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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*Employee and shareholder of Novan

Nitricil Technology

Stable storage

- Drugable nitric oxide with shelf-life stability

Therapeutic quantities

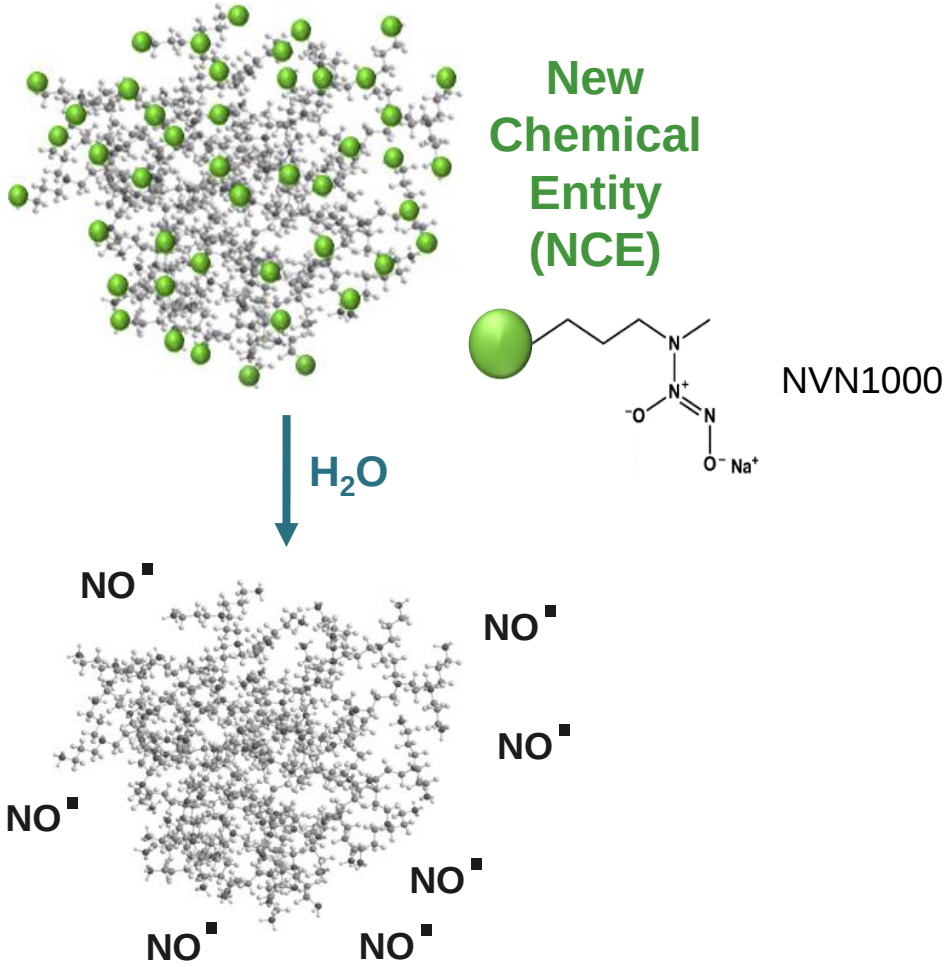
- High loading capacity previously unachievable

“Tunability”

- pH-controlled hydrolysis that releases nitric oxide

Engineered macromolecule

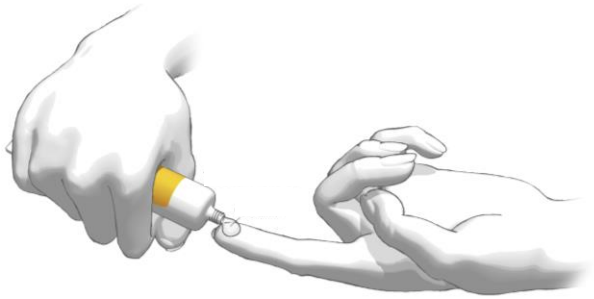
- Targets nitric oxide delivery to the skin
- Minimizes systemic exposure
- Reduces backbone toxicity



SB414: A Nitric Oxide-Releasing Cream for the Treatment of Inflammatory Skin Diseases

