Evaluation of the Efficacy, Safety and Tolerability of SB204 4% Once-Daily in Subjects with Moderate to Severe Acne Vulgaris Treated Topically for Up to 52 Weeks

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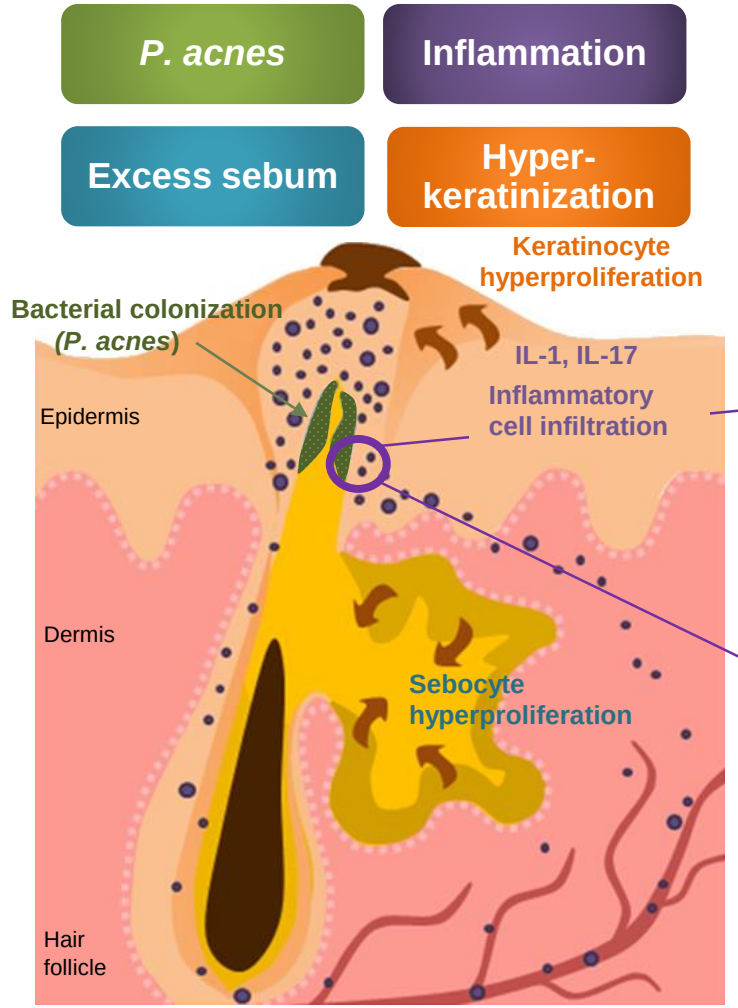
2018 American Academy of Dermatology (AAD) Annual Meeting, San Diego, CA
February 16 – 20, 2018

Disclosures

Allergan, Inc – I (Grants/Research Funding); Amgen – I (Grants/Research Funding), SP(H); Anacor Pharmaceuticals, Inc – A(H); Astellas Pharma US, Inc. – I (Grants/Research Funding); Bayer – SP(H); Cassiopia - I (Grants/Research Funding); Celgene Corporation - (Grants/Research Funding); Chugai Pharma - (Grants/Research Funding); Cutanea Life Sciences - (Grants/Research Funding); Department of DFENCE – O (Grants/Research Funding); Dermavant Sciences – I (Grants/Research Funding); Dermira – A(H), I (Grants/Research Funding); Encore Dermatology, Inc – A(H); Galderma Laboratories, LP – A(H), SP(H); GlaxoSmithKline – A(H), Data Safety Monitoring Board (H), I (Grants/Research Funding); Healthpoint – I (Grants/Research Funding); Intendis, Inc. – SP(H); Mayne Pharma Group – I (Grants/Research Funding); Medimetriks Pharmaceuticals, Inc. – I (Grants/Research Funding); Menarini Group – SP(H); Menlo Therapeutics – A(H); Merz Pharmaceuticals, LLC – I (Grants/Research Funding); NIH - (Grants/Research Funding); Novan – I (H); Novartis Pharmaceuticals Corp. – O(H); Onset Therapeutics – SP(H); Ortho Dermatologics – A(H); Pfizer Inc. – Speaker/Fucalty Education (H); Pharmaderm – A(H); PPD Inc – I (Grants/Research Funding); Prim-Med – SP(H); Promius Pharma, LLC – A(H); Promius Pharmaceuticals – A(H), I (Grants/Research Funding); Regeneron – Data Safety Monitoring Board (H); Roivant Sciences – A(H); Shionogi USA – A(IP); Sienna Biopharmaceuticals - (Grants/Research Funding); Sinclair Pharma – SP(H); Stiefel, a GSK company – A(H); TopMD – I (Grants/Research Funding); ; Valeant Pharmaceuticals International – A(H), SP(H); Vanda Pharmaceuticals Inc. – I (Grants/Research Funding);

