A Topical Nitric Oxide-Releasing Cream SB414: Results of a Phase 1b Double-Blind, Randomized, Vehicle-Controlled Study in Patients with Mild-to-Moderate Atopic Dermatitis

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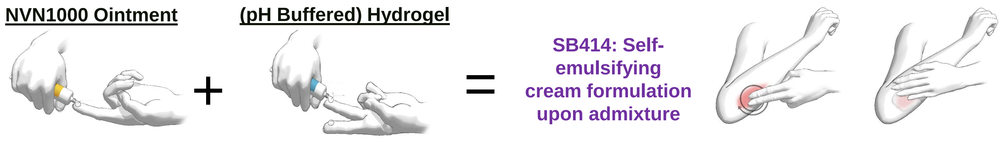
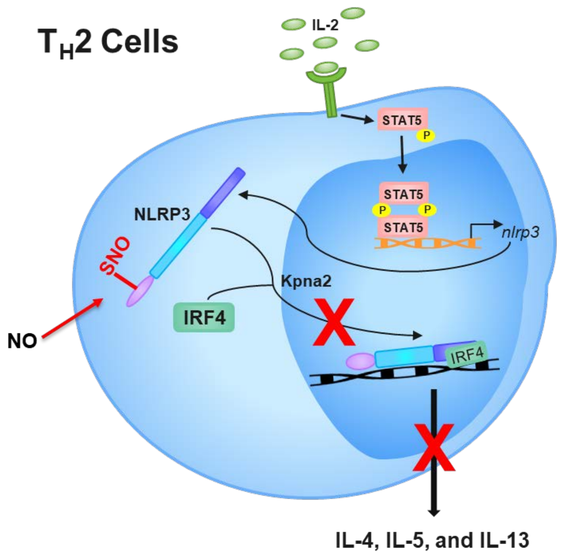
Introduction

- SB414, a nitric oxide-releasing topical drug candidate, is in development for the treatment of inflammatory skin diseases, such as atopic dermatitis
- SB414 is a two-component formulation comprised of an active ointment phase, containing the NVN1000 nitric oxide-releasing drug substance, and an inactive acetate buffered hydrogel phase that are mixed together at the time of application to form a self-emulsifying cream. The aqueous hydrogel phase provides the proton source that initiates nitric oxide release from the active ointment phase.



Targeting the NLRP3 Inflammasome



- Nucleotide-binding domain (NOD)-like receptor protein 3, or NLRP3, drives Th2 differentiation and activation and contributes to the atopic dermatitis pathogenesis[2,3]
- Nitric oxide disrupts NLRP3 function via S-nitrosation[4]

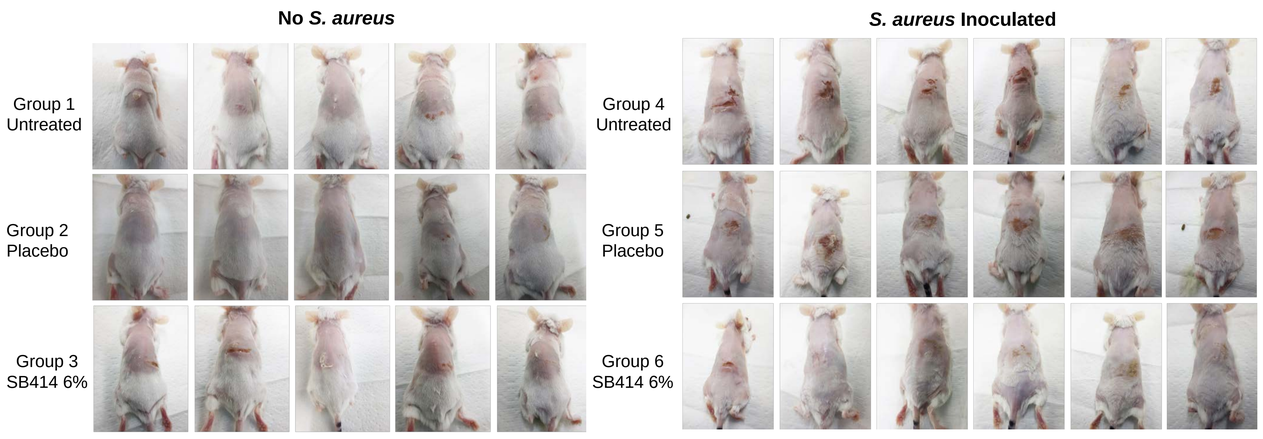
Effects of SB414 Cream on *S. aureus* and Tissue Cytokines in an Atopic Dermatitis Mouse Model[5]

