CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-159

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-159	Submission Date: 4/9/07
Submission Type; Code:	505(b)(2); 3S
Brand/Code Name:	OraVerse®; NV-101
Generic Name:	Phentolamine mesylate injection 0.4 mg
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	Novalar Pharmaceuticals, Inc.
Relevant IND(s):	65,095
Formulation; Strength(s):	Injection; 0.4 mg
Proposed Indication:	For the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor
Proposed Dosage Regimen:	• 1/2 cartridge (0.2 mg) of OraVerse when 1/2 cartridge of local anesthetic has been administered; • 1 cartridge (0.4 mg) of OraVerse when 1 cartridge of local anesthetic has been administered; • 2 cartridges (0.8 mg) of OraVerse when 2 cartridges of local anesthetic have been administered.

Table of Contents

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology Evaluation II (OCP/DCP-II) has reviewed the OraVerse® NDA submitted on 4/9/07.

From OCP perspective, the information contained in the Application is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling for OraVerse.

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

Novalar, Inc. has submitted OraVerse® Injection 0.4 mg, NDA 22-159 in accordance with 505(b)(2) of the Food, Drug and Cosmetic Act and 21 CFR 314.50 and 21 CFR 314.54, for the reversal of soft tissue anesthesia and the associated deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. The following local anesthetics were assessed in the Phase 3 trials: Lidocaine, Articaine, Prilocaine, and Mepivacaine.

Reference was made to Regitine® NDA 8-278 (a lyophilized powder of 5.0 mg phentolamine mesylate and 25.0 mg mannitol, USP, per vial; it is reconstituted with 1 mL sterile water; NDA was approved in January 1952; it was marketed by Ciba (now Novartis)), for use in the diagnosis and treatment of patients with pheochromocytoma and for treatment and prevention of dermal necrosis following intravenous administration or extravasation of norepinephrine. The **Applicant is relying on the FDA's previous** findings of safety and efficacy for Regitine, as described in the Drug Efficacy Study Implementation (DESI) finding published in the Federal Register on April 6, 1971 (DESI 8278, Federal Register Notice Volume 36, No. 66). Novartis discontinued marketing Regitine in the U.S. in 2000. A generic version was approved (ANDA 40-235; phentolamine mesylate for injection, USP) on March 11, 1998 (manufactured by Ben Venue Laboratories for Bedford Laboratories). The ANDA was granted biowaiver for its 5 mg/vial product based upon 21 CFR 320.22. This generic version is currently marketed in the U.S.

For its use in dental patients, OraVerse is to be given in units of 1 or 2 cartridges (delivering 0.4 mg and 0.8 mg of phentolamine mesylate, respectively) by intraoral submucosal injection, with the number of cartridges of OraVerse equal to the number of cartridges of anesthetic used to achieve pulpal anesthesia. A dose of ½ cartridges (0.2 mg) is indicated for children weighing more than 15 kg and less than 30 kg. These doses represent approximately 1/12 to 1/16 the approved adult dose (5-10 mg, intravenous or 5 mg, intramuscular) or 1/15 to 1/5 the approved pediatric dose (1 mg, intravenous; 3 mg, intramuscular) of phentolamine mesylate indicated in the labeling for both Regitine and the currently marketed generic product.

Data from two pharmacokinetic studies using the to-be-marketed formulation was submitted. Since the drug is applied at the local site for the local treatment, the critical clinical pharmacology aspect of this NDA was to focus on the phentolamine systemic exposure.

Exposure-response relationship

The drug is injected at the local tissue site for the local treatment effect. The phentolamine concentrations at the local site were not sampled. Therefore, there is no

exposure-response relationship for this product. However, the Applicant explored other markers (return of sensation to lips, tongue, teeth, and chin) produced by a local anesthetic injection of lidocaine/epinephrine in Phase 2 trials. OraVerse decreased the time to return to normal sensation in affected tissues.

In the Phase 3 trials, the majority of subjects were evaluated with OraVerse/lidocaine (n=82). For other local anesthetics, the evaluated subjects were some what fewer: Articaine (n=16), Prilocaine (n=13), and Mepivacaine (n=11). According to the reviewing medical officer, OraVerse decreased the time to return to normal sensation for lidocaine and for other local anesthetics **(a 'similar trend'** was observed).

Single dosing

Data are available from two single dose studies, NOVA-04-PK and NOVA-05-PEDS-PK.

The following table contains overall PK parameters. It appears that there is a clear difference in phentolamine Cmax, due to subject body weight. Phentolamine Cmax in subjects who is weighs less than 30 kg (pedia**tric subjects 3 – 8 years of age) increased** approximately 70% compared to > 30 kg body weight.

The OraVerse dosing scheme proposed by the Applicant is acceptable in that in pediatric patients weighing 15-30 kg, the maximum dose of OraVerse recommended is 1/2 cartridge (0.2 mg).

	Subjects (No. (M/F) Type Age: Median (Range)	**Treatments (Dose, Dosage Form, Route)**	**Phentolamine - Mean Parameters (SE)**						
			Cmax (ng/mL)	**AUClast (ng.hr/mL)**	**AUCinf (ng.hr/mL)**	**Tmax (min)**	**t1/2 (hr:min)**	**Cl (L/hr)**	**Vd (L)**
NOVA 04-PK	16 (7/9) Healthy subjects 23 (18-50)	NV-101, 0.4 mg intraoral submucosal	1.34	1.69	2.88	15 ± 2	3:08 ± 0:55	160.93 ± 24.02	470.61 ± 62.72
		NV-101, 0.8 mg intraoral submucosal	2.73	3.29	4.58	11 ± 1	02:14 ± 00:25	203.64 ± 36.21	499.68 ± 60.08
		NV-101, 0.4 mg IV	10.98	1.71	2.76	7 ± 3	2:24 ± 0:38	175.49 ± 30.36	441.99 ± 83.68
NOVA 05-PEDS-PK	8 (5/3) Pediatric subjects undergoing dental procedures 5 (3-8) **15 – 30 kg**	NV-101, 0.2 mg intraoral submucosal	2.60	1.93	3.62	10 ± 1	2:32 ± 0:34	58.79 ± 8.06	190.56 ± 35.69

