Pharmacokinetics of SB204 in Subjects with Acne Vulgaris

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INTRODUCTION AND LEARNING OBJECTIVES

The study was conducted to assess systemic exposure to NVN1000, a nitric oxide-releasing drug in a topical gel (SB204) in development for acne vulgaris. The pharmacokinetic (PK) profile of nitrate and hydrolyzed N-Methyl-aminopropyltrimethoxysilane (hMAP3) as markers for systemic exposure to nitric oxide and NVN1000 respectively was determined in subjects with acne vulgaris treated under maximal use conditions.

METHOD

A single-center, double-blind, randomized, 2 period cross-over study was conducted in adults with moderate to severe acne vulgaris. Subjects meeting entry criteria were randomized to receive SB204 8% or Vehicle Gel twice daily during the first 5-day treatment period. Serial blood samples were collected on Day 1 and Day 5 and analyzed for hMAP3 and nitrate. After a 9 day washout, subjects received the alternate treatment. Plasma samples were analyzed for hMAP3 by liquid chromatography-mass spectrophotometry instrumental analysis and for nitrate by liquid chromatography.

RESULTS

Eighteen (10 females; 8 males) subjects enrolled and 16 subjects completed the study. SB204 and Vehicle were generally well tolerated with no changes noted in hematology, methemoglobin, chemistry or other labs. One subject discontinued the study on the last treatment day due to local application site reaction.

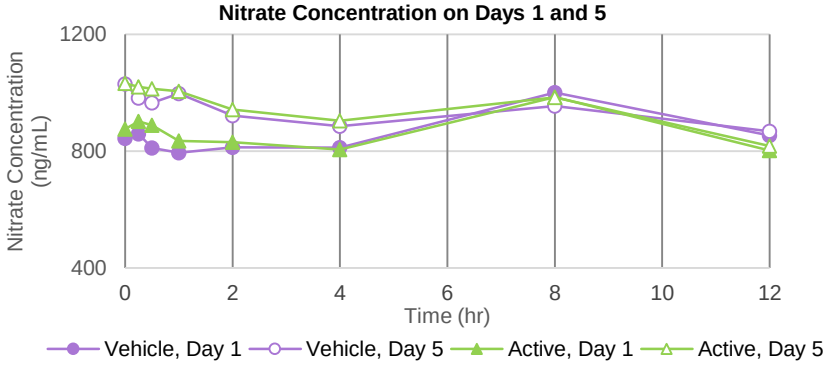
Plasma hMAP3 levels were below the level of quantification (5.0 ng/ml) for all timepoints.

Systemic exposure to nitrate following SB204 8% was bioequivalent to treatment with Vehicle Gel. The 90% CIs for comparisons of C_{max} and AUC_{0-t} for subjects treated with SB204 8% or Vehicle Gel were completely contained within the interval of 80% to 125%. There was no difference in nitrate concentration over time in subjects treated with SB204 8% or Vehicle Gel. These data indicate that there was no systemic availability of nitrate after administration of SB204 8% for 5 days.

Summary of Plasma Nitrate PK Parameters (PK Population)

Parameter (unit)	Definition	Day	SB204 8% Mean ± SD	Vehicle Gel Mean ± SD
C_{max} (ng/mL)	Max observed concentration	1	1104.8 ± 303.8	1081.8 ± 289.7
		5	1105.2 ± 257.6	1088.9 ± 274.8
AUC_{0-t} (h*ng/mL)	AUC from time = 0 to the last measurable concentration	1	10503.4 ± 2644.8	10602.8 ± 3049.6
		5	11257.8 ± 2347.6	11070.8 ± 3084.5
RA_{Cmax}	Accumulation ratio (C_{max})	5	1.04 ± 0.20	1.03 ± 0.20
RA_{AUC}	Accumulation ratio (AUC)	5	1.09 ± 0.13	1.06 ± 0.20

Nitrate Concentration on Days 1 and 5



CONCLUSION AND KEY MESSAGES

- SB204 8% Gel was generally well tolerated and not associated with significant safety issues.
- The topical administration of SB204 8% in adults with moderate to severe acne vulgaris under maximal use conditions was not associated with systemic exposure to hMAP3, a marker for NVN1000.
- Plasma nitrate levels in subjects treated with NVN1000 or Vehicle Gel were bioequivalent.

DECLARATION AND CONFLICT OF INTEREST

MJR, EdL, CG, NS are full time employees and stockholders in Novan, Inc. RG is a fulltime employee of Aclairo Pharmaceutical Development Group.

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