Pharmacokinetics of SB204 in Subjects with Acne Vulgaris

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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 ploymer backbone.
- Three pharmacokinetic (PK) studies, NI-AC101, NI-AC103, and NI-AC104, were conducted with SB204 in subjects with moderate to severe acne.
  - SB204 was applied to 17% BSA: face, shoulders, upper back, and chest.
  - Subjects received a low nitrate diet during PK collection days.
- Major Exclusion Criteria:
  - Methemoglobin >2% at screening or baseline.
  - Subjects previously treated with NVN1000 Gel/SB204.

Methods

Studies assessed systemic exposure to:

- Hydrolyzed N-methyl-aminopropyltrimethoxysilane (hMAP3), a component of the NVN1000 parent polymer backbone. The lower limit of quantitation (LLOQ) for hMAP3 was 5.00 ng/mL.

Hydrolyzed MAP3 (hMAP3)

- Nitrate (NO_3^-), a marker for systemic nitric oxide exposure. The LLOQ for nitrate was 300 ng/mL.

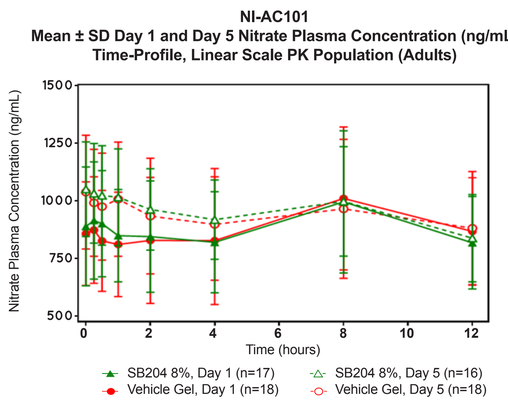
Treatment Emergent Adverse Events (TEAEs) were recorded, methemoglobin was monitored, and electrocardiogram (ECG) readings were taken.

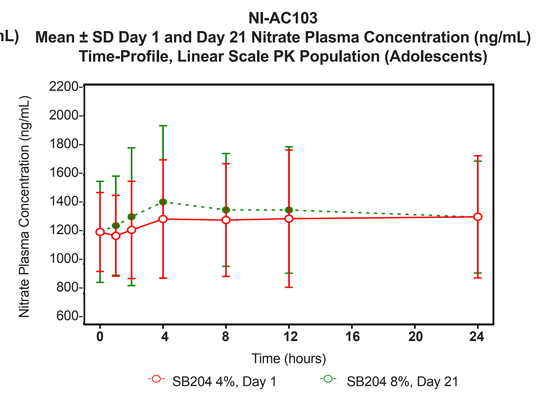
		NI-AC101 (N=18)	NI-AC103 (N=18)	NI-AC104 (N=48)
Study Design		Single-center double-blind, 2-period, randomized crossover study	Single-center, open-label pharmacokinetic study	Single-center, double-blind, double-dummy, 4-period randomized crossover study
Age		Age ≥ 18 yrs.	Age ≥ 9 - <17yrs.	Age ≥ 18 yrs.
Dose/Dosing schedule		Topical SB204 8% or Vehicle (1:1 ratio) was applied twice daily 12 hours apart days 1 to 4; in the morning once daily on day 5	Topical SB204 4% was applied once daily in the mornings for 21 days	Topical SB204 4% or SB204 12%, placebo or moxifloxacin were administered once in the morning of days 1, 5, 9, 13 of the 18-day treatment duration
PK Collection		PK profiling done day 1 and day 5 from time 0 to 12 hours post dose	PK profiling done on days 1 and 21 from time 0 to 24 hours post dose	PK profiling done on day 1 for each treatment from time 0 to 24 hours post dose
Baseline Characteristics				
Sex N (%)	Male	8 (44.4)	11 (61.1)	30 (62.5)
	Female	10 (55.6)	7 (38.9)	18 (37.5)
Completed N (%)		16 (88.9)	18 (100)	46 (95.8)
Discontinued N (%)		2 (11.1)	0	2 (4.2)

Results

- In adults (n=66) and adolescents (n=18) with moderate to severe acne vulgaris treated topically with SB204 gel:
  - Plasma hMAP3 levels were below LLOQ (5.0 ng/mL) after single or repeat SB204 application at all timepoints and for all treatments, in all three (NI-AC101, NI-AC103, NI-AC104) studies.
  - Systemic exposure to nitrate was similar following administration of SB204 4% (NI-AC103, NI-AC104), SB204 8% (NI-AC101), and SB204 12% (NI-AC104) or vehicle.
  - There were no noticeable differences in nitrate PK parameters in subjects at baseline and following repeat treatment with SB204 4% or 8% (NI-AC103, NI-AC101).

