Efficacy and Safety of SB208, an Investigational Topical Nitric Oxide-Releasing Gel, in a Phase 2 Study of Subjects with Interdigital Tinea Pedis

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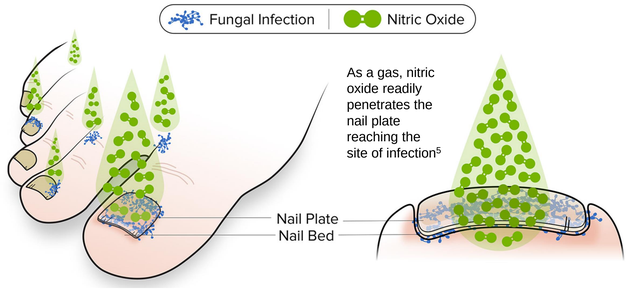
Introduction

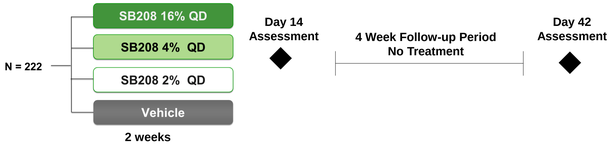
- SB208, a nitric oxide-releasing topical drug candidate, is in development for the treatment of fungal infections of the skin and nails, such as tinea pedis and onychomycosis
- The active ingredient in the silicone-based gel of SB208 is NVN1000, a polysiloxane macromolecule that stores nitric oxide on the polymer backbone and has demonstrated broad-spectrum anti-fungal 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]
- T. pedis occurs in at least 33% of onychomycosis patients and studies have demonstrated enhanced efficacy when t. pedis and onychomycosis are treated concurrently[3]

Antimicrobial Activity of Nitric Oxide in Superficial Fungal Infections

Nitric oxide exerts its fungicidal activity against a broad spectrum of fungal species, including *T. rubrum*, through inactivation of cellular enzymes, disruption of cellular respiration, and lipid peroxidation[4]



Phase 2 – Tinea Pedis (NI-AF201) Study Overview

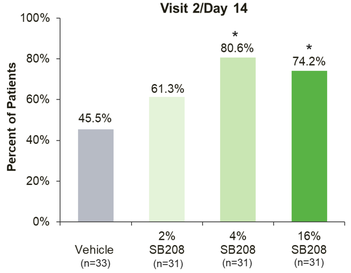


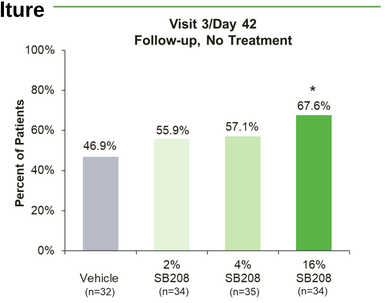
- Subjects were randomized 1:1:1:1 SB208 Gel (2%, 4% or 16%) or vehicle treatment arms
- A single dose of SB208 comprises 250 mg of an NVN1000 loaded silicone-based gel co-administered with 250 mg of an aqueous hydrogel, that upon admixture on the foot and interdigital tissue, releases nitric oxide as a fungicidal agent
- Treatment was self-administered once daily for 2 weeks (Visit 2/Day 14 assessment/evaluation) followed by a post-treatment 4-week follow-up visit (Visit 3/Day 42)
- Endpoints assessed were 1) negative fungal culture; 2) mycological cure; and, 3) clinical cure
- Mycological and clinical cure assessments reported using modified intent-to-treat (mITT) populations. mITT populations include any patient who: (a) was enrolled in the study and met inclusion/exclusion criteria; and (b) had a positive baseline skin fungal culture for *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, or *E. floccosum*; and (c) applied at least 1 dose of assigned IP
- Negative fungal culture assessments reported using patients in mITT population with evaluable culture results