	11 (8/3) Pediatric subjects undergoing dental procedures 13 (8-16) > 30 kg	NV-101, 0.4 mg intraoral submucosal	1.47	1.81	3.39	21 ± 4	2:59 ± 0:56	132.18 ± 17.59	396.50 ± 22.98

Study 04 (NOVA 04-PK)

This was a Phase 1, open-label PK, PD, and Safety in Healthy Adult Volunteers. The main study objectives were to determine the PK of phentolamine administered by intraoral (0.4 and 0.8 mg) and intravenous (IV) injections (0.4 mg) and to determine the effects of NV-101 by intraoral injection on the PK of lidocaine and epinephrine administered by intraoral injection (1 or 4 cartridges).

Phentolamine:

Phentolamine was completely bioavailable after intraoral injection (104%).

The mean phentolamine Cmax and AUC values were dose-proportional. Compared to intravenous injection, OraVerse intraoral Cmax value was 8 times less. The phentolamine t1/2, CL, and Vd values were similar for all treatments. The phentolamine Tmax was earlier (7 min.) as administered alone compared to that of with a local anesthetic, lidocaine and epinephrine (11 - 15 min.).

Lidocaine:

The lidocaine Cmax and AUC values were dose proportional (1 vs. 4 cartridges). The lidocaine t1/2 and CL values were similar for all treatments.

The lidocaine Vd was smaller when administered with OraVerse and administered alone (192 L vs. 237 L).

Epinephrine:

The epinephrine Cmax, Tmax, AUClast, AUCinf, t1/2 and Vd values were similar for all treatment groups. However, the epinephrine CL was smaller when administered with OraVerse than administered alone.

Study 05 (NOVA 05-PEDS-PK)

This was a Phase 1 open label study of OraVerse to evaluate the PK and safety in pediatric dental patients. The objectives of the study were 1) to evaluate the PK of OraVerse in pediatric dental patients who were undergoing dental procedures under

general anesthesia or conscious sedation, to the extent possible with blood sampling limited to the duration of the intravenous (IV) access line after NV-101 administration and 2) to evaluate the safety of OraVerse in pediatric dental patients as measured by the incidence and severity of adverse events and concomitant medications. Plasma concentrations of phentolamine and lidocaine were assayed with a validated LC/MS/MS method.

Phentolamine

Phentolamine AUC and t1/2 parameters were similar between 0.2 and 0.4 mg groups.

The mean phentolamine Cmax plasma concentration in the 0.2-mg dose group (lighter body weight group) was approximately 70% greater the mean in the 0.4-mg group (heavier body-weight group) from 5 to 15 minutes post administration. However, by 30 minutes, the mean plasma concentrations in the two groups were nearly identical and remained similar through the 2-hour sampling point.

The mean CL and Vd parameters were noticeably larger in the 0.4-mg group than in the 0.2-mg group.

Lidocaine

The mean plasma concentration of lidocaine in the 0.4-mg dose group was less than the mean in the 0.2-mg group from immediately prior to OraVerse injection through the 2-hour sample. Lidocaine plasma concentrations increased after OraVerse injection, peaking at 20-30 minutes post administration, followed by gradual decline. Overall, the lidocaine concentrations were lower than those that are expected are to expected to have a systemic pharmacologic effect (>1000 ng/mL) in the broader population.

Linearity

The mean phentolamine Cmax and AUC values were dose-proportional, 0.4 and 0.8 mg, as stated above.

Absolute bioavailability

Phentolamine was completely bioavailable after intraoral injection (104%), as stated above.

Multiple dosing

This product is not intended to be used in a multiple dosing setting. As such, multiple dose studies were not conducted.

Pediatric population

The Applicant requested a waiver for pediatric population under the age of [redacted] years. Study 05 assessed OraVerse exposure in pediatric subjects from 3 to 16 years of age (see above for findings from Study 05). b(4)

Phentolamine interaction with lidocaine and epinephrine concomitant administration

Phentolamine systemic exposure did not change when concomitantly administered with a local anesthetic, lidocaine and epinephrine. Lidocaine and epinephrine systemic exposure did not change when concomitantly administered with OraVerse.

Assay

The LC/MS/MS assays validated for the measurement of epinephrine, phentolamine, lidocaine and [redacted] were based on [redacted] with LLOQ of [redacted], respectively. b(4)

Overall, the information submitted in this NDA is acceptable pending a mutual agreement can be reached with the Applicant with respect to OraVerse Labeling.

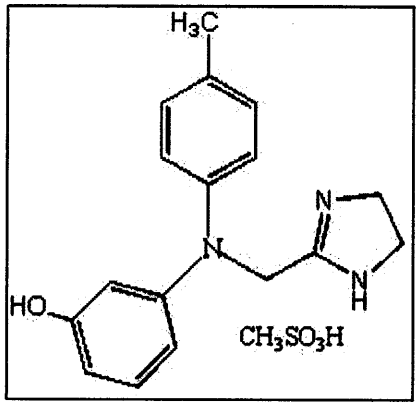
2 QBR

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Phentolamine mesylate USP is the active ingredient in OraVerse, and is a white to off-white, odorless crystalline powder with a molecular weight of 377.46. It is sparingly soluble in water, soluble in alcohol, and slightly soluble in chloroform. OraVerse (phentolamine mesylate) Injection is a clear, colorless, sterile, non pyrogenic, isotonic, preservative free solution. Each 1.7 mL cartridge contains 0.4 mg phentolamine mesylate, D-mannitol, edetate disodium, and sodium acetate. Acetic acid and sodium hydroxide may be used to adjust the pH.