Self-emulsifying cream formulation upon admixture

NVN1000 Ointment



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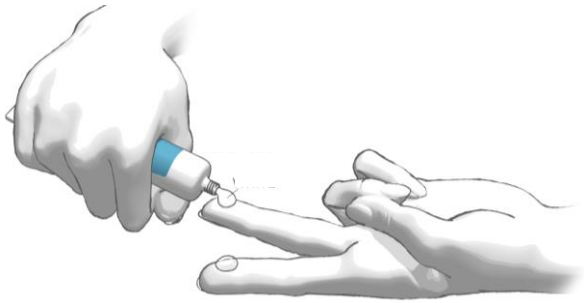
pH Buffered Hydrogel



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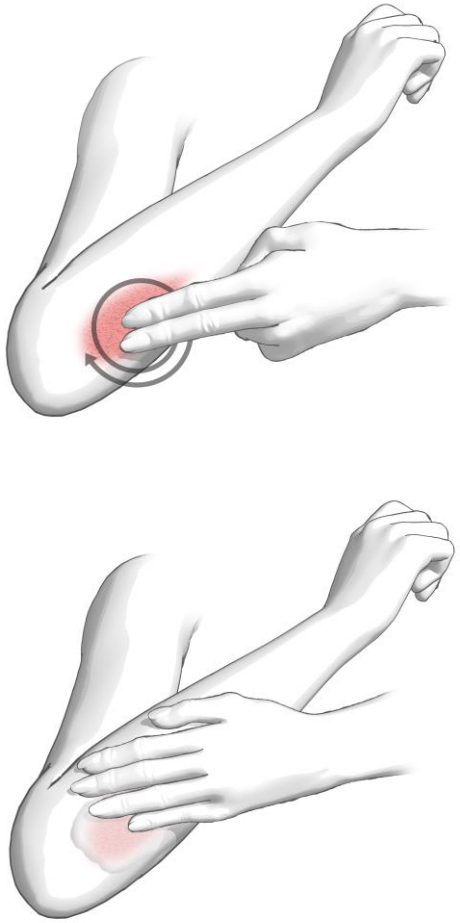
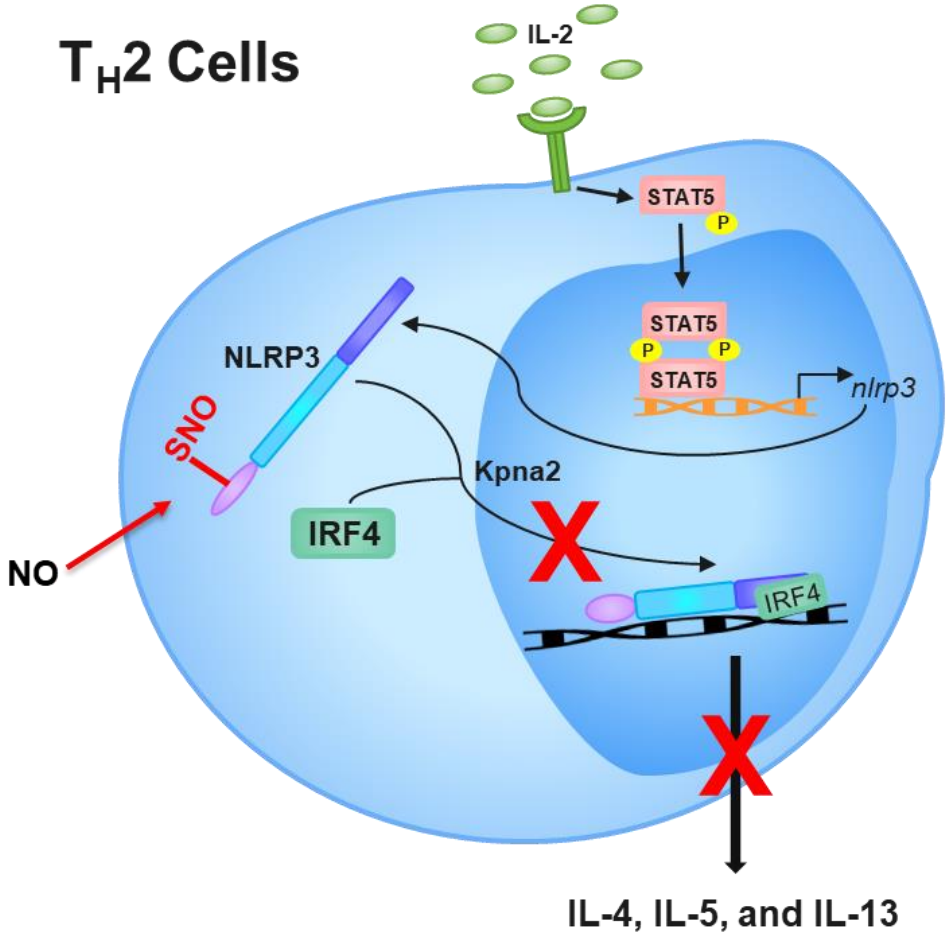