Efficacy Results

Negative Fungal Culture

*p<0.05 compared to vehicle

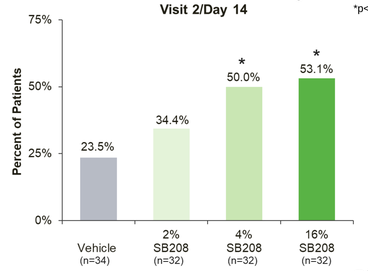


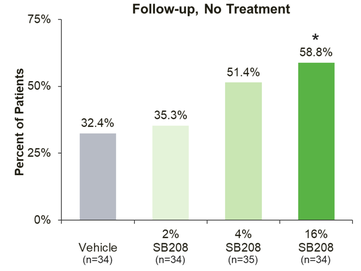


Mycological Cure

Negative KOH and negative culture

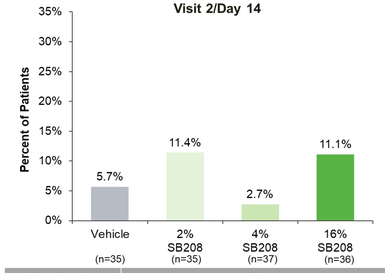
*p<0.05 compared to vehicle

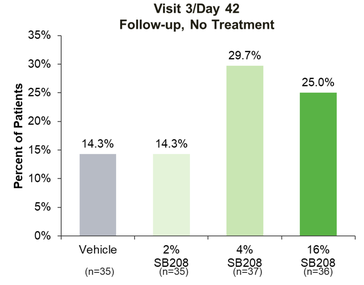




Clinical Cure

Total signs/symptoms severity score of no more than 2 with no individual symptom severity score > 1 at Visit 3/Day 42





Sign/Symptom	Description
Erythema	Redness
Scaling	Thin, dry epidermal sheets shedding from skin
Maceration	Soft, moist broken-down skin
Fissuring/Cracking	Deep furrowing clefts or slits in the skin
Pruritus	Itching as determined by the subject
Burning/Stinging	Burning, stinging or tingling as determined by the subject

Score	Assessment	Description
0	None	Complete absence of sign or symptom
1	Mild	Slight
2	Moderate	Definitely present
3	Severe	Marked, intense

Demographics

	SB208 2%	SB208 4%	SB208 8%	Vehicle
N				
Subjects in Intent-to-Treat Analysis for Safety	56	55	55	56
Subjects in Modified Intent-to-Treat Analysis	35	37	36	35
Gender, n				
Female	10 (28.6%)	17 (45.9%)	14 (38.9%)	13 (37.1%)
Male	25 (71.4%)	20 (54.1%)	22 (61.1%)	22 (62.9%)
Age, mean	43.1	46.6	41.3	43.8
Disposition, n				
Completed	40 (71.4%)	45 (81.8%)	41 (74.5%)	42 (75.0%)
Discontinued	16 (28.6%)	10 (18.2%)	14 (25.5%)	14 (25.0%)
Reason for Discontinuation				
Negative Baseline Culture	15 (26.8%)	9 (16.4%)	14 (25.5%)	14 (25.0%)
Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Decision	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Baseline Mycology Evaluations				
	SB208 2%	SB208 4%	SB208 8%	Vehicle
N	35	37	36	35
T. rubrum	32 (91.4%)	30 (81.1%)	29 (80.6%)	30 (85.7%)
T. mentagrophytes	2 (5.7%)	1 (2.7%)	4 (11.1%)	1 (2.9%)
T. tonsurans	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)
E. floccosum	3 (8.6%)	6 (16.2%)	2 (5.6%)	4 (11.4%)
Other qualifying dermatophyte	5 (14.3%)	5 (13.5%)	1 (2.8%)	2 (5.7%)

Treatment Emergent Adverse Events (TEAEs)

	SB208 2%	SB208 4%	SB208 8%	Vehicle
N	56	55	55	56
Subjects with at Least 1 TEAE	2 (3.6%)	3 (5.5%)	2 (3.6%)	2 (3.6%)
Subjects with at Least 1 TEAE of Severity				
Mild	2 (3.6%)	3 (5.5%)	2 (3.6%)	2 (3.6%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with at Least 1 TEAE by Relationship to Study Medication				
Related	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Related	2 (3.6%)	3 (5.5%)	2 (3.6%)	2 (3.6%)

Conclusions

- SB208 4% and 16% demonstrated a treatment effect (p<0.05) in mycological cure which warrants further development in additional efficacy clinical trials
- All TEAEs were mild and considered not related to study medication
- No serious adverse events were reported and no subjects discontinued due to AEs
- SB208 provides antifungal activity from an alternative class of compounds than allylamines and azoles for T. pedis alone, but when utilized in a co-infection setting in patients with onychomycosis, provides a new treatment option with a single topical product
- SB208 product profile demonstrates potential advantages over allylamines and azoles

[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. [3]Gupta AK, Studholme C. Update on Efinaconazole 10% Topical Solution for the Treatment of Onychomycosis. Skin Therapy Lett. 2016 Nov;21(6):7-11. [4]De Groote MA, et al. NO inhibitions: antimicrobial properties of nitric oxide. Clin Infect Dis. 1995 Oct;21 Suppl 2:S162-5. [5]In Vitro Nail Penetration of Nitric Oxide-releasing Formulations for the Topical Treatment of Onychomycosis http://www.novan.com/files/9214/6888/7545/ASM_Microbe_Poster_SB208_Onychomycosis.pdf