Assessment of Pharmacokinetics and Safety of Investigational Nitric Oxide-Releasing SB204 Gel in Adolescents With Acne Vulgaris

Diane Thiboutot¹, Andrea Zaenglein², Adelaide Hebert³, Lawrence Eichenfield⁴

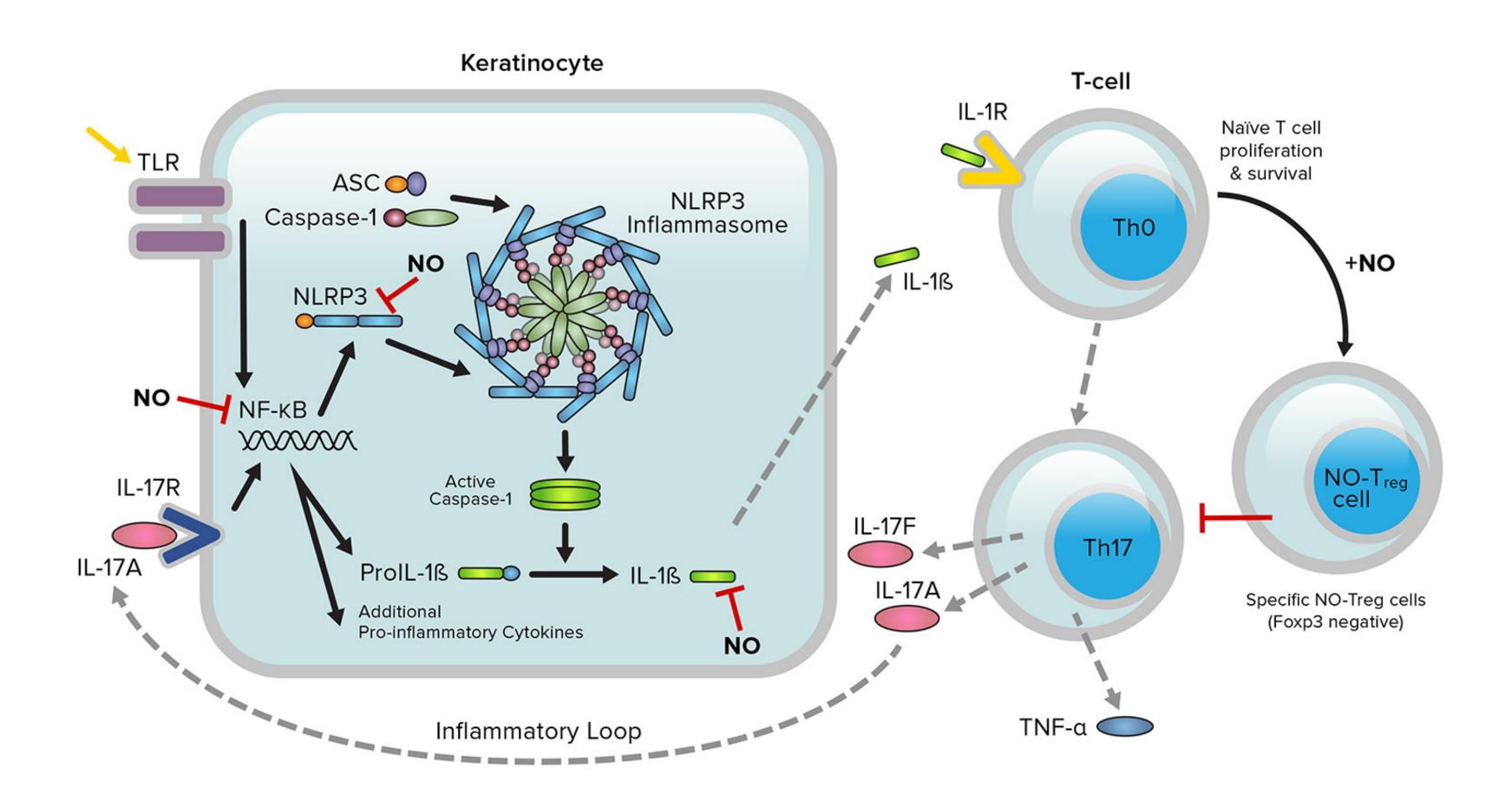
¹Department of Dermatology, Penn State Hershey, PA, ²Department of Dermatology, The University of Texas Medical School, Houston, TX, ⁴Department of Dermatology, University of California, San Diego, CA