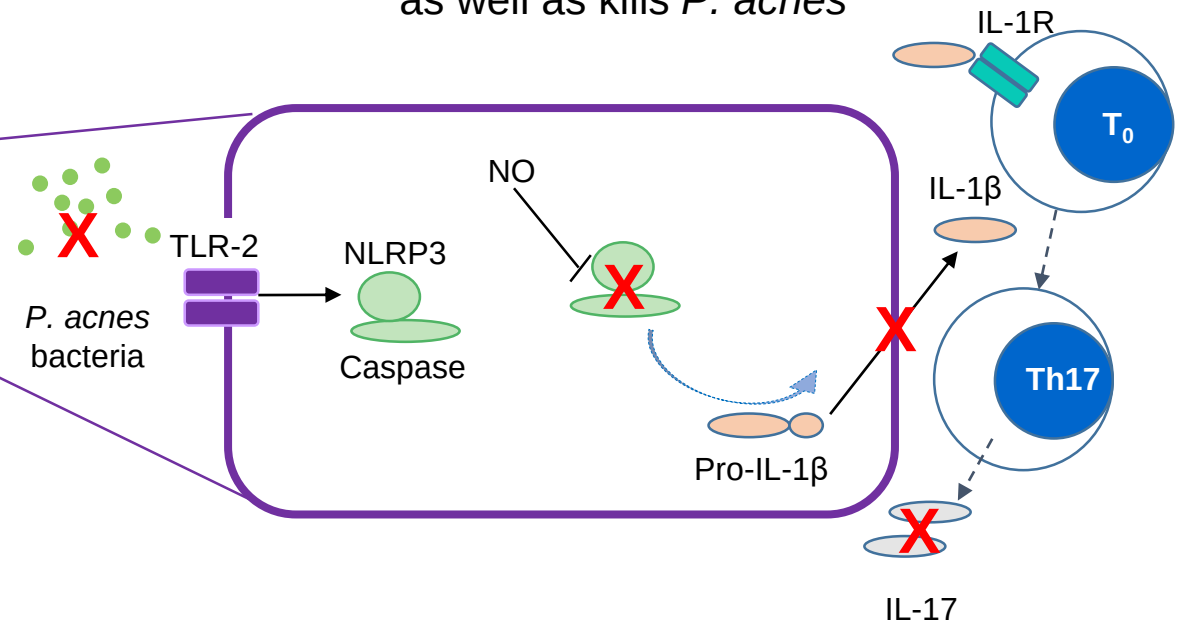
Nitric Oxide and Acne

Pathogenic Factors in Acne



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*



Hanna-Leena Kelhälä et al. IL-17/Th17 Pathway is Activated in Acne Lesions. *PLoS One*. 2014;9(8): e105238.
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.* 2015;135(11):2723-2731.

SB204 Study Objectives

- **SB204 is a nitric oxide-releasing topical drug candidate in development for the treatment of acne vulgaris**

- SB204 4% gel has been evaluated in two replicate, multi-center, randomized, double-blinded, vehicle-controlled, parallel group trials with >2600 patients with moderate-to-severe acne (NI-AC301 and NI-AC302)

- The following three co-primary endpoints were assessed in the two studies:
  - the absolute change in inflammatory lesions
  - the absolute change in non-inflammatory lesions
  - the proportion of patients with IGA success defined as IGA=0 or 1 and at least a two grade change

- Cutaneous tolerability and safety profile has been assessed in >3,200 patients dosed to date

SB204 Phase 3 Patient Disposition and Study Design

NI-AC301 Study

Randomized
N = 1307

Excluded
N = 1
Study drug not dispensed

ITT Population
N = 1306

SB204 4%
N = 652

Vehicle
N = 654

Inclusion Criteria
Ages 9 and up
20 - 40 inflammatory lesions on the face
25 - 70 non-inflammatory lesions on the face
IGA “moderate = 3” or “severe = 4”

3 Co-Primary Endpoints at Week 12/ET
Absolute change in inflammatory lesion counts
Absolute change in non-inflammatory lesion counts
Proportion of IGA Success (“clear = 0” or “almost clear = 1” AND ≥ two grade change)

Treatment Regimen
SB204 4%: Vehicle = 1:1
Once daily application (QD)
12 week treatment