Targeting the NLRP3 Inflammasome in Inflammatory Skin Diseases

Nitric oxide is a natural inhibitor of NLRP3 inflammasome activation
– *Nature Reviews Drug Discovery*[1]



- **NLRP3 drives Th2 differentiation, activation, and contributes to the atopic dermatitis pathogenesis[2,3]**
- **Nitric oxide disrupts NLRP3 function via S-nitrosylation[4]**

NLRP3: Nucleotide-Binding Domain (NOD)-Like Receptor Protein 3

1. Nat Rev Drug Discov. 2018 Aug;17(8):588-606. doi: 10.1038/nrd.2018.97. Epub 2018 Jul 20. 2. Bruchard, M. *et al.* 2015. *Nat. Immunol.* 16(8):859-870. 3. Ting, J. *et al.* 2015 *Nat. Immunol.* 16(8):794-796.
4. Mishra B et al. *Nat. Immunol.* 2013; 14(1):52-60.

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

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*

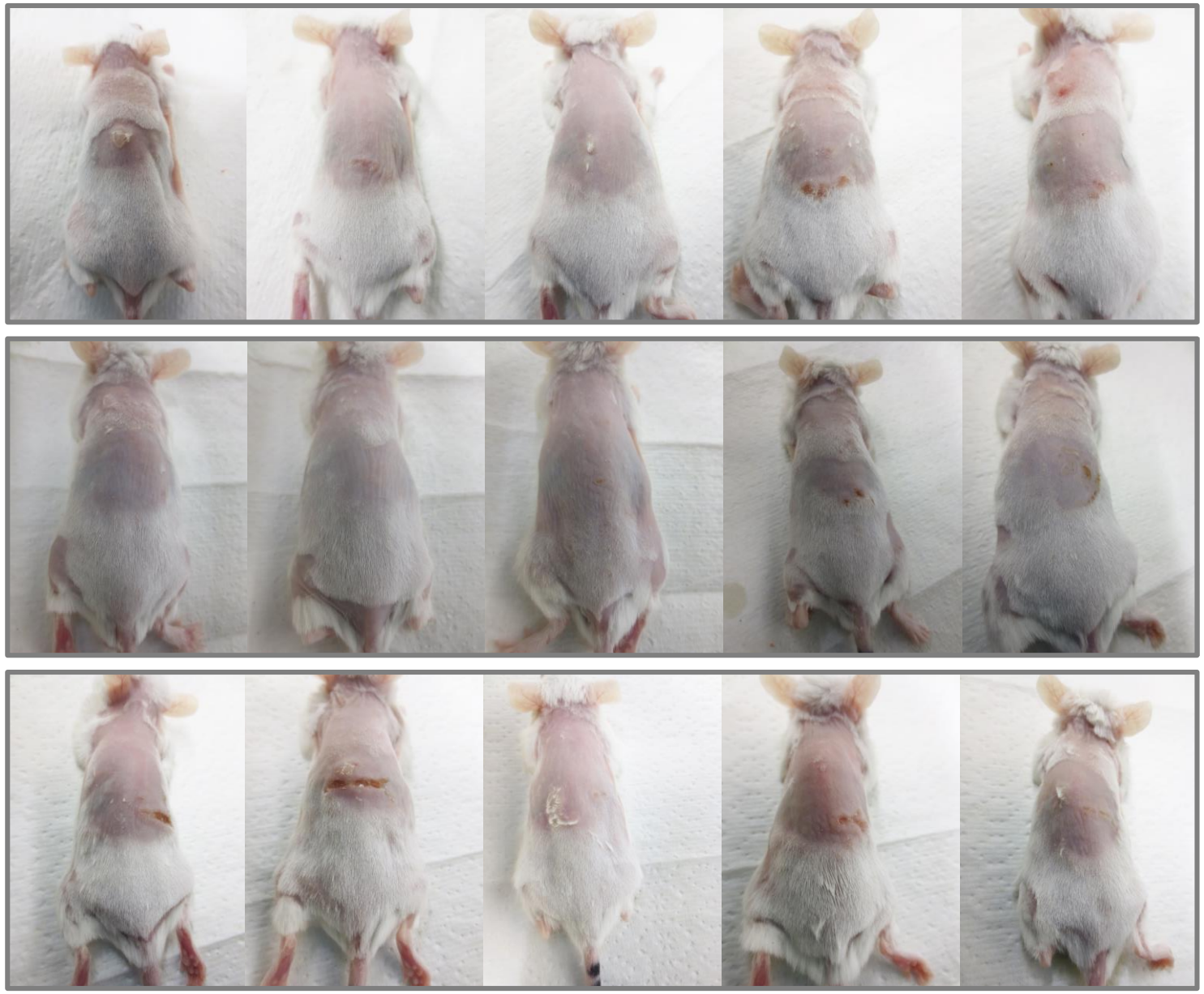
Model Description

- 33 FLGft/ft mice were sensitized by OVA-patch for 1 week + 2 weeks off x 2 cycles
- Mouse back was shaved and tape-stripped 2 days after 2nd OVA patch sensitization, and inoculated with 10^6 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

*Research collaboration with Richard Gallo, MD, PhD – UC San Diego School of Medicine

Hollenbach, S. Effects of SB414 Cream on S. aureus and Tissue Cytokines in an Atopic Dermatitis Mouse Model. Presented at 2018 IID.

