

Investigator Assessed Time to Healing in a Randomized, Double-Blind, Vehicle-Controlled Trial of a Novel Antiviral Nanoemulsion (NB-001) for Recurrent Herpes Labialis

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ABSTRACT

Background: Current topical therapies for *herpes labialis* are largely ineffective and oral therapies are not widely prescribed. NB-001 is a topically applied oil-in-water emulsion containing high energy nanometer-sized droplets that permeate to the site of infection and kill virus on contact. We assessed the clinical efficacy of 3 concentrations of NB-001 compared to vehicle in subjects with recurrent *herpes labialis*.

Methods: 919 subjects aged 18 to 80 with a history of 3 cold sore outbreaks per year received locked medication kits containing 1 of 4 treatments of NB-001 (0.1%, 0.3%, 0.5%) or vehicle. At the first sign of a recurrence, subjects received an unlock code and started applying 200 µL of treatment 5 times daily up to a maximum of 4 days. Subjects were seen daily for assessment of lesion stage until the investigator assessed the lesion as healed or aborted. A Kaplan-Meier survival analysis was used to assess the time to healing, defined as the difference in hours between first treatment and healing divided by 24 hours/day. An analysis of variance (ANOVA) was also conducted.

Results: 482 subjects had a *herpes labialis* recurrence and started treatment (intent-to-treat population). NB-001 0.3% resulted in a significant improvement in time to healing of 1.3 days compared to vehicle (p=0.006). These results were confirmed by ANOVA that showed an improvement in time to healing of 1.2 days (p=0.004).

Conclusions: NB-001 0.3% was efficacious in improving the time to healing of cold sores by more than one day in subjects with recurrent herpes labialis. The improvement in time to healing seen with this novel topical nanoemulsion formulation was similar to that reported for oral nucleoside analogues.

BACKGROUND

- Herpes simplex virus type 1 (HSV-1) is a prevalent human pathogen that causes recurrent oral and genital lesions. The currently available topical agents for herpes labialis are only marginally effective and oral therapies carry concerns over the development of drug resistant viral strains.
- Over 80% of adults have latent HSV-1 in their facial ganglia. In one-third of these individuals, HSV-1 reactivates, travels down the nerve ending and causes painful, recurrent lip lesions on the lips and skin surrounding the lips (herpes labialis) (Figure 2).
- NB-001 is a novel topical nanoemulsion composed of high energy nanometer-sized droplets that enter the epidermis and dermis via skin pores and hair follicles (Figure 1). 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.
- When latent HSV-1 reactivates, it exits at the nerve endings in the epidermal-dermal junction where the nanoemulsion droplets accumulate. NB-001 droplets surround the virus and are thermodynamically driven to fuse with the viral envelope causing membrane disruption and viral lysis (Figure 3), thus shortening the duration of the herpes lesion.
- The novel physical mechanism of NB-001 action renders the emergence of drug resistance highly unlikely (Figure 4).

MECHANISM OF ACTION OF NB-001



Figure 1. Nanoemulsion droplet.

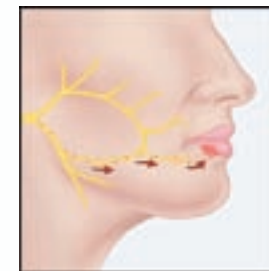


Figure 2. Herpes simplex virus, type 1 (HSV-1) reactivates and travels down the facial nerve to cause lip lesions.

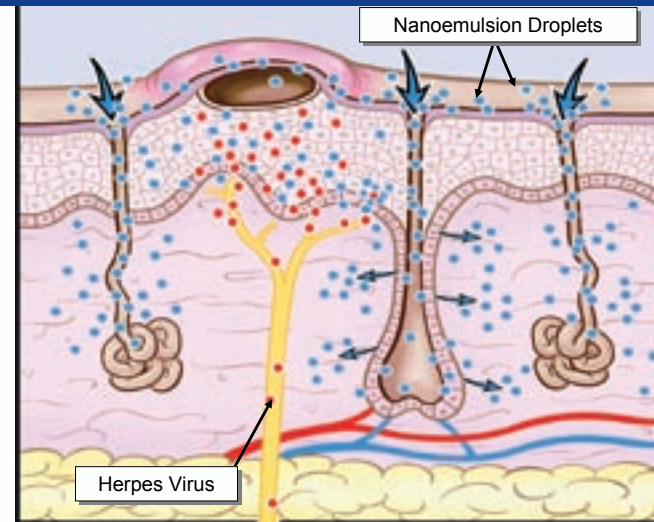


Figure 3. HSV-1 (red circles) exits the nerve ending at the dermal-epidermal junction where it is surrounded by nanoemulsion droplets (blue circles) and is lysed.