Phentolamine mesylate structure:



Drug product composition

OraVerse existing formulations:

Ingredient	Phase 2 Formulation (per mL)	Phase 3/Commercial Formulation (per mL)
Phentolamine mesylate, USP (Reliable Chemical)	[redacted]	0.235 mg
EDTA Na2, USP	[redacted]	[redacted]
D-Mannitol, USP	[redacted]	[redacted]
Sodium acetate trihydrate, USP	[redacted]	[redacted]
Acetic acid, USP	[redacted]	[redacted]
WFI	[redacted]	[redacted]

b(4)

Only one clinical study was conducted with P2 formulation, namely Study NOVA 03-001. All other studies were conducted with to-be-marketed formulation.

Note regarding degradation product [redacted] in the formulation:

The Applicant stated that [redacted] is a degradation product [redacted]. This is a degradation product in the drug substance may increase over time during long term storage of the OraVerse. [redacted] was measured in plasma samples collected in the adult pharmacokinetic study, Study 04, to evaluate the extent of *in vivo* conversion of phentolamine into [redacted]. The results from Study 04 indicated that the measured [redacted] plasma concentrations were mostly below the limit of quantification, indicating that phentolamine did not significantly convert to [redacted] following intraoral submucosal or IV administration of NV-101.

b(4)

Comparison of OraVerse and Regitine formulations

It is noted that the Reference Listed Drug, Regitine® NDA 8-278 (NDA was approved in January 1952; not currently marketed) is a simple drug product which contains lyophilized powder of [redacted] phentolamine mesylate and [redacted] mg mannitol, USP, per vial. It is reconstituted with [redacted] sterile water. As indicated in the table above, there are

b(4)

no significant differences between the two products, except that OraVerse contains less than [redacted] of additional inactive ingredients. b(4)

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

OraVerse is indicated for the reversal of soft tissue anesthesia and the associated deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

Drug development plan

The development of phentolamine mesylate for local anesthetic reversal is based on the idea that competitive inhibition of administered vasoconstrictor and increased local blood flow resulting from vasodilatation will enhance the clearance of the local anesthetic agent(s) from the nerves and surrounding tissue. The ability of phentolamine to block the vasoconstrictor activities of catecholamines has been reportedly demonstrated in many settings; the most relevant being the oral cavity as well as the dental pulp and oral mucosa of cats leading sponsor hypothesize that phentolamine mesylate could be effective in dental patients and the rationale for developing phentolamine mesylate as an agent to accelerate recovery of sensation and associated functional deficits following local dental anesthesia.

Mechanism of action

The mechanism by which OraVerse reverses soft tissue anesthesia and the associated functional deficits is not well understood. The active moiety, phentolamine mesylate, is a sympatholytic competitive alpha-adrenergic blocker that non-selectively antagonizes both alpha-1 and -2 receptors, and when administered to vascular smooth muscle, phentolamine produces an alpha-adrenergic block of relatively short duration resulting in vasodilatation.

Pre-clinical support of tissue vasodilatation due to phentolamine

Phentolamine mesylate at the plasma concentrations achieved in pre-clinical studies appears to have no direct binding on the sodium ion channels that are the target proteins of local anesthetics used in these studies. Therefore, phentolamine mesylate is unlikely to compete with the local anesthetics for ion channel binding in nerve axons. After local injection into the oral mucosa of **dogs, OraVerse 'stimulated' local blood flow** in the ipsilateral but not contralateral jaw of beagle dogs. In this study, no effects were detected on blood pressure measured centrally. It was concluded that OraVerse likely increases the blood flow to the local tissue as demonstrated in dogs and enhancing the clearance of the local anesthetic from the tissue while not damaging local tissues.

In clinical settings, the plasma concentration of lidocaine increased immediately after an intraoral injection of OraVerse when given as an intraoral submucosal injection 30

minutes after injection of lidocaine, possibly indicating that lidocaine is released from the local tissues into the systemic circulation, decreasing the unpleasantness of local soft tissue anesthesia.

2.1.3 What are the proposed dosage and route of administration?

The recommended dose of OraVerse for intraoral procedures when using a local anesthetic containing a vasoconstrictor is:

- 1/2 cartridge (0.2 mg) of OraVerse when 1/2 cartridge of local anesthetic has been administered;
- 1 cartridge (0.4 mg) of OraVerse when 1 cartridge of local anesthetic has been administered;
- 2 cartridges (0.8 mg) of OraVerse when 2 cartridges of local anesthetic have been administered.

OraVerse is administered using the same location(s) and same techniques(s) (infiltration or block injection) used for the administration of local anesthetic.

In pediatric patients weighing 15-30 kg, the maximum dose of OraVerse recommended is 1/2 cartridge (0.2 mg). More than 1 cartridge [0.4 mg] of OraVerse has not been studied in children less than 12 years of age.)

Use in pediatric patients under [redacted] years of age [redacted] <15 kg is not recommended. b(4)

2.2 General Clinical Pharmacology

2.2.1 What type of information has been submitted?

The Applicant submitted two pharmacokinetic studies. Aside from these studies, the **Applicant requested a Bioavailability/Bioequivalence (BA/BE) waiver, specifically 'a study comparing the proposed product to the listed drug (if any),' per 21 CFR 314.90 for** the requirement stated in the Guidance for Industry: Applications Covered by Section **505(b)(2), dated October 1999. The Applicant's waiver request was granted prior to the** submission of this NDA (pre-NDA meeting, December, 2006), based on the fact that the Regitine, the reference listed drug (RLD) is no longer marketed and the Applicant conducted clinical studies, including OraVerse absolute bioavailability study (comparing phentolamine systemic concentrations from a local tissue injection to that of the systemic injection).