NI-AC302 Study

Randomized
N = 1330

Excluded
N = 3
Study drug not dispensed

ITT Population
N = 1327

SB204 4%
N = 663

Vehicle
N = 664

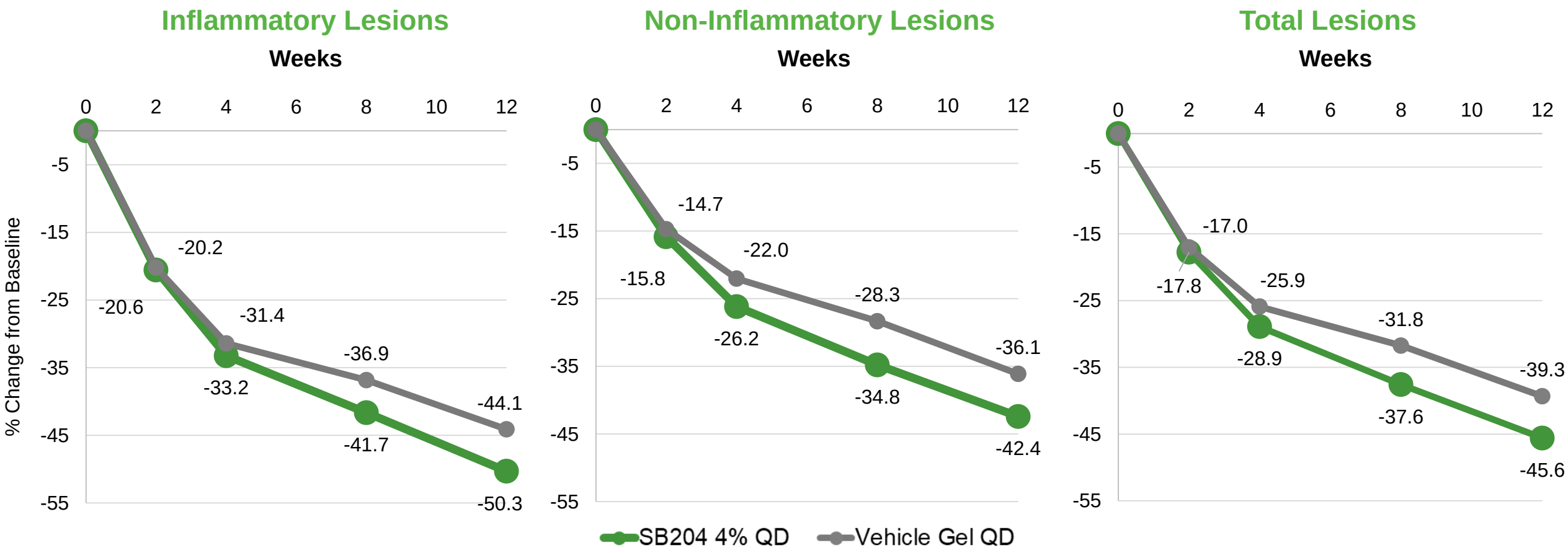
Pooled N = 2637

	Pooled SB204	Vehicle
Discontinuation	**164 (12.5%)**	**152 (11.5%)**
Adverse event	22 (1.7%)	4 (0.3%)
Lack of efficacy	0 (0.0%)	2 (0.2%)
Subject request	57 (4.3%)	56 (4.2%)
Lost to follow-up	85 (6.5%)	90 (6.8%)

SB204 Phase 3 Pooled Demographics and Baseline Characteristics (ITT Population)

	Pooled SB204 (N = 1315)	Vehicle (N = 1318)
Age, years		
Mean (SD)	21.3 (8.4)	21.6 (8.6)
Min to max	9 – 65	9 – 73
Gender		
Male	504 38.3%	514 39.0%
Female	811 61.7%	804 61.0%
Lesion Counts at Baseline		
Inflammatory, mean (SD)	27.4 (5.6)	27.5 (5.7)
Non-Inflammatory, mean (SD)	40.2 (12.5)	39.9 (12.4)
Baseline IGA Scores		
“Moderate” or a score of 3	1156 88.0%	1162 88.2%
“Severe” or a score of 4	158 12.0%	155 11.8%

Percent Reduction in Lesions (Pooled)

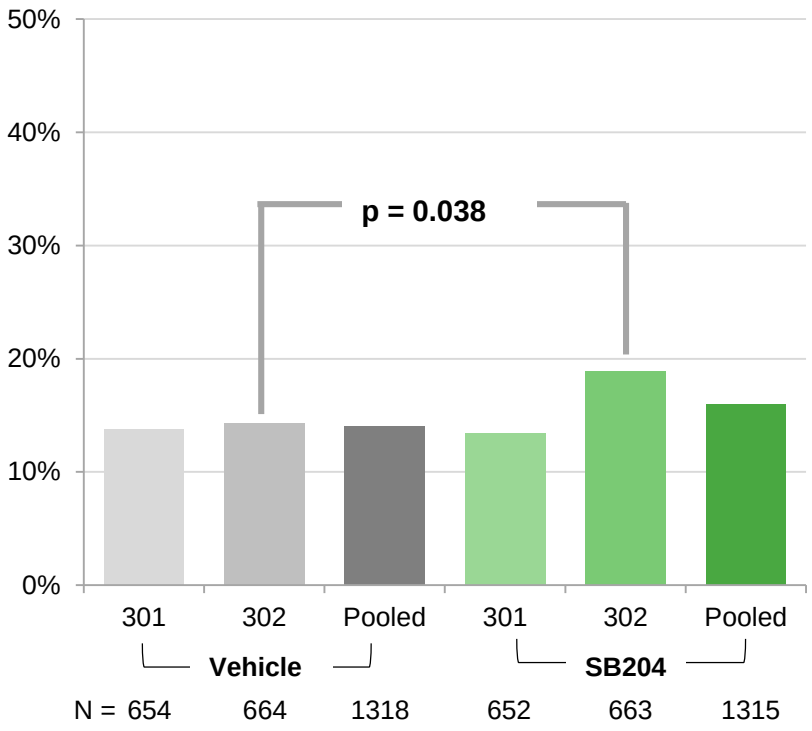


Absolute change from baseline for pooled SB204 vs vehicle were: -12.48 vs -10.88 (p<0.001) for inflammatory lesions, -15.06 vs -12.70 (p<0.001) for non-inflammatory lesions and -27.52 vs -23.75 (p<0.001) for total lesions.