Groups 1, 2 and 3 – 48 Hours with No *S. Aureus* Inoculation



Group 1: No *S. aureus* + Untreated

Group 2: No *S. aureus* + Placebo

Group 3: No *S. aureus* + SB414 6%

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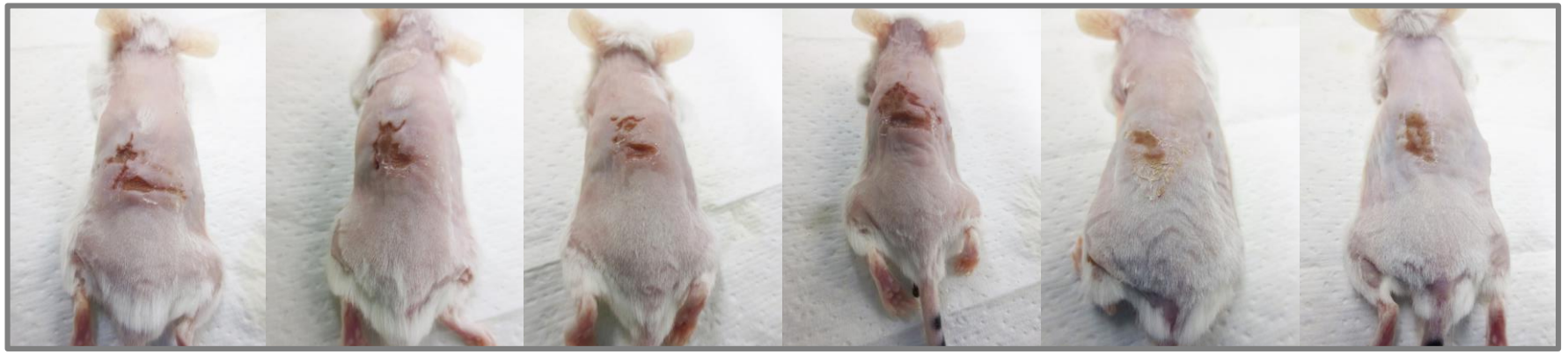
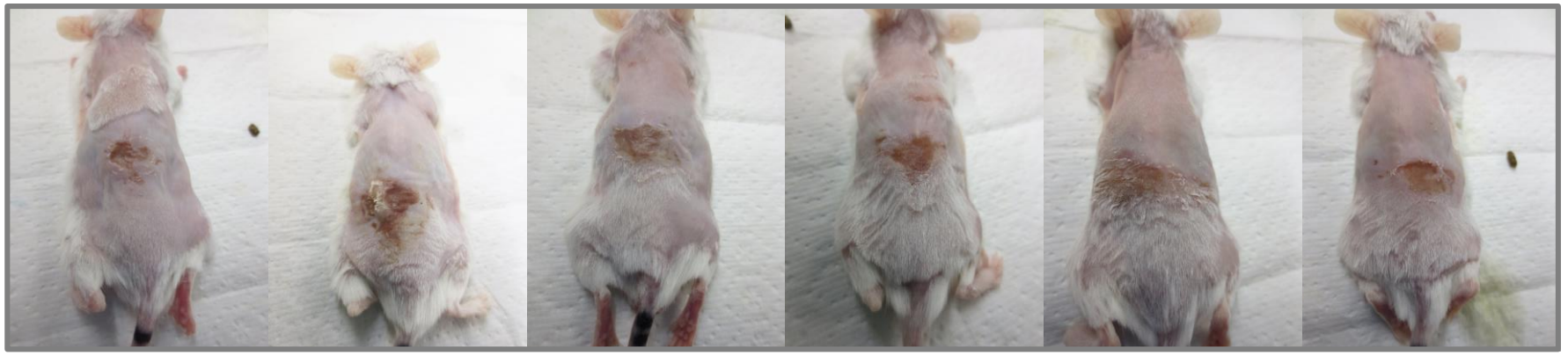
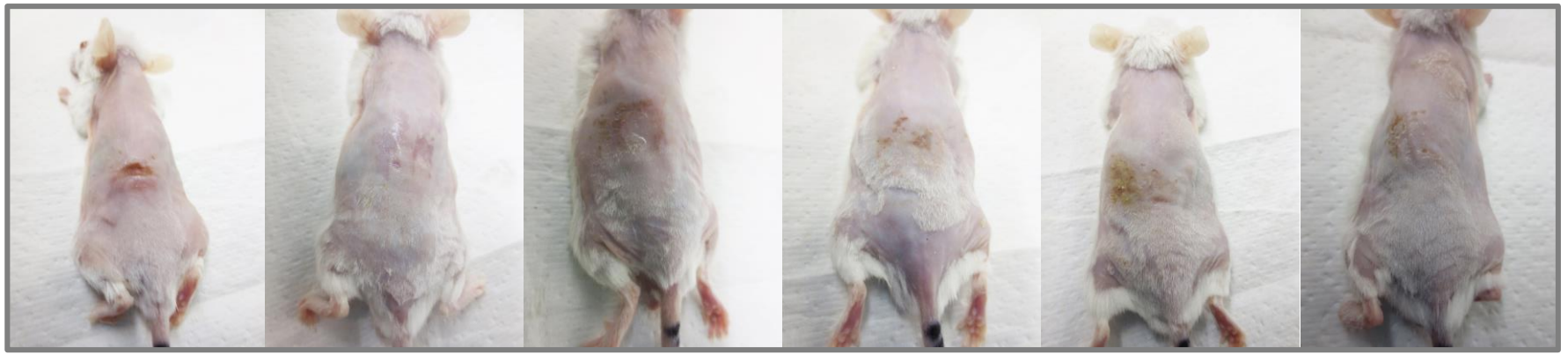
Groups 4, 5 and 6 – 48 Hours Post *S. aureus* Inoculation