From the clinical pharmacology perspective, data from the OraVerse absolute BA study is relevant in providing the 505 (b)(2) linkage in that Regitine and OraVerse formulations are practically similar in composition and there are no concerns of expecting different phentolamine mesylate availability in vivo from the two formulations. See Section 2.1.1 of this review for formulation discussion. Thus, OraVerse systemic injection served as a **'replacement' for the Regitine systemic injection.**

The Applicant determined that the absolute bioavailability OraVerse by intraoral submucosal injection was 104% when compared to an intravenous injection OraVerse. The Cmax of phentolamine (1.34 ng/mL) following an intraoral submucosal OraVerse **injection, which was 8 times lower than the 'Cmax'** (10.98 ng/mL) following the intravenous injection of the same dose of OraVerse.

Regitine (NDA 8-278) as RLD

Regitine is listed in the FDA Orange Book as the reference listed drug (RLD) for phentolamine mesylate (a lyophilized powder of [redacted] phentolamine mesylate and [redacted] mg mannitol, USP, per vial; it is reconstituted with [redacted] sterile water; NDA was approved in January 1952), for and marketed by Ciba (now Novartis), for use in the diagnosis and treatment of patients with pheochromocytoma and for treatment and prevention of dermal necrosis following intravenous administration or extravasation of **norepinephrine. It is the Applicant's intention to rely on the FDA's previous findings of** safety and efficacy for Regitine, as described in the Drug Efficacy Study Implementation (DESI) finding published in the Federal Register on April 6, 1971 (DESI 8278, Federal Register Notice Volume 36, No. 66). Novartis discontinued marketing Regitine in the U.S. in 2000. b(4)

Phentolamine mesylate injection

A generic version was approved (ANDA 40-235; phentolamine mesylate for injection, USP) on March 11, 1998 (manufactured by Ben Venue Laboratories for Bedford Laboratories). The ANDA contained a waiver request (which was granted by FDA) of *in vivo* bioequivalance for its 5 mg/vial product based upon 21 CFR 320.22. This generic version is currently marketed in the U.S.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (If yes, refer to II. F, Analytical Section; if no, describe the reasons)

Yes.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety and efficacy?

The OraVerse is injected at the local tissue site for the local treatment effect. The phentolamine concentrations at the local site were not analyzed. Study 04 attempted to explore the concentration-response relationship in 16 healthy subjects. Due to the minimal number of subjects and slightly different study design compared to other P2 and

3 studies, the E-R relationship was not conclusive. For the pediatric PK study, the Applicant attempted to look at the dose-body weight correlation.

However, the Applicant explored dose-response relationships in P2 studies. Lastly, the systemic phentolamine concentrations were assessed for possibly assessing the systemic adverse events. Overall, OraVerse decrease the time to return to normal sensation in affected tissues.

Phase 1 Study 05 (NOVA 05-PEDS-PK) (see next section for the description of study design) on effect of body weight

It should be noted that the correlation coefficients(r) were calculated between body weight and the phentolamine Cmax and AUCinf parameters in treatments A, B, and C from Study 04. The results indicated that no significant relationships were found between body weight and Cmax or AUCinf values.

The dosing in the pediatric PK study was based on the subject's body weight. These weight-based dose levels fall within the dose range given, and deemed safe, in the Phase 2 study (NOVA 03-001) in which doses of 0.4 mg and 0.8 mg were administered to adults and adolescents weighing 45 to 115 kg. All subjects in NOVA 05-PEDS-PK were required to weigh at least 15 kg.

The individual body weights, Cmax values, and AUC values from Study 05 are presented in the next two tables for subjects dosed with 0.2 and 0.4 mg OraVerse. A significant inverse correlation was found between body weight and Cmax values in the smaller subjects, but not between AUC values and body weight. Among the larger subjects, no relationships were found between body weights and either Cmax or AUC.

Relationships between Body Weight and Pharmacokinetic Values in Pediatric Subjects Given 0.2 mg NV-101 in Study NOVA 05-PEDS-PK

Subject ID	Dose (mg/kg)	Body Weight (kg)	C_{max}	AUC_{inf}
01-001	0.0100	20	2.5	3.13
01-002	0.0118	17	3.2	6.49
01-003	0.0125	16	4.3	2.32
01-004	0.0080	25	1.9	2.44
02-001	0.0083	24	2.4	n/a
02-002	0.0095	21	1.7	3.08
02-003	0.0125	16	5.3	4.66
03-012	0.0077	26	1.5	4.93
Mean ± SD	0.0100 ± 0.0020	21 ± 4	2.9 ± 1.3	3.86 ± 1.54
Pearson R (vs. Body Weight)	NA	NA	-0.85**	-0.17

Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum concentration; NA, not applicable; SD, standard deviation

** = $p < 0.01$

Relationships between Body Weight and Pharmacokinetic Values in Pediatric Subjects Given 0.4 mg NV-101 in Study NOVA 05-PEDS-PK

Subject ID	Dose (mg/kg)	Body Weight (kg)	C_{max} (ng/mL)	AUC_{inf} (ng.hr/mL)
03-001	0.0052	127	1.2	2.68
03-002	0.0133	30	1.6	4.12
03-003	0.0060	67	2	2.59
03-004	0.0080	50	1.2	1.76
03-005	0.0083	48	1.7	6.35
03-006	0.0051	78	1.6	3.00
03-007	0.0082	49	1.3	2.93
03-008	0.0098	41	1.3	2.23
03-009	0.0111	36	2.2	2.72
03-010	0.0085	47	0.9	NA
03-011	0.0108	37	1.6	11.57
Mean ± SD	0.0084 ± 0.0029	55 ± 27	1.5 ± 0.4	4.00 ± 2.95
Pearson R (vs. Body Weight)	NA	NA	-0.21	-0.29

Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum concentration; NA, not applicable; SD, standard deviation

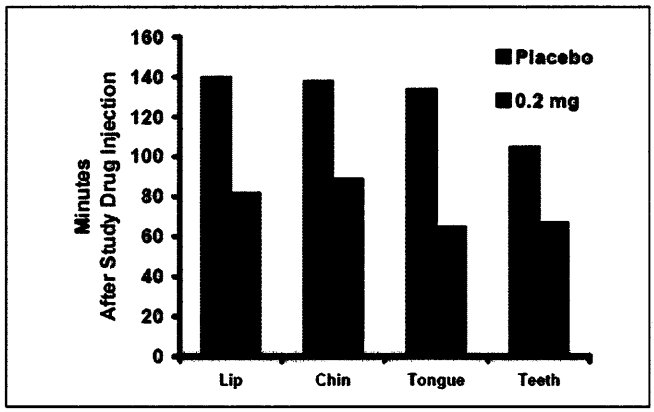
Therefore, administration of 0.2 mg OraVerse for subjects between 15 - 30 kg was considered reasonable. These studies further demonstrated that 0.2 and 0.4 mg of phentolamine mesylate in ½ or 1 cartridge of NV-101, respectively, administered after the treatment and in the same manner and location as the local anesthetic/vasoconstrictor, was safe for pediatric individuals.