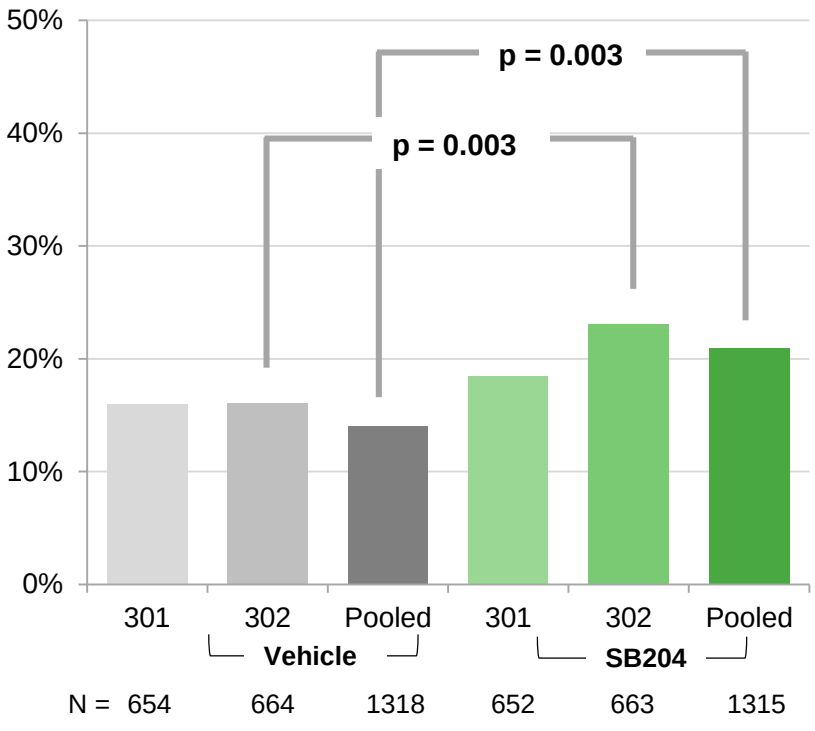
Standard error ≤1.2 for all data points presented

Investigator Global Assessments (IGA)
Baseline to Week 12

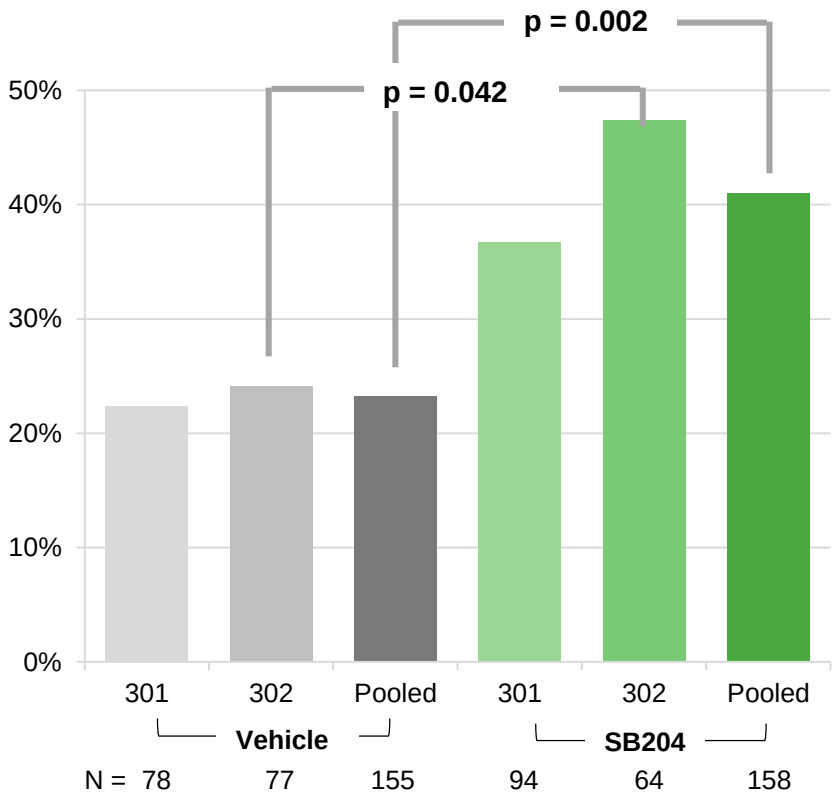
Moderate & Severe at Baseline
IGA = 0 or 1 & 2 Grade Change



