverse events, and no drug-related adverse events. All of the subjects had dermal irritation scores of 0 or 1 indicating nil or minimal skin irritation. There were no detectable levels of surfactant in any of the pharmacokinetic samples (limit of detection=1 ng/mL).

Conclusion: NB-002 is a novel antifungal agent for topical application with activity against the dermatophytes that cause onychomycosis, including spores. These data indicate that NB-002 is well tolerated in humans at doses that are over 1000-fold higher than the minimum fungicidal concentration. The drug appears to work by local mechanisms that do not require systemic levels of active drug. This could provide a significant advance for onychomycosis therapy in terms of safety and drug resistance. Based on these data, a phase 2 study is currently under way recruiting over 400 subjects at 22 centers in the United States and Canada.

INTRODUCTION

- Onychomycosis is a common refractory fungal infection of the nail bed associated with nail deformity, pain, and disability
- Current oral antifungal agents have significant risks including hepatic toxicity,[1] cardiac toxicity,[2] and drug interactions[3,4]
- NB-002 is a novel oil-in-water emulsion for topical application currently in phase 2 development for the treatment of onychomycosis (Figure)
- Potent in vitro antifungal activity of nanoemulsions has been demonstrated in organisms associated with onychomycosis (Table 1)

TABLE 1. IN VITRO ACTIVITY AGAINST FUNGAL PATHOGENS

Fungal isolates	Minimum lethal concentration (µg/mL)
Trichophyton rubrum (ATCC 28188)	1.56
Trichophyton mentagrophytes (9533)	1.56
Epidermophyton floccosum (52063)	3.12
Microsporum gypseum (24102)	3.12
Candida albicans (10231)	3.12

METHODS

Phase 1

- 20 subjects with distal subungual onychomycosis (DSO)* were randomized to receive 0.25% or 0.5% NB-002 topically twice daily for 28 days† (Table 2)
- Subjects visited the clinic on days 1, 3, 7, 14, 21, 28, and 58 for adverse event (AE) reporting and dermal irritation assessments‡
- Blood draws for pharmacokinetic analysis were carried out on days 1, 3, 7, 14, 21, and 28§

Phase 2 interim safety analysis

- The first 60 randomized subjects in a 443-subject DSO** trial who completed 12 weeks of treatment† were included in the interim analysis. Subjects received either vehicle (QD or BID) or NB-002 (0.25% BID, 0.5% QD, or 0.5% BID) (Table 2)
- Subjects visited the clinic at baseline and weeks 1, 3, 6, and 12 for AE reporting and dermal irritation assessments‡

TABLE 2. SUBJECT DEMOGRAPHIC CHARACTERISTICS

Parameter	Phase 1 overall (N=20)	Phase 2 overall (N=60)
Age, years		
Mean (SD)	53.3 (9.0)	49.6 (10.0)
Median	55.0	49.6
Minimum, maximum	30.5, 64.9	21.6, 66.0
Sex, n (%)		
Male	12 (60)	50 (83)
Female	8 (40)	10 (17)
Race, n (%)*		
White	17 (85)	57 (95)
Black	3 (15)	2 (3)
Other	0 (0)	2 (3)

SD = standard deviation. *A subject may be categorized into more than 1 race.