Phase 2

Study NOVA 02-01: A Phase 1/2, Single Center, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of a Single Injection of Phentolamine Mesylate in Healthy Subjects

The objective of this study was to evaluate safety and the effect of an injection of phentolamine mesylate on the duration of anesthesia in the lips, tongue, teeth, and chin produced by an injection of lidocaine/epinephrine. Twenty subjects received a conventional inferior alveolar nerve block (IANB) using 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 µg). Subjects were randomly assigned to receive a single injection of placebo (1.8 mL) or 0.2 mg of phentolamine mesylate (1.8 mL of a 0.11 mg/mL solution) at 60 minutes after administration of the IANB, in the same site where the anesthetic was injected. The following information was presented by the Applicant.

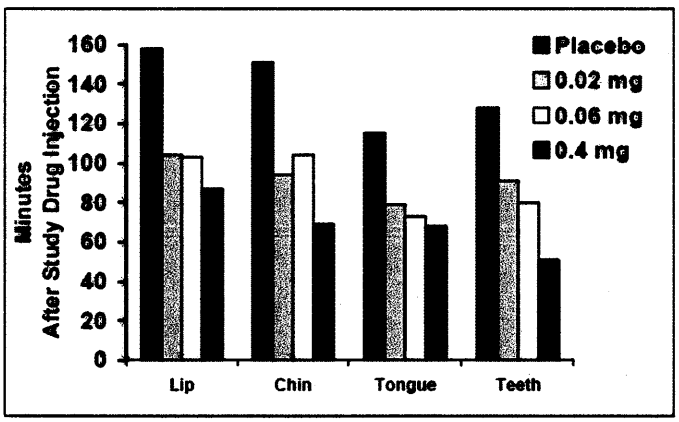
Time to return to normal sensation in affected tissues:



Study No. NOVA 02-02: A Dose-Ranging, Single Center, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of a Single Injection of Phentolamine Mesylate in the Mandibular Region of Healthy Subjects

The objectives of this study were to evaluate the safety and the effect of an injection of phentolamine mesylate on the duration of anesthesia in the lips, tongue, teeth, and chin produced by an injection of lidocaine/epinephrine. Forty subjects received a conventional IANB using 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 µg). Subjects were randomly assigned to receive a single injection of placebo, 0.02, 0.06, or 0.4 mg of phentolamine mesylate (1.8 mL of 0, 0.011, 0.033, or 0.2267 mg/mL solution, respectively) at 60 minutes after administration of the IANB, in the same site where the anesthetic was injected. The following information was presented by the Applicant.

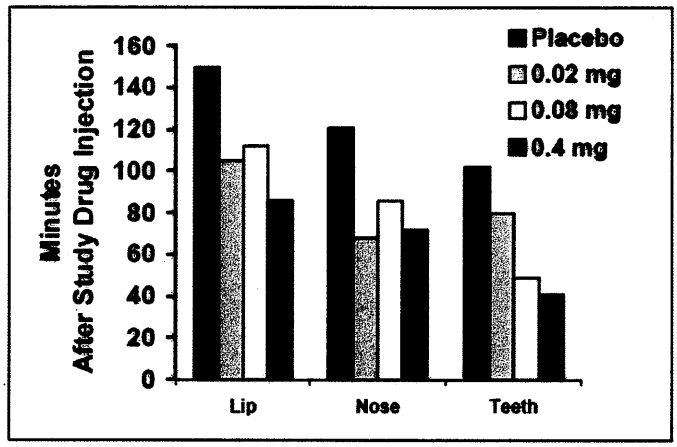
Time to return to normal sensation in affected tissues:



Study NOVA 02-03: A Dose-Ranging, Single Center, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of a Single Injection of Phentolamine Mesylate in the Maxillary Region of Healthy Subjects

The objectives of this study were to evaluate the safety and the effecacy of an injection of phentolamine mesylate on the duration of anesthesia in the upper lip, teeth, and nose produced by an injection of lidocaine/epinephrine. Thirty-two subjects received a maxillary lateral incisor infiltration using 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 μg). Subjects were randomly assigned to receive a single injection of placebo, 0.02, 0.08, or 0.4 mg of phentolamine mesylate (1.8 mL of a 0, 0.011, 0.2267, or 0.044 mg/mL solution, respectively) at 40 minutes after administration of the local anesthetic, in the same site where the anesthetic was injected. The following information was presented by the Applicant.

Time to return to normal sensation in affected tissues:



Study NOVA 03-001: A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of NV-101 in Dental Patients

The main objective of this study was to evaluate the efficacy of NV-101 to reduce the duration of local anesthesia in the lip, chin, nose, and tongue produced by any one of four local anesthetic agents formulated with a vasoconstrictor. One hundred twenty-two patients requiring one of four routine dental procedures were enrolled (61 active; 61 placebo). The investigators were licensed dentists in private practice. Patients received a single 1.8 mL injection of NV-101 (0.4 mg phentolamine mesylate) or placebo in each site at which injections of anesthetic had been given. The following information was presented by the Applicant.