Moderate & Severe at Baseline
2 Grade Change



Severe Only at Baseline
2 Grade Change

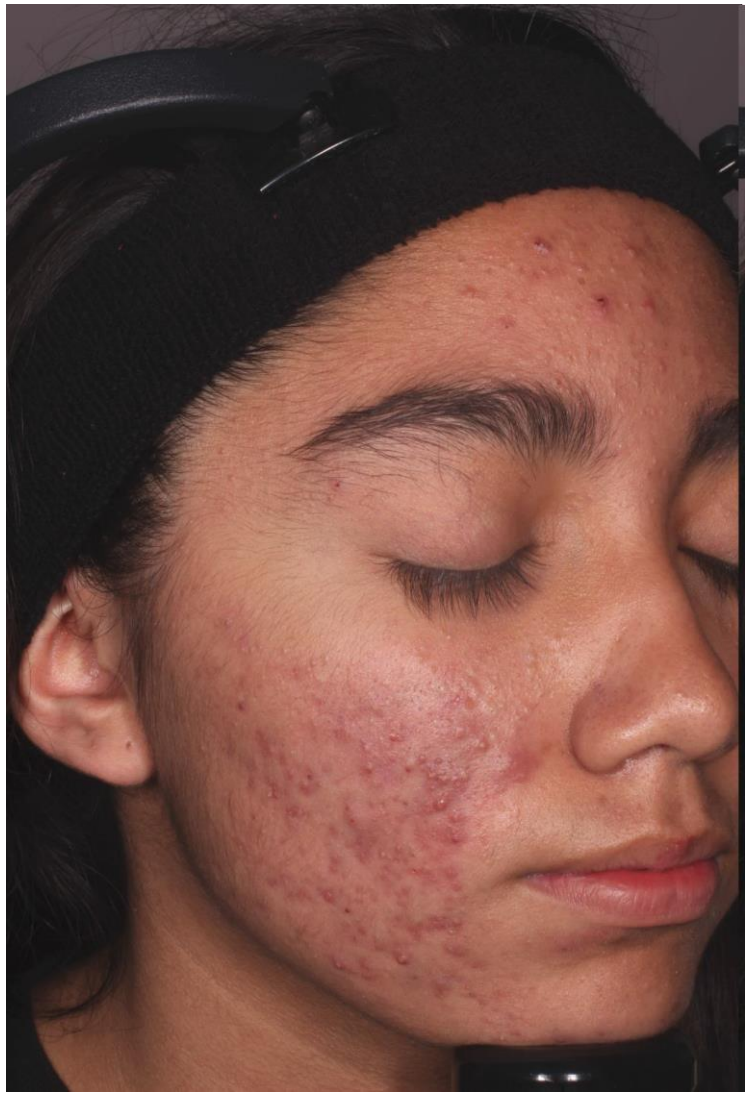


Response percentages were obtained after multiple imputation (MCMC) for missing data.

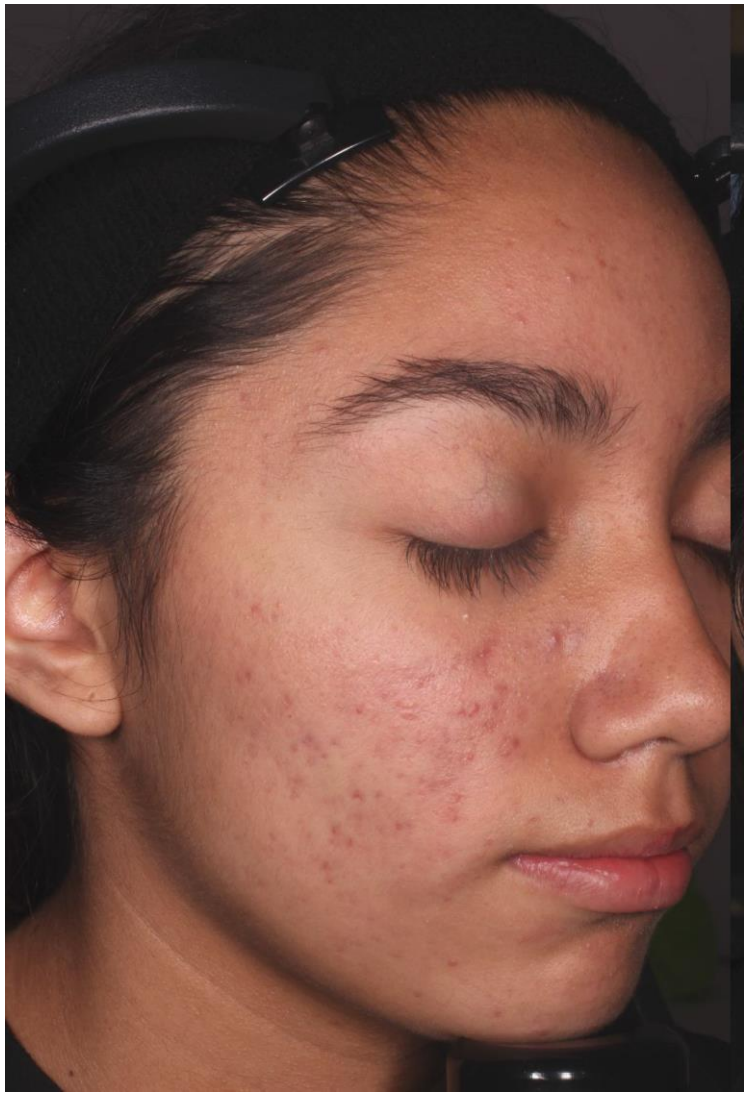
SB204 Phase 3 Representative Clinical Photos