Group 4: *S. aureus* + Untreated



Group 5: *S. aureus* + Placebo

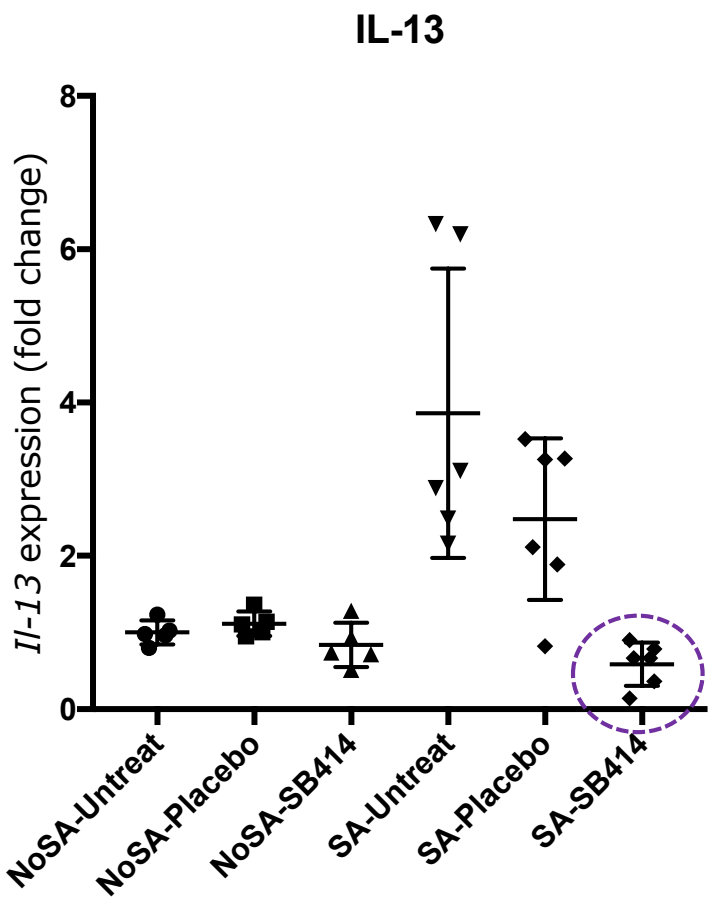


Group 6: *S. aureus* + SB414 6%

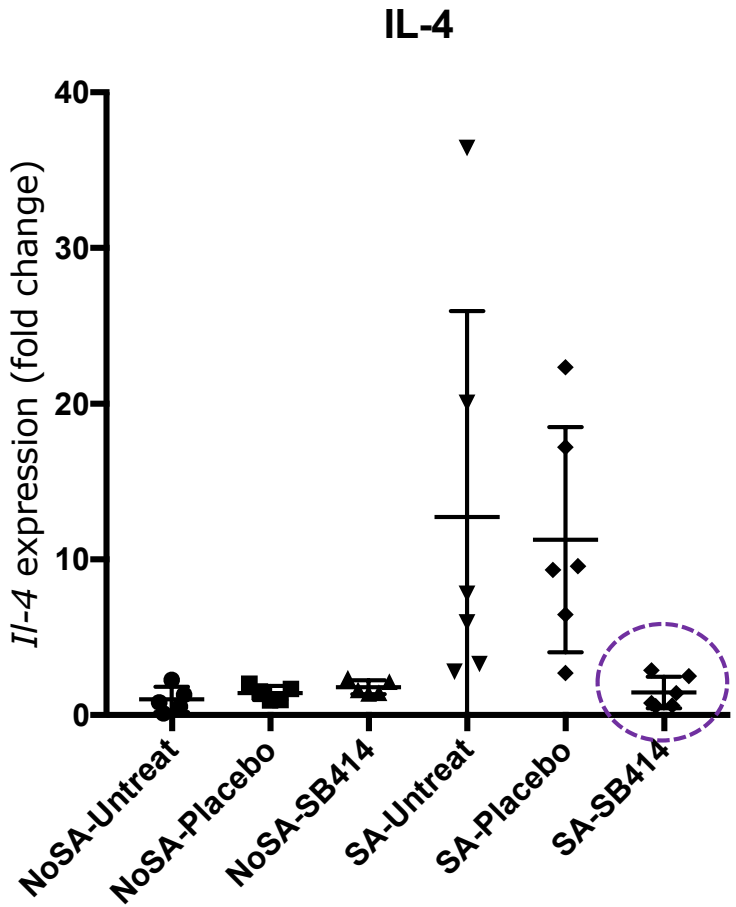
Hollenbach, S. Effects of SB414 Cream on S. aureus and Tissue Cytokines in an Atopic Dermatitis Mouse Model. Presented at 2018 IID.