Reductions in recovery times in the lip with 0.4 mg OraVerse:

Anesthetic	Maxilla			Mandible		
	n	Mean (Minutes)	%Reduction Relative to Placebo	*n*	Mean (Minutes)	%Reduction Relative to Placebo
Articaine	15	85	49	15	35	21
Lidocaine	15	101	67	15	71	46
Mepivacaine	18	78	50	18	56	32
Prilocaine	13	47	42	13	60	46

Overall, the following table was presented by the Applicant on the reduction in recovery time to normal lip sensation by OraVerse dose group:

Table 15: Reduction in Recovery Time to Normal Lip Sensation by Dose Group

Phentolamine Mesylate Dose	Study	Mean Reduction (minutes)	Percent Reduction Compared to Placebo	p-Value
0.02 mg	NOVA 02-02	53.0	34%	0.002
0.02 mg	NOVA 02-03	39.9	26%	0.110
0.06 mg	NOVA 02-02	57.5	36%	< 0.001
0.08 mg	NOVA 02-03	38.1	25%	0.138
0.2 mg	NOVA 02-01	58.0	41%	0.001
0.4 mg	NOVA 02-02	70.7	45%	< 0.001
0.4 mg	NOVA 02-03	65.4	43%	0.011
0.4 mg	NOVA 03-001	64.7	43%	not available
0.8mg	NOVA 03-001	87.4	49%	not available
0.4 mg and 0.8 mg (combined)	NOVA 03-001	66.9	44%	< 0.001

2.2.3.2 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

This product is not intended to be used in a multiple dosing setting. Multiple dose studies were not conducted.

Single dose

Study 04 (NOVA 04-PK)

This was a Phase 1, open-label PK, PD, and Safety in Healthy Adult Volunteers. The study objectives were 1) to determine the PK of phentolamine administered by intraoral and intravenous (IV) injections; 2) to determine the effects of NV-101 by intraoral injection on the PK of lidocaine and epinephrine administered by intraoral injection; 3) to evaluate the PD of NV-101 as measured by time to normal sensation of the lip(s) in Treatments A, C, and D; and 4) to evaluate the safety and tolerability of NV-101. Blood samples were drawn to assay for phentolamine, lidocaine, epinephrine, [redacted] b(4)

[redacted]

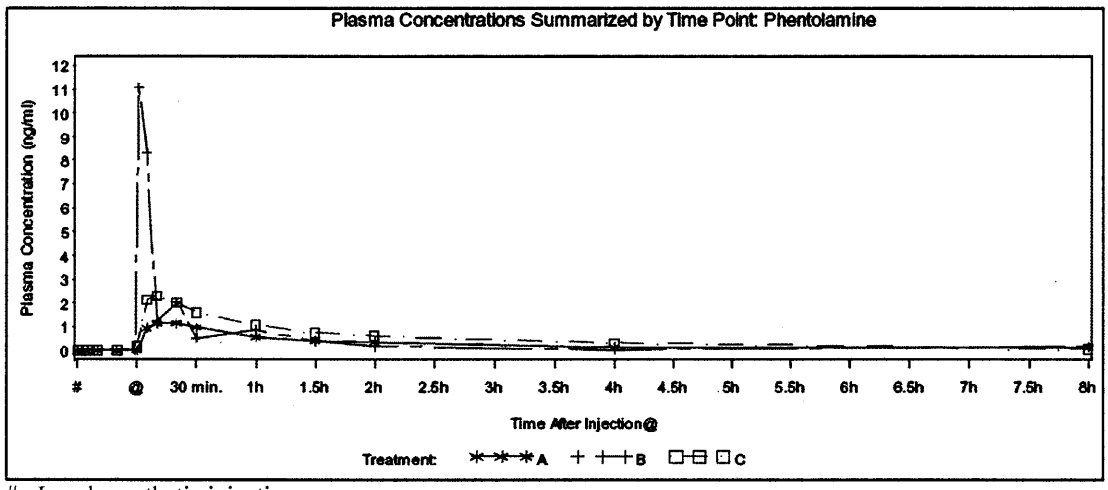
b(4)

	Local anesthetic*	NV-101	Comments
Trt A	1 cartridge	1 cartridge (0.4 mg)	- Lido/epi given as a supraperiosteal infiltration over the first molar in the maxilla. - NV-101 injected 30 minutes later where anesthetic was given.
Trt B		1 cartridge as Intravenous injection	
Trt C	4 cartridges	2 cartridges (0.8 mg)	- 2 cartridges of lido/epi as an inferior alveolar nerve block; 2 cartridges of lido/epi as a supraperiosteal infiltration over the first motar in the maxilla. These injections were administered in the same side of the face. - 2 cartridges of NV-101 injected (one cartridge at each site) 30 minutes later where anesthetic was given
Tr D	4 cartridges		Same as Treatment C, without NV-101

Notes:
1. 1 cartridge 2% lidocaine HCI with 1:100,000 epinephrine - 1.8 mL
2. 1 cartridge NV-101: 0.4 mg phentolamine in 1.7 mL