SB204 Treatment Group

Baseline

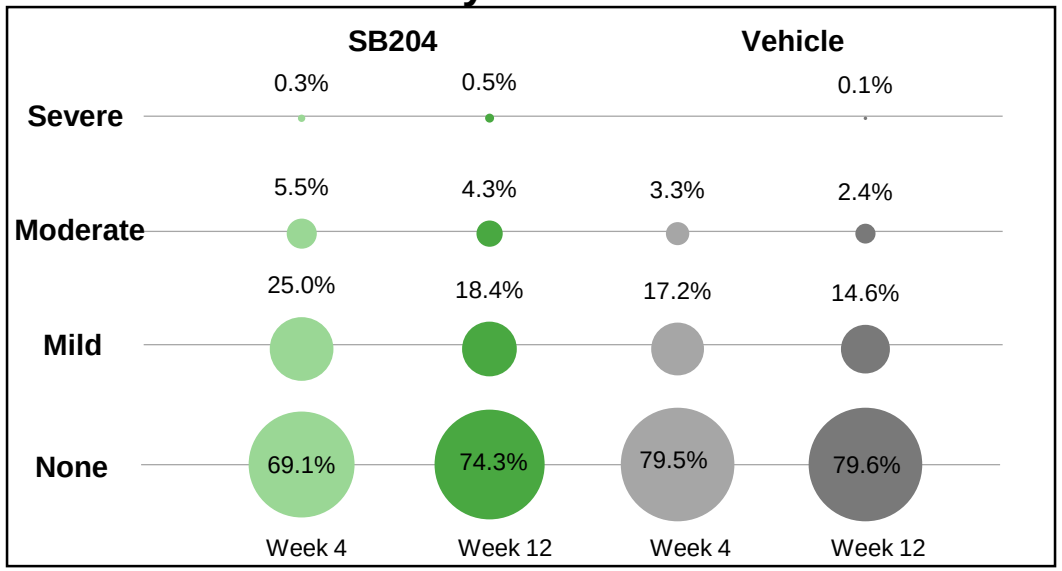


Week 12

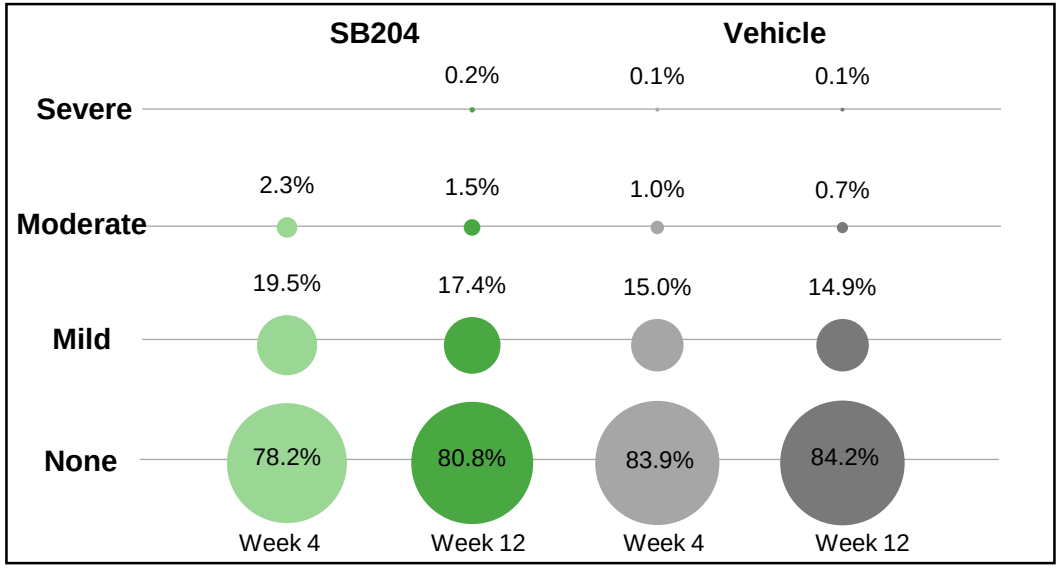


SB204 Phase 3 Pooled Tolerability

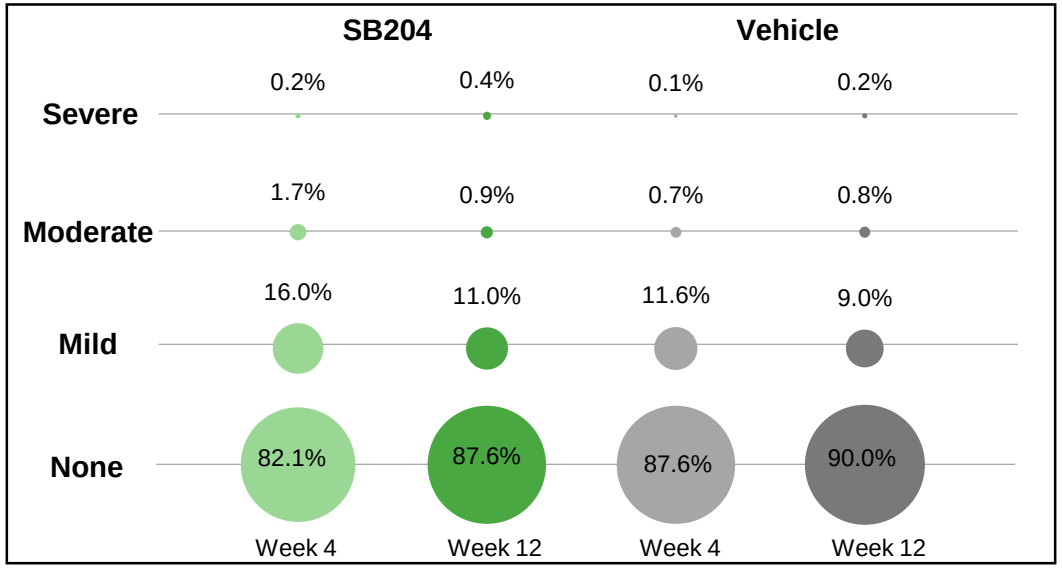
Erythema



Dryness



Burning / Stinging

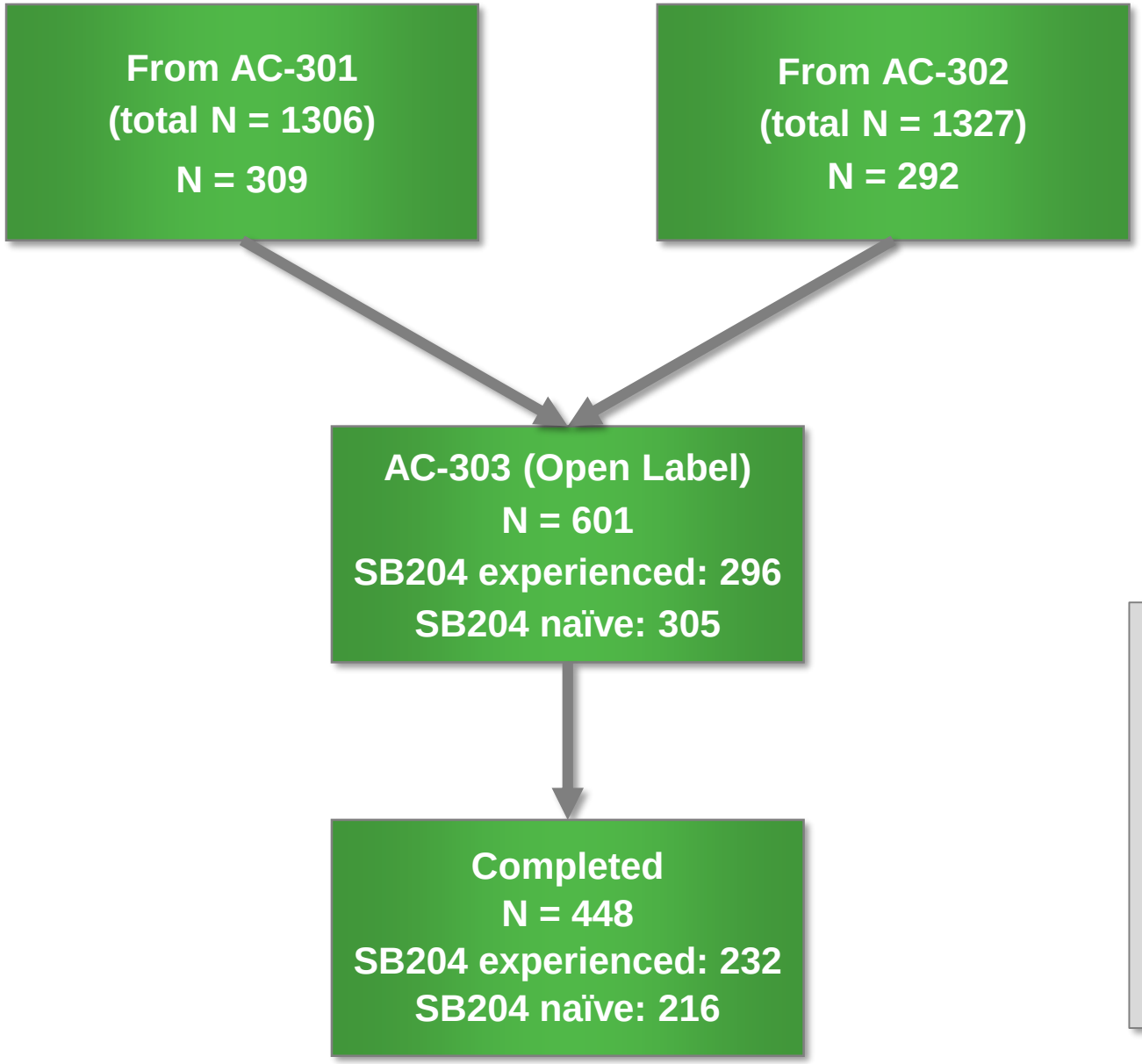


SB204 Phase 3 Treatment Emergent Adverse Events (TEAEs) (Safety Population)

	NI-AC301 SB204 (N = 666)	NI-AC301 Vehicle gel (N = 661)	NI-AC302 SB204 (N = 654)	NI-AC302 Vehicle gel (N = 652)	Pooled SB204 (N = 1320)	Pooled Vehicle gel (N = 1313)
General Disorders and Administration-Site Conditions	49 (7.5%)	12 (1.8%)	29 (4.4%)	11 (1.7%)	78 (5.9%)	23 (1.8%)
Application site pain	21 (3.2%)	3 (0.5%)	14 (2.1%)	4 (0.6%)	35 (2.7%)	7 (0.5%)
Application site erythema	11 (1.7%)	1 (0.2%)	10 (1.5%)	2 (0.3%)	21 (1.6%)	3 (0.2%)
Application site pruritus	16 (2.4%)	3 (0.5%)	6 (0.9%)	4 (0.6%)	22 (1.7%)	7 (0.5%)
Application site dryness	7 (1.1%)	2 (0.3%)	5 (0.8%)	1 (0.2%)	12 (0.9%)	3 (0.2%)
Other TEAEs						
Nasopharyngitis	11 (1.7%)	10 (1.5%)	15 (2.3%)	18 (2.7%)	26 (2.0%)	28 (2.1%)
Headache	5 (0.8%)	1 (0.2%)	10 (1.5%)	1 (0.2%)	15 (1.1%)	2 (0.2%)

The most common TEAEs were application site reactions; less than 2% of patients discontinued due to AEs. No treatment-related SAEs were reported.