A filaggrin-defect atopic dermatitis mouse model (Flgft/ft mice) was used to assess the reduction in St*aphylococcus aureus* (SA) colonization and key pro-inflammatory cytokines following topical intervention with SB414 6% Cream

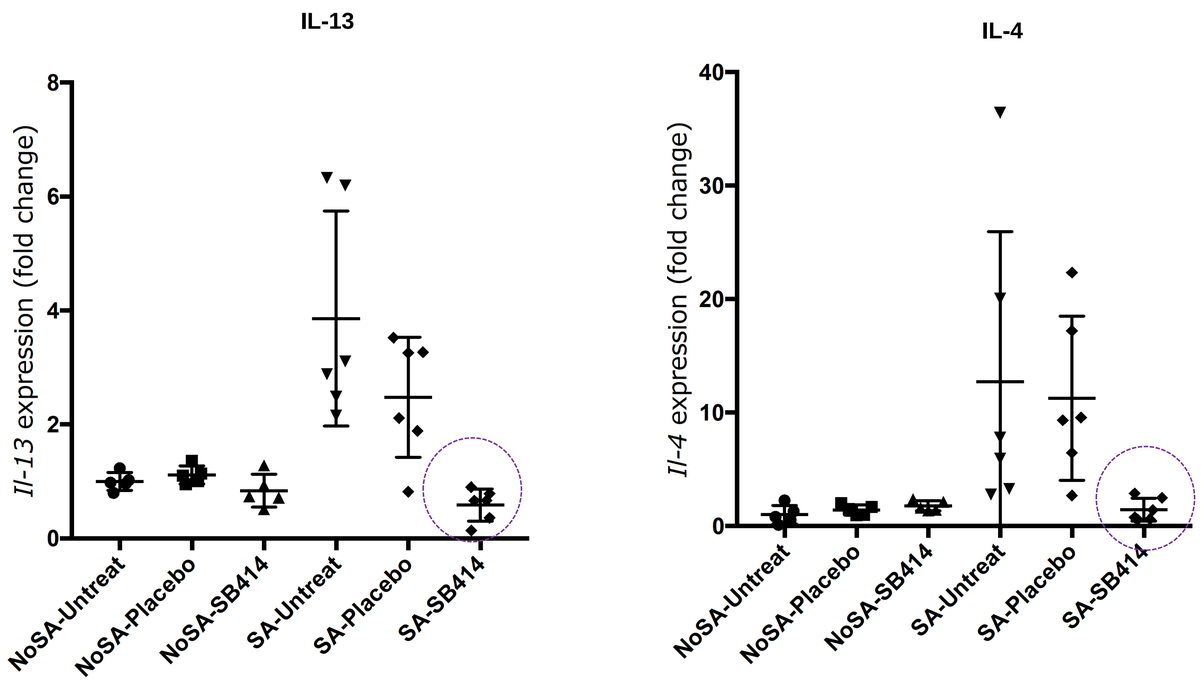
Model Description

- 33 Flgft/ft mice were sensitized by OVA-patch for 1 week on + 2 weeks off x 2 cycles
- Mouse back was shaved and tape-stripped 2 days after 2nd OVA patch sensitization, and inoculated with 106 CFU *S. aureus* (or control) and covered with tegaderm for 24 hours
- SB414 6% Cream was topically applied 0 hrs and 8 hrs after removing tegaderm
- Skin swab and skin biopsies were obtained @ 24 hrs after removing tegaderm to evaluate *S. aureus* CFUs and tissue cytokines

