Topical Nitric Oxide-Releasing Therapy with SB208 Increased Fingernail Growth

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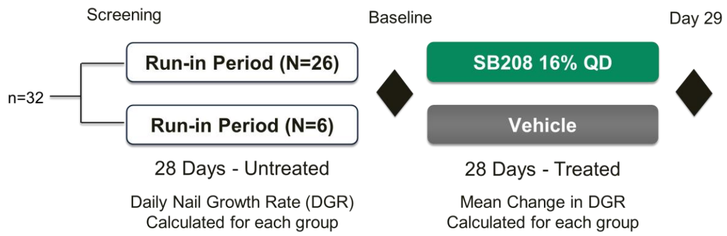
Introduction

- SB208, a nitric oxide-releasing topical drug candidate, is in development for the treatment of fungal infections of the skin and nails, such as tinea pedis and onychomycosis
- The active ingredient in the silicone-based gel of SB208 is NVN1000, a polysiloxane macromolecule that stores nitric oxide on the polymer backbone and has demonstrated broad-spectrum antifungal activity in vitro
- Causative agents for both diseases are primarily the dermatophytes *T. rubrum, T. mentagrophytes* and *E. floccosum*[1]
- Recent studies suggest that the nail plate, interdigital space and surrounding cutaneous tissue may serve as an overlooked reservoir of dermatophytes, perpetuating reinfection and co-infection of onychomycosis and tinea pedis[2]
- In addition to nitric oxide's antimicrobial properties, it also has the ability to enhance blood flow and enhance nail growth through neovascularization

Study Design



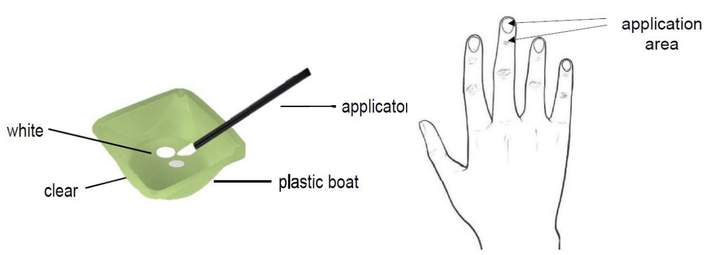
- 32 adult women between the ages of 18 and 40 years
- Patients were randomized 3:1 SB208 Gel 16% or vehicle treatment arms
- A singe dose of SB208 comprises 250 mg of an NVN1000 gel co-administered with 250 mg of hydrogel that, upon admixture and application on the finger, releases nitric oxide as a fungicidal agent
- At screening, target nail (both index fingernails) was notched using a scalpel, deep and wide enough to be observed for the study duration. The distance between the proximal nail fold (PNF) and notch was measured at each visit
- Efficacy endpoint assessed was daily growth rate (DGR) of target nails at screening, baseline, day 15 and day 29

Daily Growth Rate Calculation

$$\text{Daily growth rate } i+1 = \frac{\text{distance from PNF to notch at v}i+1 - \text{distance from PNF to notch at v}i}{\text{Number of days from v}i \text{ to v}i+1}$$

Application Instructions

- At bedtime, patients mixed a pea-sized amount of test material from each tube using a provided applicator in a provided plastic container
- Once mixed, patients applied a thin layer of mixed test materials using applicator to all fingernails by coating each fingernail, cuticle and skin between the fingernail and knuckle closest to the fingernail



Efficacy Results

Daily Growth Rate Comparison of Run-In Period and With Treatment
(mm/day)
***p<0.001 for DGR at Day 29 from baseline compared to Run-In**

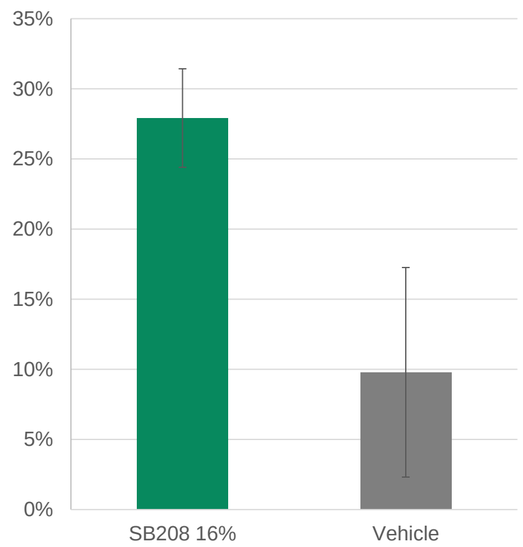
Treatment	SB208 16%*		Vehicle Gel	
Time Interval	Screening to Baseline	Baseline to Day 29	Screening to Baseline	Baseline to Day 29
N	26	26	6	6
Mean	0.099	0.122	0.090	0.105
Standard Deviation	0.015	0.018	0.013	0.011

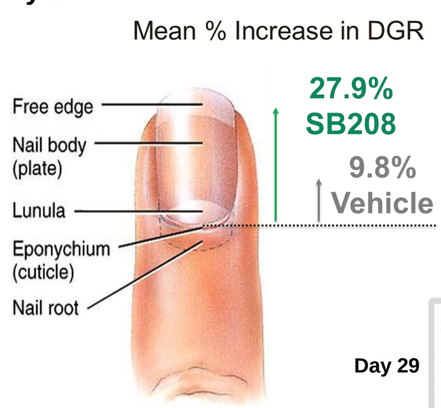
Mean (SE) Absolute Change From Run-in of Daily Nail Growth Rate
(mm/day)