Reduction of IL-4 and IL-13 in AD Mouse Model

IL-13 decreased by 76% compared to Placebo Control



IL-4 decreased by 87% compared to Placebo Control



SA levels in the skin of SB414-treated mice were decreased to $0.5x10^5$ CFUs, representing a >90% reduction over untreated and vehicle treated mice

SB414 reduced key Th2 cytokines, IL-13 and IL-4, and reduced Staphylococcus aureus (SA) burden in vivo[1]

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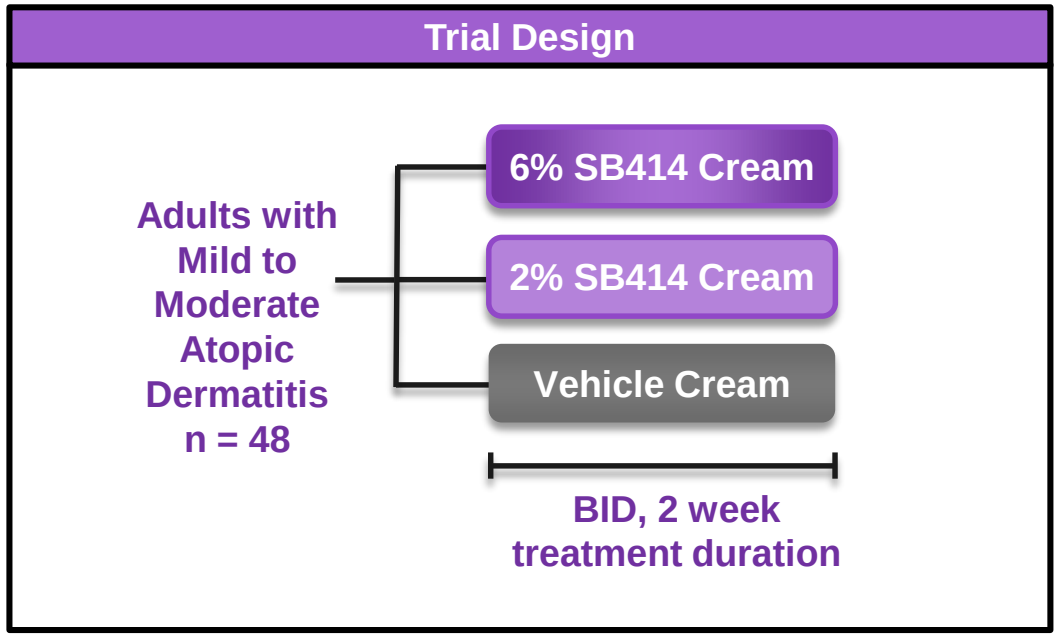
Phase 1b Trial Design for Atopic Dermatitis (AD-101)

Randomized, double-blind, vehicle-controlled Phase 1b trial to assess:

- Efficacy as measured by EASI (Eczema Area and Severity Index) score
- Efficacy as measured by Itch NRS – 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
- IL-4, IL-5, IL-13, and other key inflammatory cytokines