48 Hours Post Inoculation



gDNA for Cytokine qPCR Analysis

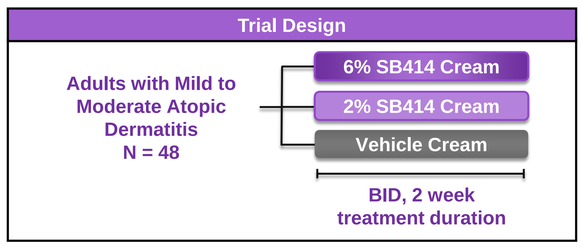


References

1. Bruchard, M. *et al.* 2015. *Nat. Immunol.* 16(8):859-870. 2. Ting, J. *et al.* 2015 *Nat. Immunol.* 16(8):794-796.
3. Mishra B et al. *Nat. Immunol.* 2013; 14(1):52-60. 4. Mishra B et al. *Nat. Immunol.* 2013; 14(1):52-60.
5. Hollenbach, S. Effects of SB414 Cream on S. aureus and Tissue Cytokines in an Atopic Dermatitis Mouse Model. Presented at 2018 IID.

Phase 1b Clinical Results

- Efficacy as measured by EASI (Eczema Area and Severity Index) score
- Efficacy as measured by Itch NRS (Numeric Rating Scale) – reported by patient on an 11-point numerical rating scale
- Safety and cutaneous tolerability (investigator and patient assessment)
- Systemic exposure via PK assessments of NVN1000 on Day 1 and Day 14



Demographics

	Vehicle (N = 14)	SB414 2% (N = 17)	SB414 6% (N = 17)	Overall (N = 48)
EASI Score at Baseline				
Mean (SD)	8.2 (5.2)	4.7 (2.0)	7.2 (3.3)	6.7 (3.8)
Median	8.1	4.4	6.2	5.9
Min, Max	2, 19	2, 8	4, 14	2, 19
Total TLSS Score at Baseline				
Mean (SD)	7.3 (3.0)	5.9 (1.1)	6.5 (1.4)	6.5 (2.0)
Median	6.0	6.0	6.0	6.0
Min, Max	5, 15	5, 8	5, 10	5, 15
Itch NRS at Baseline				
Mean (SD)	6.3 (1.7)	6.9 (2.2)	6.4 (2.1)	6.6 (2.0)
Median	7.0	8.0	7.0	7.0
Min, Max	3, 9	0, 9	3, 10	0, 10

Disposition

	Vehicle	SB414 2%	SB414 6%	Overall
# of Patients in ITT Population, n (%)	14 (100.0)	17 (100.0)	17 (100.0)	48 (100.0)
# Patients Completing Trial, n (%)	12 (85.7)	16 (94.1)	15 (88.2)	43 (89.6)
# Patients Discontinued, n (%)	2 (14.3)	1 (5.9)	2 (11.8)	5 (10.4)
Reason for Discontinuation, n (%)				
Adverse Event(s)	1 (7.1)	0	2 (11.8)	3 (6.3)
Lost to Follow-Up	1 (7.1)	0	0	1 (2.1)
Other	0	1 (5.9)	0	1 (2.1)

EASI Change

	Vehicle	SB414 2%	SB414 6%
EASI Score at Baseline			
n	14	17	17
Mean (SD)	8.2 (5.2)	4.7 (2.0)	7.2 (3.3)
Median	8.1	4.4	6.2
Change from Baseline in EASI Score			
n	13	17	17
Mean (SD)	-1.02 (2.13)	-1.21 (1.35)	-1.79 (3.21)
Median	-1.20	-1.20	-1.60
Percent Change from Baseline in EASI Score			
n	13	17	17
Mean (SD)	-21.41 (29.01)	-23.22 (29.14)	-21.63 (51.80)
Median	-15.79	-28.57	-25.81
Responder Analysis			
EASI50	21 (3/14)	18 (3/17)	24 (4/17)
EASI75	0	0	12 (2/17)