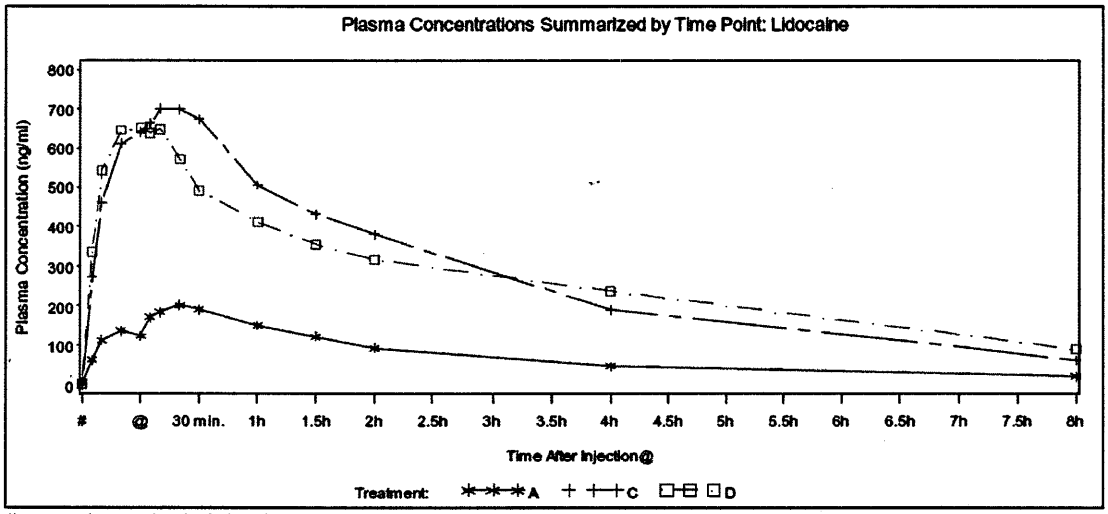
The following plasma profiles were obtained:

1) Phentolamine mean plasma concentration profile



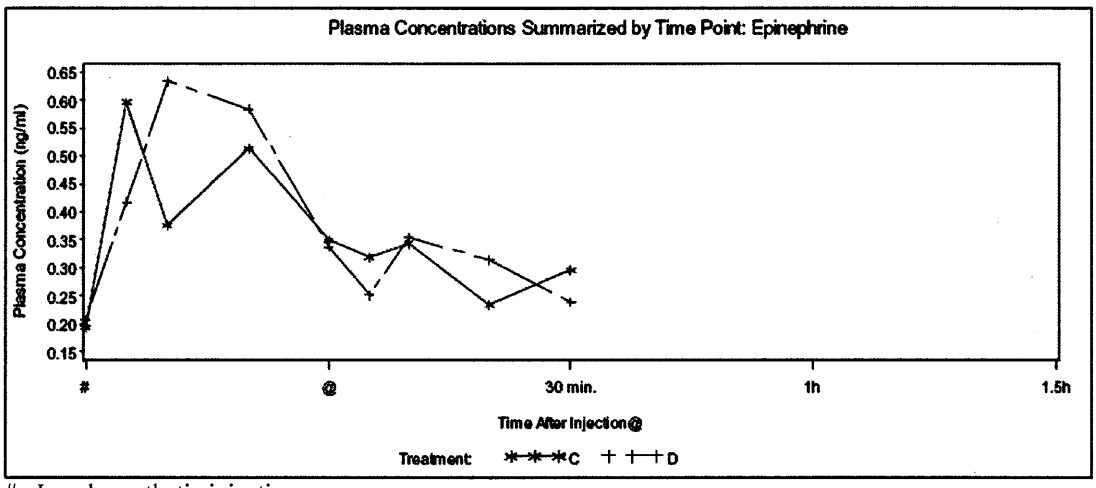
: Local anesthetic injection
@ : OraVerse injection (30 minutes after local anesthetic injection)

2) Lidocaine mean plasma concentration profile



: Local anesthetic injection
@ : OraVerse injection (30 minutes after local anesthetic injection)

3) Epinephrine mean plasma concentration profile



: Local anesthetic injection

@ : OraVerse injection (30 minutes after local anesthetic injection)

[redacted]

b(4)

The following PK parameters were obtained:

Table 3: Pharmacokinetic Parameters of Phentolamine, Lidocaine, and Epinephrine in Study NOVA 04-PK

Parameter	Phentolamine[a]			Lidocaine[b]			Epinephrine[b]	
	A	B	C	A	C	D	C	D
C_{max} (ng/mL)								
Adjusted geometric mean	1.34	10.98	2.73	212.26	799.82	716.67	0.95	0.75
90% CI for C/D					(77.76, 103.24)		(89.17, 183.77)	
AUC_{last} (ng.hr/mL)								
Adjusted geometric mean	1.69	1.71	3.29	639.15	2371.71	2137.11	0.27	0.26
90% CI for C/D					(78.95, 102.85)		(71.37, 152.09)	
AUC_{inf} (ng.hr/mL)								
Adjusted geometric mean	2.88	2.76	4.58	736.46	2602.95	2533.72	0.55	0.41
90% CI for C/D					(81.84, 115.78)		(55.59, 328.19)	
T_{max} (hr:min)								
Adjusted mean (± SE)	00:15 (±00:02)	00:07 (±00:03)	00:11 (±00:01)	00:50 (±00:03)	00:43 (±00:04)	00:28 (±00:03)	00:22 (±00:05)	00:20 (±00:05)
95% CI for C/D					(00:03, 00:25)		(-00:08, 00:12)	
$t_{1/2}$ (hr:min)								
Adjusted mean (± SE)	03:08 (± 00:55)	02:24 (± 00:38)	02:14 (± 00:25)	02:42 (± 00:15)	02:21 (± 00:16)	03:02 (± 00:15)	00:27 (±00:15)	00:29 (±00:16)
95% CI for C/D					(-01:26, 00:03)		(-01:40, 01:36)	
Cl (L/hr)								
Adjusted mean (± SE)	160.93 (± 24.02)	175.49 (± 30.36)	203.64 (± 36.21)	50.34 (± 4.49)	56.45 (± 4.70)	60.10 (± 4.50)	147.92 (± 27.81)	206.33 (±28.30)
95% CI for C/D					(-16.85, 9.54)		(-107, -9.44)	
Vd (L)								
Adjusted mean (± SE)	470.61 (± 62.72)	441.99 (± 83.68)	499.68 (± 60.08)	182.16 (± 13.77)	191.62 (± 14.24)	236.70 (± 13.80)	76.06 (±20.79)	97.06 (±22.50)
95% CI for C/D					(-76.51, -13.66)		(-151, 109.2)	

Source: Table 26, Table 27.1, Table 27.2, and Table 27.3 in CSR NOVA 04-PK, Section 5.3.3.1

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; Cl, clearance; C_{max}, maximum concentration; SE, standard error; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vd, volume of distribution

[a] No NV-101 was administered in treatment D.