AD101 Demographics

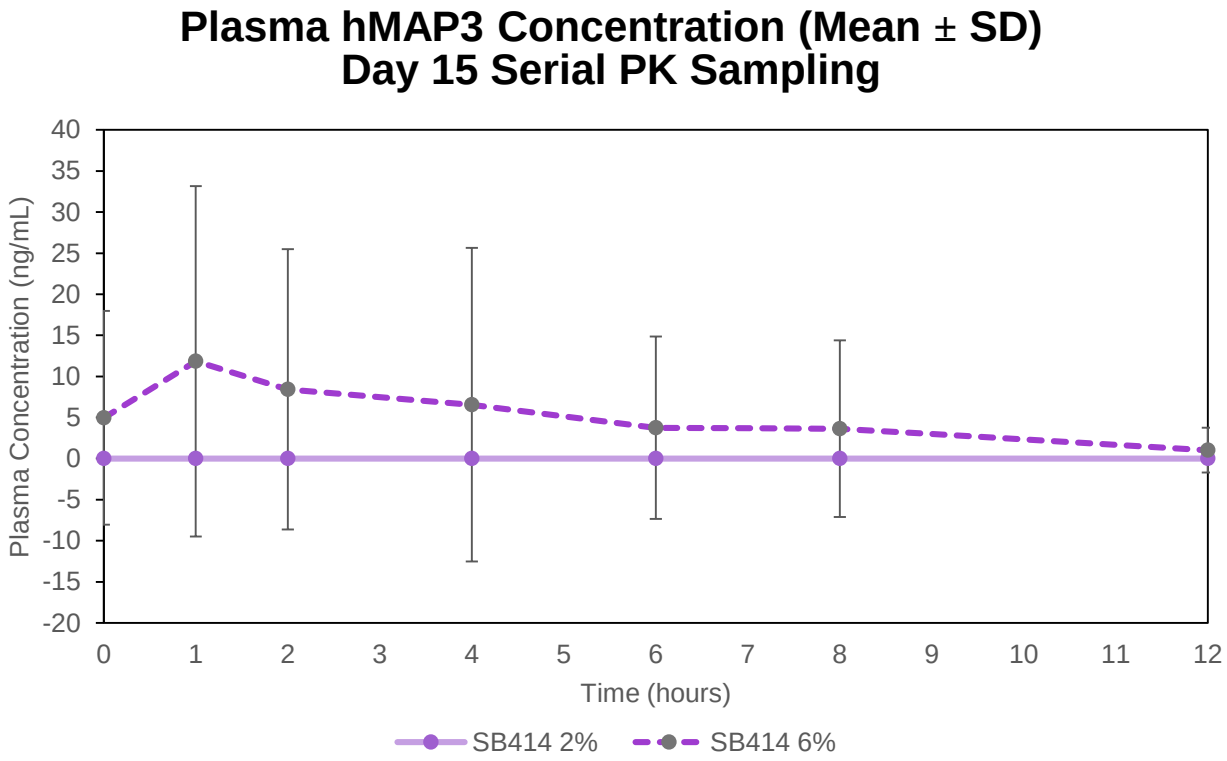
	Vehicle (N=14)	SB414 2% (N=17)	SB414 6% (N=17)	Overall (N=48)
EASI Score at Baseline				
Mean (SD)	8.2 (5.2)	4.7 (2.0)	7.2 (3.3)	6.7 (3.8)
Median	8.1	4.4	6.2	5.9
Minimum, Maximum	2, 19	2, 8	4, 14	2, 19
Total TLSS Score at Baseline				
Mean (SD)	7.3 (3.0)	5.9 (1.1)	6.5 (1.4)	6.5 (2.0)
Median	6.0	6.0	6.0	6.0
Minimum, Maximum	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
Minimum, Maximum	3, 9	0, 9	3, 10	0, 10

AD101 Disposition

	Vehicle	SB414 2%	SB414 6%	Overall
Number of Patients in ITT Population, n (%)	14 (100.0)	17 (100.0)	17 (100.0)	48 (100.0)
Number of Patients Completing the Trial, n (%)	12 (85.7)	16 (94.1)	15 (88.2)	43 (89.6)
Number of 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)

AD101 Systemic Exposure

- Systemic exposure was observed in a subset of patients who were treated with SB414 6%
- Highest observed exposure to date is Cmax of 71.4 ng/mL and AUC 523 ng.h/mL in AD patient (21% BSA)



	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.

AD101 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)

AD101 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
Minimum, Maximum	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%)

*Itch Numeric Rating Scale (NRS): Itching due to AD for the preceding 24 hours was reported by the patient on the Itch NRS, an 11-point scale, ranging from 0 to 10, 10 being the worst possible itching.

AD101 AEs

	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 TEAEs				
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)

SB414 Summary

Nonclinical

- In the mouse model that assess critical components of atopic dermatitis disease pathology:
  - SB414 demonstrated the ability to reduce key Th2 cytokines like IL-4 and IL-13 in an atopic dermatitis mouse model
  - SB414 reduced Staphylococcus aureus >90%

Clinical

- In a 2-week, multi-center, randomized, vehicle-controlled trial:
  - SB414 demonstrated trends suggestive of efficacy
  - SB414 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

Hollenbach, S. Effects of SB414 Cream on S. aureus and Tissue Cytokines in an Atopic Dermatitis Mouse Model. Presented at 2018 IID.
Hollenbach, S. Nitric Oxide-Releasing Topical Therapeutic for Atopic Dermatitis. Presented at 2017 SID.