Introduction

- SB204, a nitric oxide releasing topical drug candidate, is in development for the treatment of acne vulgaris
- The active ingredient in SB204 is NVN1000, a polysiloxane macromolecule that stores nitric oxide on the polymer backbone
- SB204 has potential immunomodulating and broad-spectrum antimicrobial activity
- Three studies with SB204 4% applied **once daily** in adolescents assessed:
- Systemic exposure (NI-AC103) to
- hydrolyzed N-methyl-aminopropyltrimethoxysilane (hMAP3), a component of NVN1000
- Nitrate, a marker for nitric oxide
- Safety (NI-AC103, NI-AC301 and NI-AC302)
- Efficacy (NI-AC301 and NI-AC302)

Immunomodulatory and Antimicrobial Activity of — Nitric Oxide in Acne

• Nitric oxide inhibits the NLRP3 inflammasome, decreasing the downstream release of IL-1β and IL-17, as well as, kills P. acnes



Mishra B et al. Nitric oxide controls the immunopathology of tuberculosis by inhibiting NLRP3 inflammasome—dependent processing of IL-1β. Nature Immunology. 2013;14:52-60. Niedbala W et al. Regulation of Type 17 Helper T-Cell Function by Nitric Oxide During Inflammation Proc Natl Acad Sci USA. 2011;108(22):9220-9225. Niedbala W et al. Nitric Oxide-Induced Regulatory T Cells Inhibit Th17 but Not Th1 Cell Differentiation and Function. J Immunol. 2013;191(1):164-170. Qin M et al. Nitric Oxide Releasing Nanoparticles Prevent Propionibacterium Acnes Induced Inflammation by Both Clearing the Organism and Inhibiting Microbial Stimulation of the Innate Immune Response. J Invest Dermatol.

NI-AC301/302 STUDY OVERVIEW

- Studies in 2600 subjects with moderate to severe acne. Data presented is from subset of 905 adolescents, ages ≥9 - <17
- Subjects were randomized 1:1 ratio of SB204 4% or vehicle



- SB204 4% gel (900mgs) or vehicle (900mgs) were applied once daily to the entire face
- Primary efficacy endpoints assessed:
- counts from baseline to week 12 Success on Investigator's Global Assessment (IGA) at week 12 (IGA success was defined as a score of clear (0) or almost

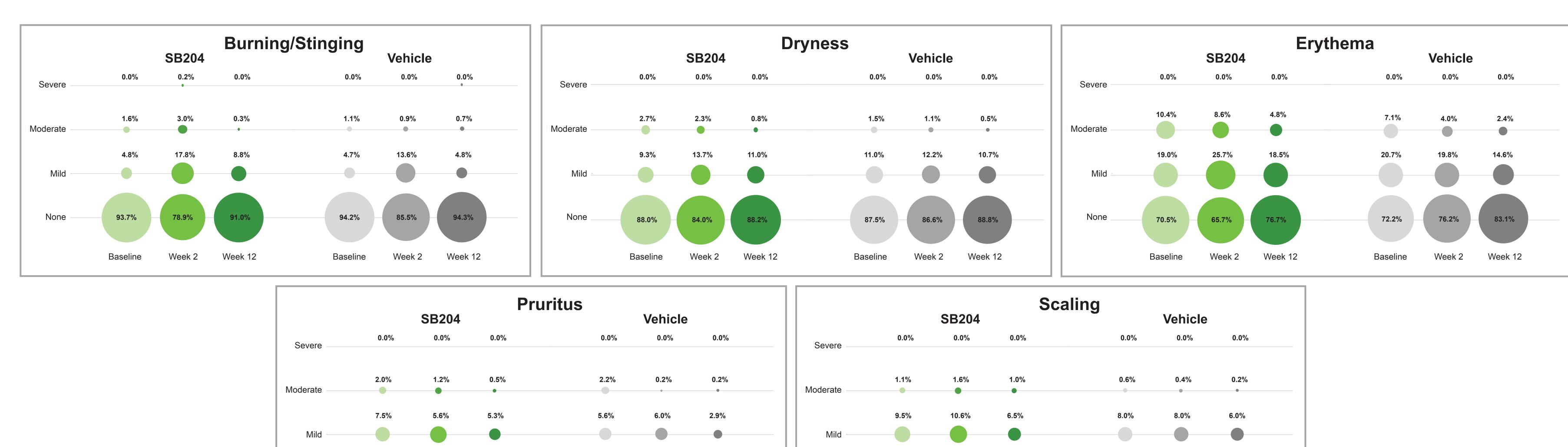
clear (1) and ≥2 grades less than baseline)