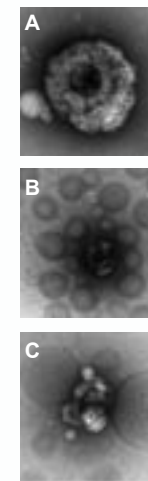


Fig 4. HSV-1 (A) is surrounded by NB-001 droplets (B) that fuse with HSV-1, resulting in envelope disruption and viral lysis (C).

METHODS

- We performed a prospectively randomized, double-blind, vehicle-controlled, dose-ranging trial in 482 subjects at 28 US sites.
- Subjects received pre-randomized, locked medication kits containing vehicle or NB-001 (0.1%, 0.3%, or 0.5%).
- At the onset of symptoms, subjects called to receive a code to unlock their box and applied treatment (200 µL) five times daily until lesion healing or a maximum of 4 days
- Subjects returned to the clinic within 12 hours of symptom onset and daily thereafter for Investigator assessments of lesion stage (prodrome, erythema, blister, ulcer, scab or healed). Lesions were considered healed when the skin was returned to normal and no scabs remained.
- The Investigator assessed time to healing in days was analyzed using Kaplan-Meier Life Table methods in all subjects who received at least one dose of medication (ITT population). Results were confirmed by ANOVA
- Safety, tolerance and pharmacokinetics were assessed as described in Poster P2517, Center 3.

RESULTS

- There were no significant differences baseline demographic parameters between the treatment groups and all treatments were well tolerated with no safety concerns or systemic absorption (See Poster P2517).
- The Investigator assessed time to healing showed a highly significant improvement (p = 0.006) for subjects treated with 0.3% NB-001 compared to vehicle (Table 1), consistent with the permeation data in human cadaver skin indicating that the 0.3% dosage form gives the highest tissue levels of NB-001 (Figure 5).
- This treatment effect is higher than that reported for the current topical therapies and is equal to that reported for high-dose oral nucleoside regimens (Figure 6).
- A subset analysis of subjects considered (by the investigator) to be at the prodrome or erythema stage at baseline indicated a mean time to healing of 3.6 days for subjects treated with 0.3% NB-001 (Table 3) nearly 2 days improvement over vehicle.

CONCLUSIONS

- NB-001 is novel topical virucidal nanoemulsion that is safe, well-tolerated and is highly efficacious, regardless of baseline lesion stage.
- In subjects with no lesion at baseline, the time to healing was 3.6 days, providing a significant clinical advantage over current topical and systemic agents.
- The novel physical mechanism of action renders the emergence of drug resistance highly unlikely, making NB-001 an ideal candidate for wide spread treatment of common conditions, such as herpes labialis.

RESULTS

	Median	Mean	p
Vehicle (N = 99)	6.0	6.7	
0.1% NB-001 (N = 127)	5.5	6.5	0.3795
0.3% NB-001 (N = 102)	5.0	5.4	0.0064
0.5% NB-001 (N = 101)	5.9	6.5	0.6775

1.0 Days 1.3 Days

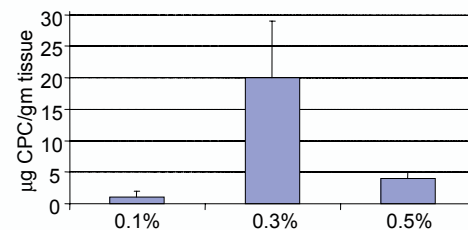


Figure 5 : Dermal permeation (top) and cross-polar imaging (bottom) 24 hours following 5 applications of NB-001 (0.1, 0.3 or 0.5%) to human cadaver skin over 12 hours (~3 hours apart). Darkening with the 0.5% dose indicates blockage of light by crystalline CPC. Blockage of skin pores reduces penetration of 0.5% NB-001.

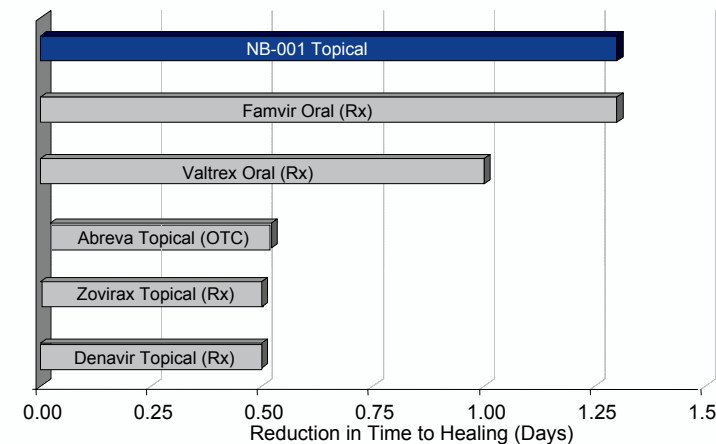


Figure 6 : Reduction in healing time of herpes lesions with NB-001 compared with times reported in the product label for currently available topical and oral products.