

Safety, Tolerability and Pharmacokinetics of NB-001 in a Phase 2 Dose Ranging Trial in Subjects with Recurrent Herpes Labialis

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ABSTRACT

Background: NB-001 is a topically applied oil-in-water emulsion containing high energy nanometer-sized droplets that permeate skin pores and hair follicles to enter the epidermis and dermis where they kill the virus on contact. At 180 nm, the droplets are excluded by tight junctions between epithelial cells and thus do not disrupt tissue matrices or enter blood vessels. This minimizes skin irritation and systemic absorption. We assessed the reported adverse events (AEs) including skin irritation and systemic drug absorption of 3 concentrations of NB-001 (0.1%, 0.3% and 0.5%) compared to vehicle.

Method: 484 subjects with recurrent herpes labialis were randomized to NB-001 (0.1%, 0.3% 0.5%) or vehicle. Subjects applied 200 µl of medication 5 times daily for a maximum of 4 days. Safety including dermal irritation was evaluated daily by AE query. A subset of subjects had pharmacokinetic sampling following application of medication to an open lesion (Day 3 ± 1 day). Samples were analyzed for circulating levels of the active ingredient using a validated HPLC method (limit of detection 1 ng/mL).

Results: 482 subjects started treatment and were included in the safety population. There were no significant drug-related AEs in any treatment groups, no serious AEs and no subjects withdrew from the study due to treatment-related AEs. Overall, all active treatments were well tolerated with <1% of subjects reporting application site irritation. There were negligible levels of active ingredient detected in plasma following topical application of NB-001, indicating a lack of systemic absorption.

Conclusions: There were no significant safety or dermal irritation concerns in any of the treatment groups and pharmacokinetic sampling indicated no significant systemic absorption. NB-001 is safe and well tolerated in subjects with recurrent herpes labialis.

BACKGROUND

- Herpes simplex virus type 1 (HSV-1) is a prevalent human pathogen causing painful recurrent blisters around the mouth (herpes labialis) and an increasing proportion of recurrent genital infections (herpes genitalis). The currently available topical treatments for HSV-1 are only marginally effective and oral therapies carry concerns over the development of drug resistance.

- NB-001 is a novel topical nanoemulsion composed of high energy nanometer-sized droplets (Figure 1). When latent HSV-1 reactivates, it travels down the nerve axon and exits at the nerve endings in the skin tissues surrounding the mouth. NB-001 reaches these tissues via skin pores and hair follicles (Figure 2).

- Upon contact with the virus, NB-001 droplets are thermodynamically driven to fuse with the viral envelope causing disruption and viral lysis (Figure 3). As NB-001 lyses the virus in the skin tissues, it lessens the viral mediated tissue damage and shortens the duration of herpes lesions. This novel physical mechanism of action renders the emergence of drug resistance highly unlikely.

- Since the size of the nanoemulsion droplets (180 nm) prevents them from entering the tight junctions of epithelial cells, there is no irritation or systemic absorption. Thus, we performed a dose-ranging trial in subjects with recurrent herpes labialis to assess the safety, tolerability and systemic absorption of NB-001 in humans.

MECHANISM OF ACTION OF NB-001

Figure 1. Nanoemulsion droplet.

- Cetylpyridinium chloride
- Polysorbate
- Oil

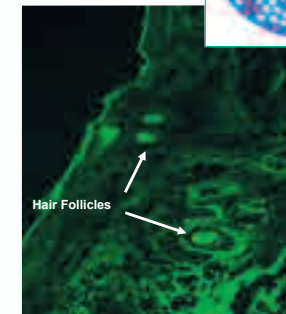
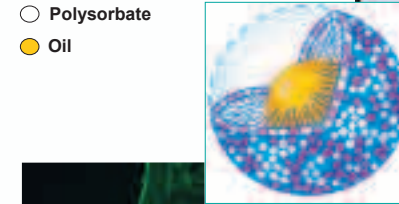


Figure 2. Accumulation of fluorescein-labeled NB-001 in hair follicles and diffusion to skin tissues.

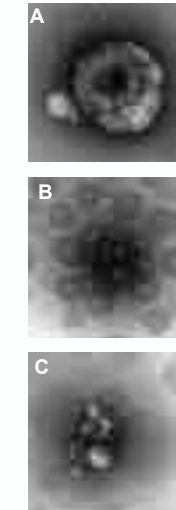
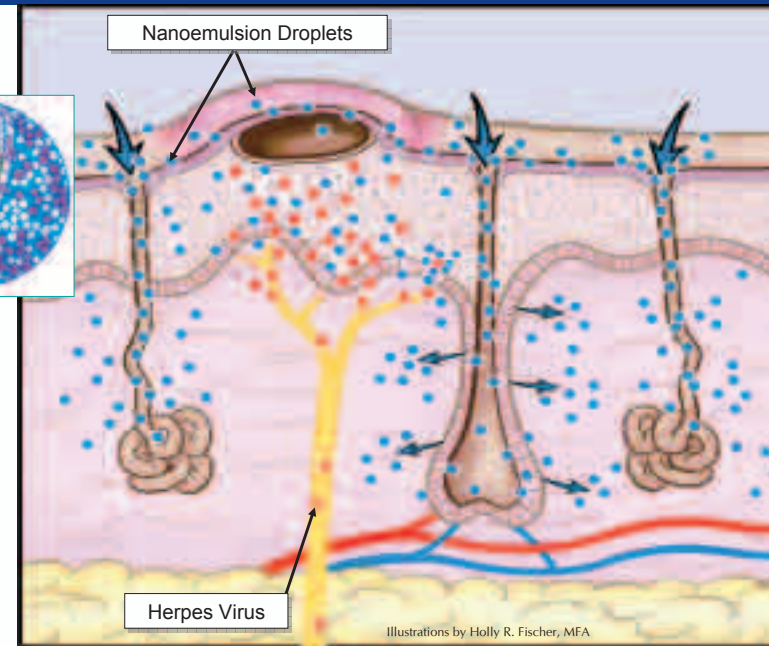