Plasma Nitrate (Single and Multi Dose)



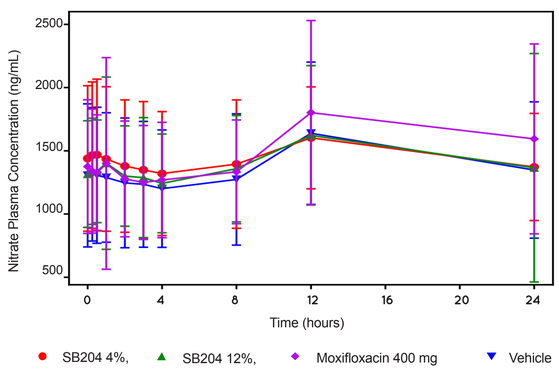


NI-AC101 (Adults)				NI-AC103 (Adolescents)	
Parameter (unit)	Day	SB204 8% Mean (SD) n	Vehicle Gel Mean (SD) n	Day	SB204 4% Mean (SD) n
C_{max} (ng/mL)	1	1104.8 (303.78) n = 17	1081.8 (289.65) n = 18	1	1690.1 (471.69) n=18
	5	1105.2 (257.62) n = 16	1088.9 (274.79) n = 18	21	1665.6 (486.73) n=18
*AUC_{0-t} (h·ng/mL)	1	10503.39 (2644.842) n = 17	10602.83 (3049.625) n = 18	1	31082.2 (6562.49) n=18
	5	11257.84 (2347.643) n = 16	11070.76 (3084.510) n = 18	21	32354.6 (8574.26) n=16
RA_{Cmax}	5	1.035 (0.1916) n = 16	1.033 (0.1971) n = 18	21	1.0297 (0.3191) n=18
RA_{AUC}	5	1.094 (0.1336) n = 16	1.060 (0.1670) n = 18	21	1.0490 (0.2318) n=18

*AUC_{0-t} NI-AC101 was 0-12 hours and NI-AC103 was 0-24 hours

Legend:
C_{max}: maximum observed plasma concentration value
AUC_{0-t}: area under the plasma concentration-time curve from time = 0 to the time of the last measurable time point
RA_{AUC}: accumulation ratio for AUC_{0-t}
RA_{Cmax}: accumulation ratio for C_{max}

Plasma Nitrate (Single Dose; Therapeutic and Supratherapeutic)



NI-AC104 (Adults)					
Day	Parameter (unit)	SB204 4%	SB204 12%	Vehicle	Moxifloxacin
		Mean (SD) n			
1 Day (0-24 hrs)	C_{max} (ng/mL)	1739 (490.88) n=47	1879 (1016.6) n=48	1722 (593.69) n=48	1969 (922.90) n=47
	AUC_{0-t} (h·ng/mL)	33995 (10393.1) n=47	33667 (11932.2) n=48	33209 (11499.0) n=48	36295 (13964.5) n=47

Legend:
C_{max}: maximum observed plasma concentration value
AUC_{0-t}: area under the plasma concentration-time curve from time = 0 to time of the last measurable time point

Treatment Emergent Adverse Events (TEAEs)

- In all 84 treated subjects – no clinically significant changes in laboratory assessments including methemoglobin values, ECG results, and physical examinations were observed.
- One subject discontinued in NI-AC101 due to local application site adverse events.

Adverse Event (AE)	NI-AC101		NI-AC103	NI-AC104		
	SB204 8% (N=18) n (%)	Vehicle (N=18) n (%)	SB204 4% (N = 18) n (%)	SB204 4% (N = 47) n (%)	SB204 12% (N = 48) n (%)	Vehicle (N = 48) n (%)
Number of subjects reporting at least one AE	8 (47.1)	6 (33.3)	1 (5.6)	9 (19.1)	11 (22.9)	8 (16.7)
Number of AEs	19	8	2	15	14	10
Nervous system disorders	4 (23.5)	5 (27.8)	-	0	1 (2.1)	2 (4.2)
Skin and subcutaneous system disorders	4 (23.5)	0	1 (5.6)	2 (4.3)	4 (8.3)	0
Gastrointestinal disorders	2 (11.8)	1 (5.6)	-	3 (6.4)	3 (6.3)	3 (6.3)
General disorders and administration site conditions	2 (11.8)	0	-	2 (4.3)	1 (2.1)	3 (6.3)
Musculoskeletal and connective tissue disorders	1 (5.9)	1 (5.6)	-	1 (2.1)	1 (2.1)	1 (2.1)
Respiratory, thoracic and mediastinal disorders	1 (5.9)	1 (5.6)	-	1 (2.1)	1 (2.1)	0
Injury, poisoning, and procedural complications	-	-	1 (5.6)	-	-	-

Conclusion

- Following single and repeat application of topical SB204 at doses between 4%-12% in adult or adolescent subjects with moderate to severe acne:
  - There was no detectable hMAP3 in any subject, at all timepoints, and for all treatments, in all three (NI-AC101, NI-AC103, NI-AC104) studies, including under maximal use conditions.
  - Plasma nitrate levels in subjects treated with SB204 4%, 8% and 12% (NI-AC101, NI-AC104) were bioequivalent with those after administration of vehicle. There were no noticeable differences in nitrate PK parameters at baseline and following treatment with SB204 (NI-AC103).
- All doses of SB204 administered in the studies were well tolerated and the adverse event profile was similar in active and vehicle treated subjects.

Acknowledgements

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