Absolute change in inflammatory and noninflammatory lesion

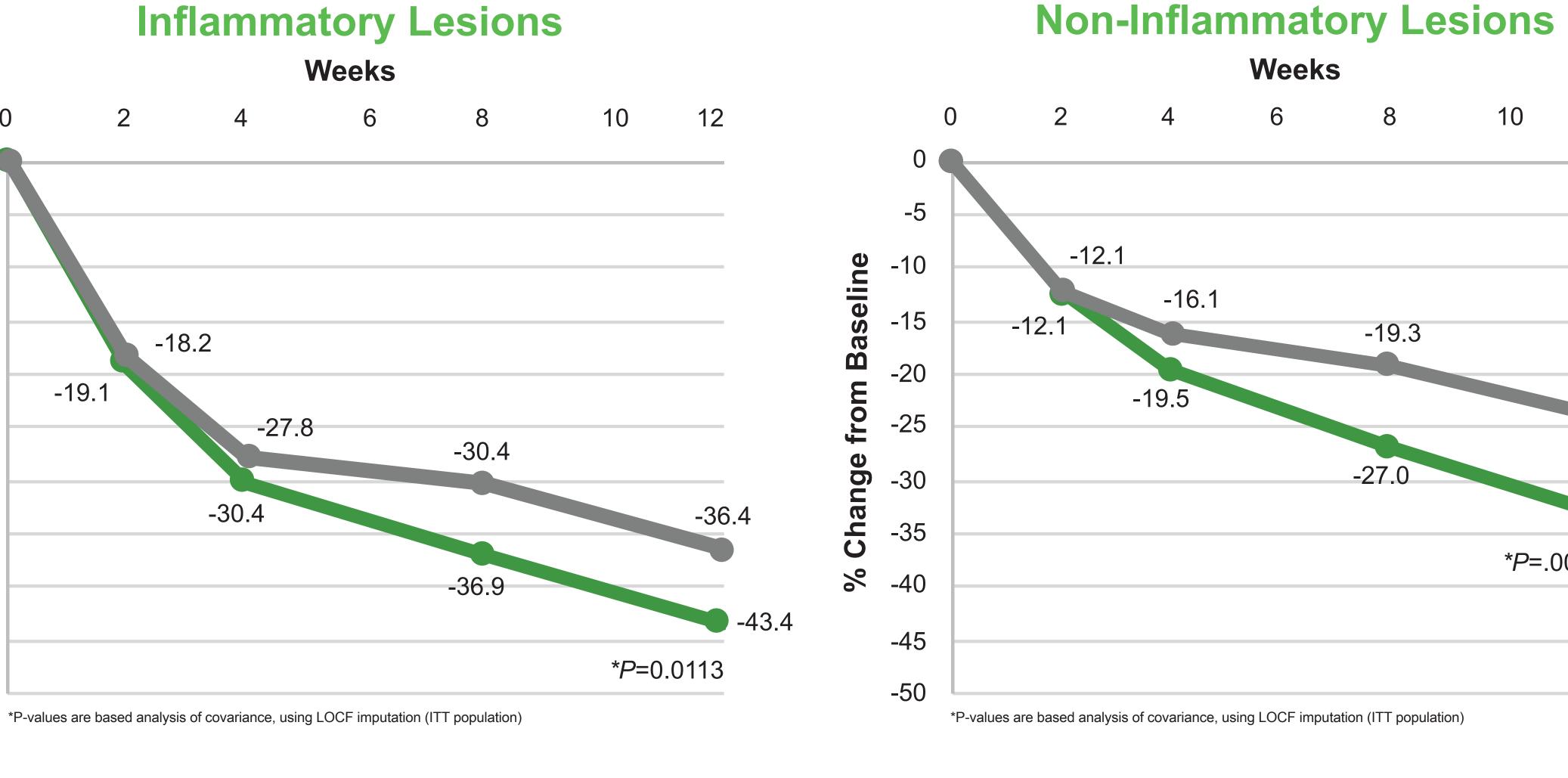
- NI-AC301/302 Demographics -

NI-AC301 and NI-AC302							
	SB204 4% (n, pooled = 439)	Vehicle once daily (n, pooled = 466)					
Gender, n							
Male	228 (52%)	255 (55%)					
Female	211 (48%)	211 (45%)					
Age, mean	14	14					
Baseline, mean (SD)							
Inflammatory Lesion	28 (5.7)	28 (5.9)					
Non-Inflammatory Lesion Count	42 (13)	42 (13)					