Figure 3. HSV-1 (A) is surrounded by NB-001 droplets (B) that fuse with HSV-1, resulting in envelope disruption and viral lysis (C).

METHODS

- 484 subjects with a history of recurrent herpes labialis (three or more outbreaks in the prior year) were randomized to one of four treatment arms; vehicle or NB-001 (0.1%, 0.3% or 0.5%) (Table 3).

Table 3. Subject disposition

	Vehicle	NB-001		
		0.1%	0.3%	0.5%
Randomized Population	116	123	116	129
Intent-to-Treat/Safety Population	116 (100%) ^a	121 (98.4%)	116 (100%)	129 (100%)
Pharmacokinetic Population	9 (7.8%)	9 (7.3%)	9 (7.8%)	5 (3.9%)

^a(% of randomized)

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

Table 4. Subject demographics

	Vehicle N=116	NB-001		
		0.1% N=123	0.3% N=116	0.5% N=129
Age				
Median	43.3	43.5	41.5	43.5
Min, Max	18.7, 75.8	18.2, 80.9	18.2, 70.7	18.4, 77.3
Sex				
Women	77 (66.4%) ^a	82 (66.7%)	88 (75.9%)	95 (73.6%)
Race				
White	110 (94.8%)	113 (91.9%)	110 (94.8%)	122 (94.6%)

^a(% of randomized)

- Subjects applied 200 µL of medication five times daily for a maximum of four days. Safety, including dermal irritation, was evaluated by AE query at daily clinic visits and a 30-day post-treatment telephone call.

- A subset of subjects had blood draws on Day 3 (± 1 day) pre-dose, 15, 30, 60, 120 and 180 minutes post-dose to detect plasma CPC following topical application of study medication to an open herpes lesion (Table 3).

CONCLUSIONS

- NB-001 is a novel antiviral agent that is safe and well tolerated in subjects with recurrent herpes labialis.
- The excellent safety profile and lack of systemic exposure, along with a low risk for development of drug resistance, represent significant therapeutic advantages over current herpes therapies.
- Efficacy results from this trial will be presented in Session 267 (Herpes Viruses) on October 28, 2008 [Slide session V-3771].

RESULTS

SAFETY

- There were few AEs and they were generally mild to moderate and as expected for the population. One subject in the 0.1% NB-001 group had "facial burning" at the application site that was rated as severe, but considered by the Investigator to be unrelated to study treatment (Table 1).

- Two subjects discontinued early for AEs that were considered by the Investigator to be unrelated to study medication; one subject had a second herpes lesion and the other had lip tattoo irritation, both of which interfered with the ability to assess healing of the primary lesion.

TOLERABILITY

- NB-001 was well tolerated with no significant dryness, irritation or other findings at the application site (Table 2).

PHARMACOKINETICS

- There was no significant systemic absorption of NB-001. There was no detectable cetylpyridinium chloride (CPC) in 99% of the plasma samples. Four samples had minimally detectable levels of CPC that ranged from 1.03-2.18 ng/mL. Since two of these samples were obtained from vehicle subjects, these levels were considered not specifically related to study medication.

Table 1. Summary of adverse events by treatment

Adverse Events	Vehicle N=116	NB-001		
		0.1% N=121	0.3% N=116	0.5% N=129
Subjects with Severe AEs	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Subjects with Serious AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with AEs leading to discontinuation of drug	1 (0.9%)	0 (0.0%)	1(0.9%)	0 (0.0%)
Subjects with drug-related AEs	7 (6.0%)	8 (6.6%)	9 (7.8%)	8 (6.2%)

Table 2. Adverse events experienced by ≥2% of subjects

Preferred Term	Vehicle N=116	NB-001		
		0.1% N=121	0.3% N=116	0.5% N=129
Application Site Irritation	2 (2.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Application Site Reaction	4 (3.4%)	2 (1.7%)	1 (0.9%)	0 (0.0%)
Second Herpes Lesion	7 (6.0%)	9 (7.4%)	11 (9.5%)	13 (10.1%)
Nasopharyngitis	4 (3.4%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
Headache	1 (0.9%)	3 (2.5%)	3 (2.6%)	0 (0.0%)
Shoulder Pain	3 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)