Time Interval	SB208 16% Mean (SE)	Vehicle Gel Mean (SE)	Mean Difference (SE)	95% Confidence Interval	P-value[a]
Baseline to Day 29	0.025 mm (0.003)	0.007 mm (0.007)	0.018 (0.008)	0.001, 0.035	0.0361

[a]Hypothesis tested that the mean difference between treatments equals zero. Results based on an analysis of covariance with change from the run-in daily nail growth rate as response variable, treatment as a categorical variable, and the run-in daily nail growth rate as a continuous covariate. Means presented are model-adjusted means

Mean (SE) % Change from Run-In of Daily Nail Growth Rate Baseline to Day 29





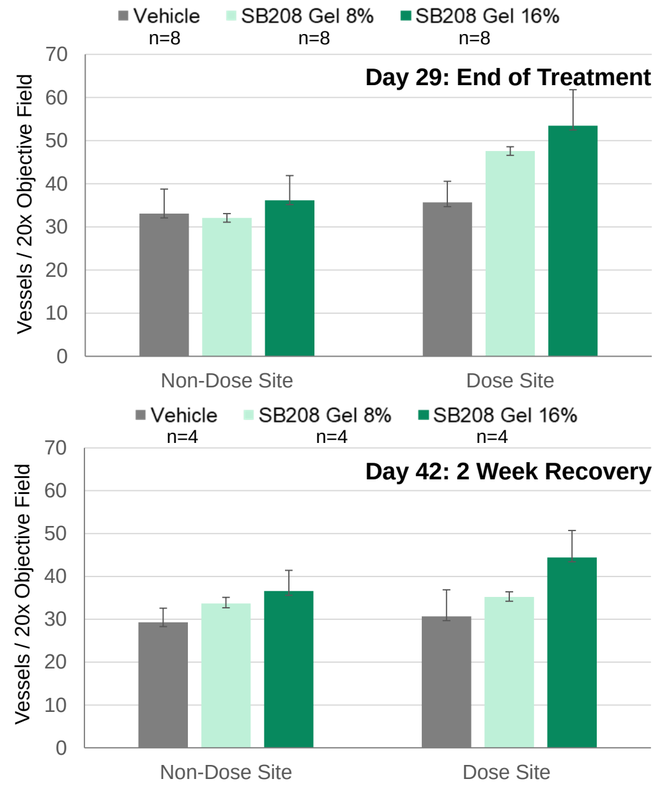
Demographics

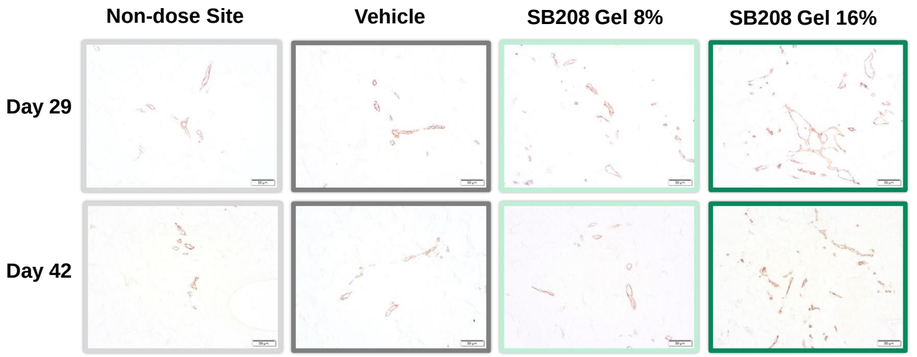
	SB208 16%	Vehicle Gel
N	26	6
Gender, n		
Female	26 (100%)	6 (100%)
Age, mean	33.8	33.8
Reason for Discontinuation		
Investigator Decision	0	0
Lost to Follow-up	0	0

Nonclinical Study

- SB208 was evaluated in a 28-day toxicology study in mini-pigs to evaluate local and systemic toxicity and toxicokinetics. As a component of the study, pharmacological mechanism of action of topical nitric oxide through immunohistochemistry of CD31 stained blood vessels in the skin was evaluated.
- SB208 8%, SB208 16% or vehicle was applied twice-daily to approximately 10% of total body surface area to 36 minipigs.
- Animals were observed starting Day 1 through end of treatment (Day 28). The skin sections were obtained at Day 29 and Day 42 for CD31 quantification of blood vessels.

CD31 Blood Vessel Quantification





Conclusions

- In a Phase 1 clinical trial:
  - SB208 16% demonstrated statistically significant greater mean daily nail growth rate for the treatment period for the average of both target nails when compared with run-in period
  - Differences in the mean percent increase in daily nail growth rate from the run-in period were statistically significant in favor of SB208 16% over Vehicle from baseline to day 29
  - SB208 16% was well tolerated and no AEs related to use were reported
- In a nonclinical toxicology study:
  - SB208 16% increased dermal blood vessel counts in dose site skin following the 28-day exposure period and remained elevated after the 14-day recovery period
- The increased angiogenesis observed in vivo may be a potential mechanism by which the enhanced nail growth rate with SB208 16% was observed following topical application in humans

[1]Bell-Syer SE, et al. Oral treatments for fungal infections of the skin of the foot. Cochrane Database Syst Rev. 2012 Oct 17;10:CD003584. [2]Gupta AK, et al. Update on Efinaconazole 10% Topical Solution for the Treatment of Onychomycosis. Skin Therapy Lett. 2016 Nov;21(6):7-11