FIGURE. MECHANISM OF ACTION OF NB-002

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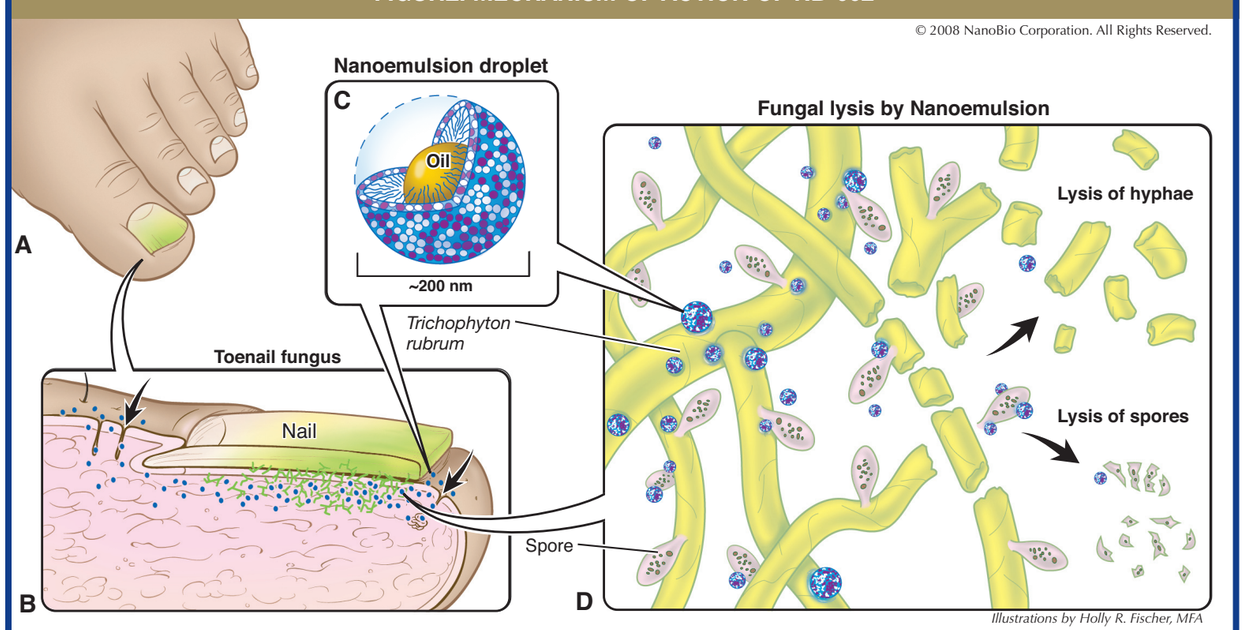

Illustrations by Holly R. Fischer, MFA

A) Onychomycosis is a fungal infection of the nail bed, matrix, or plate caused primarily by *Trichophyton rubrum.* B) NB-002 traverses the skin without irritating the epithelium or being absorbed systemically. C) NB-002 is a unique topical oil-in-water emulsion composed of high-energy, positively charged nanodroplets (200 nm). D) Lysis of both hyphae and microconidia (spores) occurs when the nanodroplets fuse with the membrane of the target cell types.

RESULTS

Phase 1

- All enrolled subjects completed the study and had at least 95% compliance with the treatment applications
- 5 subjects recorded mild dermal irritation scores on 1 or more days that resolved with continued treatment (Table 3)
- Adverse events were generally mild to moderate in severity and as expected; there were no drug-related AEs (Table 4)
- There was no evidence of systemic absorption of NB-002††

Phase 2 interim safety analysis

- 19 subjects reported mild and 3 subjects reported moderate dermal irritation scores associated with the use of study medication (Table 3)
- AEs reported for all subjects in the trial at the time of the interim analysis (approx 377) were generally mild to moderate in severity and as expected; there was 1 reported serious AE (appendectomy); none of the AEs were considered drug related (Table 4)

TABLE 3. SUBJECTS WITH DERMAL IRRITATION

Dermal irritation score	Phase 1 overall (N=20)	Phase 2 overall (N=60)
>0	5	22
>1	0	3
>2	0	0

TABLE 4. SUMMARY OF ADVERSE EVENTS

AE parameter	Phase 1 overall (N=20)	Phase 2 overall (N=377)
Number of AEs	5	8
Number of SAEs	0	1
Number of treatment-related AEs	0	0

AE = adverse event; SAE = serious adverse event.

CONCLUSIONS

- Topical treatment with NB-002 was safe and well tolerated, with no dermal irritation concerns in subjects with onychomycosis
- There was no systemic absorption of NB-002
- NB-002 offers important safety advantages over systemic therapies for onychomycosis

FOOTNOTES: *DSO involving at least 25% of both great toenails (based on investigator visual assessment and confirmed by microscopic examination) with onycholysis on at least 5 toenails. †Material was applied on all 10 toenails and on 5 mm of skin surrounding each toenail. ‡Dermal irritation was assessed at each visit by grading the application site with respect to erythema, dryness/scaling, burning/stinging, and itching; each graded on a standard scoring scale where 0=none, 1=mild, 2=moderate, 3=severe. §Samples were analyzed by reversed-phase high performance liquid chromatography using an SB-Phenyl column maintained at 35°C. **DSO involving 25-67% of at least one great toenail without lunular or proximal involvement (based on investigator visual assessment) and positive mycology (KOH test and culture). ††Active ingredient was below the quantifiable limit for the assay for all subjects and at all time points.

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Presented at American Academy of Dermatology Annual Meeting
February 1-5, 2008; San Antonio, Texas

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Poster preparation supported by NanoBio Corporation.