SB204 Long-Term Safety Design and Disposition



Treatment Regimen

SB204 4%
Once Daily Application (QD)
40 week treatment

Efficacy Endpoints

Change in inflammatory lesions
Change in non-inflammatory lesions
Tolerability and Safety

Primary Reason for Study Discontinuation

- Adverse events: 9
- Withdrawal by patients: 76
- Physician decision: 1
- Protocol violation: 1
- Lost to follow-up: 61
- Pregnancy: 2
- Other: 3 (non-compliance with taking study drug and duplicate patients)

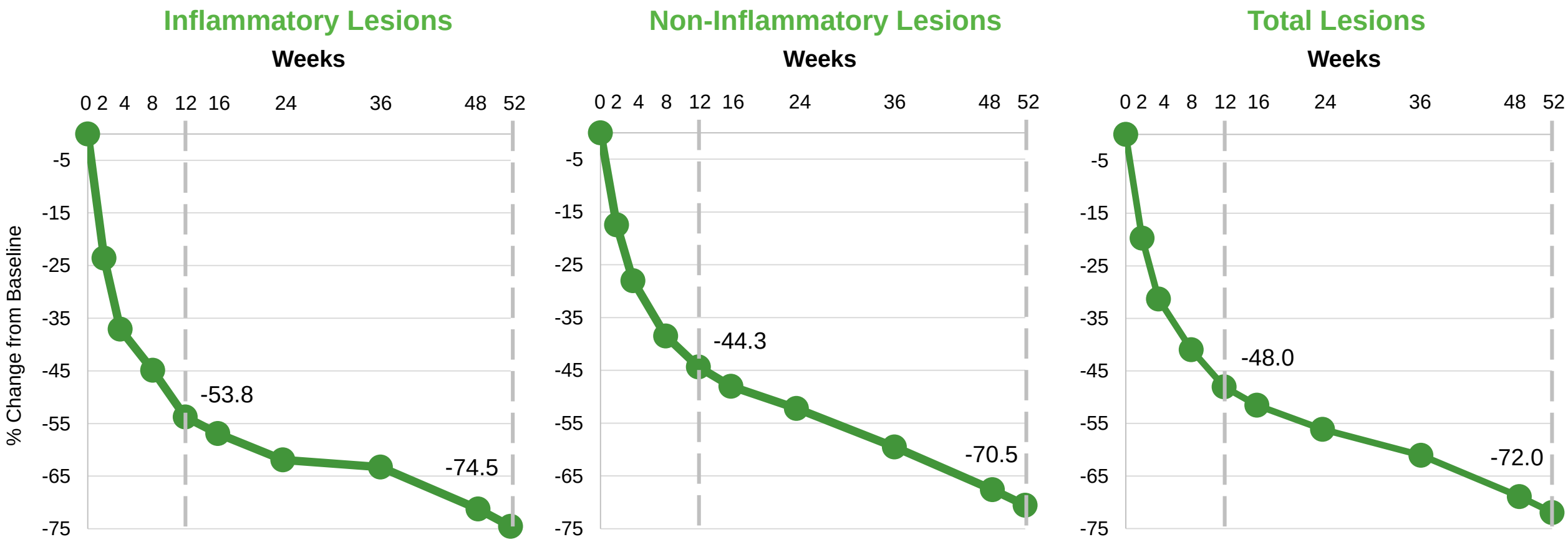
SB204 Long-Term Safety (Safety Population)

	Overall N = 601
General Disorders and Administrative Site Conditions	**26 (4.3%)**
Application site dryness	9 (1.5%)
Application site pruritus	9 (1.5%)
Application site pain	6 (1.0%)
Application site erythema	4 (0.7%)
Application site exfoliation	3 (0.5%)
Application site pyrexia	3 (0.5%)

	Overall
Other Events	
Nasopharyngitis	19 (3.2%)
Headache	8 (1.3%)
Influenza	7 (1.2%)
Upper respiratory tract infection	6 (1.0%)
Bronchitis	3 (0.5%)
Migraine	3 (0.5%)
Nausea	3 (0.5%)
Tooth impacted	3 (0.5%)
Back pain	3 (0.5%)
Anxiety	3 (0.5%)
Cough	3 (0.5%)

Any TEAE: n = 112 (18.6%)
Treatment-related TEAE: n = 23 (3.8%)
Discontinuation due to AE: n = 9 (1.5%) (1.3% - application site reactions)
No deaths
SAE: 6 patients (1%) (none of them were considered by the Investigator to be related to study treatment)
Two pregnancies: Early discontinuation (One delivered a healthy baby girl, no complications with the pregnancy. One had a spontaneous abortion.)

Percent Reduction in Lesions (SB204 Experienced Only)



Overall, a 75% reduction in inflammatory lesion counts was observed over 52 weeks of treatment, showing a long-term benefit of continuous treatment with SB204.

Standard error ≤2.2 for all data points presented

Summary

In a pooled analysis from two Phase 3 trials (NI-AC301 and NI-AC302):

- At Week 12, SB204 had statistically significant greater reduction over vehicle in:
  - inflammatory lesions (-50.3% vs -44.1%)
  - non-inflammatory lesions 12 (-42.4% vs -36.1%)
  - total lesions (-45.6% vs -39.3%)
- Among patients in the severe group (IGA = 4), the percent of respondents with at least a 2 grade improvement in IGA was approximately two times higher for SB204 than vehicle.
- The most frequent adverse events were application site reactions, but mostly in the mild category. Overall, less than 2% of patients discontinues due to AEs.

In the long-term safety study:

- Continuous treatment with SB204 showed further benefit.
- The 40 week safety profile was consistent with the 12 week trial. Application site reaction (4.3%) and nasopharyngitis (3.2%) were the most frequent adverse events.

A separate study (NI-AC101) showed no measurable systemic exposure when treating 17% BSA of 18 patients with moderate-to-severe acne.

SB204 has shown evidence of efficacy in treating acne vulgaris with a favorable long-term safety profile.