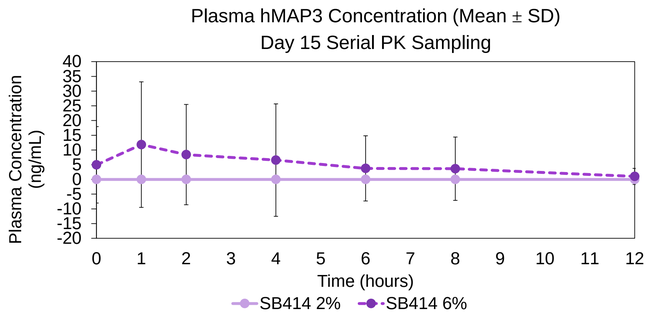
Itch Reduction

	Vehicle	SB414 2%	SB414 6%
Baseline Total Score			
n	14	17	17
Mean (SD)	6.3 (1.7)	6.9 (2.2)	6.4 (2.1)
Median	7.0	8.0	7.0
Min, Max	3, 9	0, 9	3, 10
Change from Baseline			
n	13	17	17
Mean (SD)	-2.31 (2.78)	-3.47 (2.43)	-3.12 (2.78)
Median	-2.00	-4.00	-3.00
Itch Reduction (NRS*)			
Itch Reduction >=3	6 (43%)	12 (71%)	10 (59%)
Itch Reduction >=4	4 (29%)	10 (59%)	7 (41%)

Adverse Events

	Vehicle (N = 14)	SB414 2% (N = 17)	SB414 6% (N = 17)	Overall (N = 48)
Treatment-Emergent Adverse Events (TEAEs)				
Number of Patients, n (%)	3 (21.4)	1 (5.9)	2 (11.8)	6 (12.5)
Treatment-Related AEs				
Number of Patients, n (%)	2 (14.3)	0	2 (11.8)	4 (8.3)
General disorders and administration site conditions	2 (14.3)	0	2 (11.8)	4 (8.3)
Application site edema	0	0	1 (5.9)	1 (2.1)
Application site pain	1 (7.1)	0	1 (5.9)	2 (4.2)
Application site pruritus	1 (7.1)	0	1 (5.9)	2 (4.2)
Serious AEs (All)				
Number of Patients, n (%)	0	0	0	0
AEs Leading to Study Medication Discontinuation				
Number of Patients, n (%)	1 (7.1)	0	2 (11.8)	3 (6.3)

Systemic Exposure



	N	SB414 6%
C_{max} (ng/mL)	5	34.46 (26.58)
T_{max} (h)	5	Median: 1h
$AUC_{0\text{-}tau}$ (ng*h/mL)	3	265.98 (243.26)

hMAP3 (hydrolyzed N-methyl-aminopropyltrimethoxysilane) is a component of the nitric oxide-releasing active pharmaceutical ingredient, NVN1000 and a marker for systemic exposure. It is not present in vehicle and, therefore, was not tested.

Conclusions

In two in vivo models that assess critical components of atopic dermatitis disease pathology:

- SB414 displayed potent anti-staphylococcal activity in partial-thickness skin wounds infected with a methicillin- resistant *S. aureus* strain isolated from an AD patient
- SB414 demonstrated the ability to reduce key Th2 cytokines like IL-4 and IL-13 in an atopic dermatitis mouse model

In a 2-week, multi-center, randomized, vehicle-controlled trial:

- SB414 demonstrated trends suggestive of efficacy
- SB414 2% displayed an improvement on the pruritus (itch) numeric rating scale (NRS) compared to vehicle
- Both SB414 2% and 6% were well tolerated, but the lower dose had a more favorable local tolerability profile
- SB414 2% did not show quantifiable systemic exposure, while SB414 6% demonstrated quantifiable exposure in some patients