Total Lesions	70 (15)	70 (16)					
Baseline IGA Scores							
"Moderate" or a score of 3	377 (86%)	401 (86%)					
"Severe" or a score of 4	62 (14%)	65 (14%)					
Disposition, n							
Completed	397 (90%)	421 (90%)					
Discontinued	42 (10%)	45 (10%)					

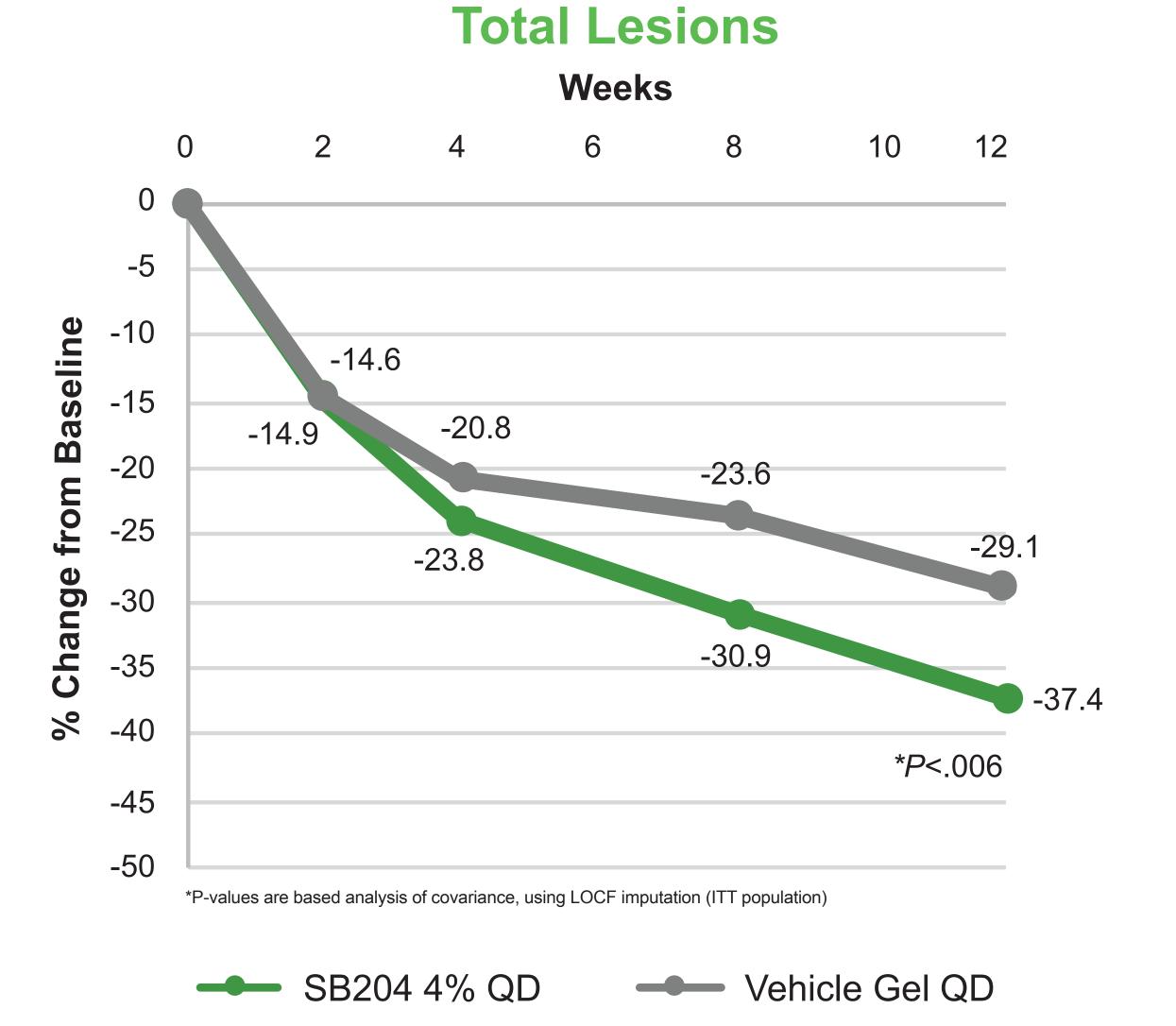
NI-AC301/302 Results: Tolerability







*P-values are based analysis of covariance, using LOCF imputation (ITT population) Vehicle Gel QD Vehicle Gel QD **──** SB204 4% QD



NI-AC301/302 Treatment Emergent Adverse Events (TEAEs)

NI-AC301/302												
	Number of AEs	Dermatitis	Dryness	Erythema	Exfoliation	Pain	Pruritus	Rash	Reaction	Swelling	Malaise	Pyrexia
SB204 4% (N=439) n incidence	38	1 (0.23%)	3 (0.68%)	2 (0.46%)	1 (0.23%)	7 (1.59%)	3 (0.68%)	2 (0.46%)	1 (0.23%)	1 (0.23%)	1 (0.23%)	1 (0.23%)

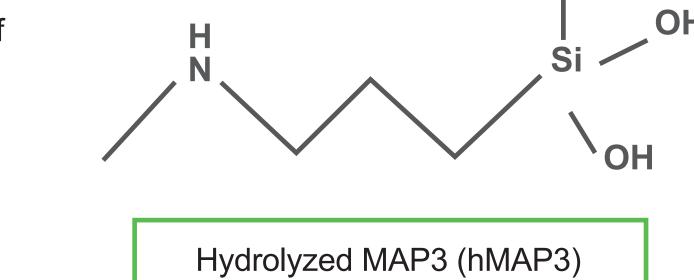
-NI-AC103 Study-

NI-AC103 STUDY OVERVIEW

NI-AC103 (N=18)				
Study Design		Single-center, open-label pharmacokinetic study		
Age		Age ≥9 - <17 yrs.		
Dose/Dosing Schedule		Topical SB204 4% was applied once daily in the mornings for 21 days		
PK Collection		PK profiling done on days 1 and 21 from time 0 to 24 hours post dose		
Sex, N	Male	11 (61%)		
	Female	7 (39%)		
Completed, N		18 (100%)		
Discontinued, N		0		

The following systemic exposure were assessed:

- hydrolyzed N-methyl-aminopropyltrimethoxysilane (hMAP3), a component of the NVN1000 parent compound backbone. The lower limit of
- quantitation (LLOQ) for hMAP3 was 5.0 ng/mL. Nitrate, a marker for systemic nitric oxide exposure. The LLOQ for nitrate
- was 300 ng/ml. • Treatment Emergent Adverse Events (TEAEs) were recorded, methemoglobin



was monitored and electrocardiogram (ECG) readings were taken

Emergent Adverse Events

 In all subjects, no clinically significant changes in laboratory assessments, including methemoglobin values, ECG results and physical examinations, were observed

NI-AC103			
	SB204 4% (N=18) n incidence		
Number of subjects reporting at least one AE	1 (5.6%)		
Number of AEs	2		
Skin and subcutaneous system disorders	1 (5.6%)		
Injury, poisoning, and procedural complications	1 (5.6%)		

— NI-AC103 Treatment — NI-AC103 Results —

In the open label pharmacokinetic study (NI-AC103) in adolescents (age ≥9 - <17 yrs.; n=18):

- Plasma hMAP3 levels were below LLOQ (5.0 ng/mL) after single application SB204 4% at all timepoints
- There were no noticeable differences in nitrate PK parameters in subjects at baseline and following treatment with SB204 4%

Conclusions

- Following single and repeat application of topical SB204 4% in adolescent subjects with moderate to severe acne in NI-AC103:
- There was no detectable hMAP3 in any subject, at all timepoints, and for all treatments studies, including under maximal use
- There were no statistically significant differences in nitrate PK parameters at baseline and following treatment with SB204
- SB204 4% once daily showed a statistically significant reduction in inflammatory, non-inflammatory and total lesions while maintaining a good safety and tolerability profile in adolescent subjects in NI-AC301 and NI-AC302
- All doses of SB204 administered in the studies were well tolerated and the adverse event profile was similar in active and vehicle treated subjects