[b] No local anesthetic/vasoconstrictor was administered in treatment B.

Notes: Unadjusted mean values are presented for phentolamine; adjusted LS means are presented for lidocaine and epinephrine. The 4-hour phentolamine value of [redacted] for treatment B for subject PK-01-16 and the 30-minute epinephrine value of [redacted] for treatment D for subject PK-01-19 were regarded as outliers and treated as missing in the PK calculations, figures, and parameter estimates. Estimation of phentolamine pharmacokinetic parameters using log concentrations was also performed to see if there was a marked effect of the sharp peak in phentolamine concentration.

b(4)

Phentolamine PK parameters:

a) The phentolamine Cmax values for Treatments A and C were dose-proportional. The phentolamine Cmax value for Treatment B (iv injection) was 8 times larger than the value for Treatment A.
b) The phentolamine AUClast and AUCinf values were dose proportional, with Treatments A and B similar in value, and Treatment C approximately twice the value of Treatments A and B.
c) The phentolamine Tmax was earlier for Treatment B (7 minutes) than for Treatments A (15 minutes) or C (11 minutes).
d) The phentolamine t1/2, CL, and Vd values were similar for Treatments A, B, and C.
e) Phentolamine was completely bioavailable after intraoral injection (Treatment A) (104% or 111%, using linear or log trapezoidal methods, respectively, for AUC calculation, compared to its bioavailability after intravenous injection (Treatment B).

Lidocaine PK parameters:

a) The lidocaine Cmax, AUClast and AUCinf values were all dose proportional, with similar values for Treatments C and D, and values for Treatment A that were approximately one-fourth the values of Treatments C and D.
b) The lidocaine t1/2 and CL values were similar for Treatments A, C, and D.
c) The lidocaine Vd value was statistically significantly smaller in Treatment C than in Treatment D.

d) The observed difference in lidocaine Vd, 192 liters in Treatment C and 237 liters in Treatment D, although statistically significant, is not clinically meaningful because neither Cmax nor AUC values differed significantly between these two treatments.

Epinephrine PK parameters:

a) Treatments C and D were evaluated for epinephrine PK parameters. (No local anesthesia was administered in Treatment B, and it was felt that the epinephrine concentrations resulting from the injections in Treatment A might be so low that they would not be discernable from endogenous epinephrine.)
b) The epinephrine Cmax, Tmax, AUClast, AUCinf, t1/2 and Vd values were all similar among treatment groups.
c) The epinephrine CL for Treatment C was statistically significantly smaller than the epinephrine CL for Treatment D. The decreased CL of epinephrine in Treatment C relative to Treatment D, although statistically significant, is not considered to be clinically meaningful. Epinephrine clearance could be calculated for only 8 of the 16 subjects and might thus be a biased estimate of epinephrine clearance.

[redacted] PK parameters: The plasma concentrations of [redacted] were almost entirely below the limit of quantitation. Therefore, PK parameters were not estimated for [redacted] b(4)

All causalities (treatment-related) Treatment-Emergent AEs occurring in at least 2 subjects after at least 1 treatment (number of subjects):

Adverse Event	Study Treatment A N = 16	B N = 16	C N = 16	D N = 16
(Preferred Term)				
Hypotension	5 (3*)	5 (3*)	2 (2*)	9 (3*)
Bradycardia	4 (2*)	2 (1*)	0 (0*)	0 (0*)
Headache	2 (1*)	1 (0*)	3 (1*)	0 (0*)
Paraesthesia	0 (0*)	0 (0*)	2 (1*)	4 (0*)
Facial pain	1 (0*)	0 (0*)	2 (0*)	0 (0*)
Dizziness	0 (0*)	0 (0*)	0 (0*)	2 (0*)
Pain in jaw	0 (0*)	0 (0*)	2 (0*)	0 (0*)

A = 1 cartridge of local anesthetic and 1 cartridge of NV-101; B = 1 cartridge of IV injection of NV-101;
C = 4 cartridges of local anesthetic and 2 cartridges of NV-101; D = 4 cartridges of local anesthetic.
*Treatment-related = related to study injection.

Study 05 (NOVA 05-PEDS-PK)

This was a Phase 1 open label study of OraVerse to evaluate the PK and safety in pediatric dental patients. The objectives of the study were 1) to evaluate the PK of OraVerse in pediatric dental patients who were undergoing dental procedures under general anesthesia or conscious sedation, to the extent possible with blood sampling

limited to the duration of the intravenous (IV) access line after NV-101 administration and 2) to evaluate the safety of OraVerse in pediatric dental patients as measured by the incidence and severity of adverse events and concomitant medications. Plasma concentrations of phentolamine and lidocaine were assayed with a validated LC/MS/MS method.

	Local anesthetic*	NV-101	Comments
Treatment A 15 - 30 kg	1/2 cartridges	1/2 cartridges (0.2 mg)	NV-101 was administered by submucosal injection approximately 30 minutes after the injection of local anesthetic (2% lidocaine with 1:100,000 epinephrine) and completion of the dental procedure using the same location and same technique used for the administration of local anesthetic.
Treatment B ≥ 30 kg	1 cartridge	1 cartridge (0.4 mg)	

Notes:
1. 1 cartridge 2% lidocaine HCl with 1:100,000 epinephrine - 1.8 mL
2. 1 cartridge NV-101: 0.4 mg phentolamine in 1.7 mL

Subject Disposition Summarized by Age Group and Treatment

	AGE Group						Overall N=19
	3 – 6 years		**7 – 11 years**		**12 – 17 years**		
NV-101 Dose Group	0.2 mg N=6	0.4 mg N=0	0.2 mg N=2	0.4 mg N=4	0.2 mg N=0	0.4 mg N=7	
Number of subjects	6	-	2	4	-	7	19

OraVerse doses by body weight:

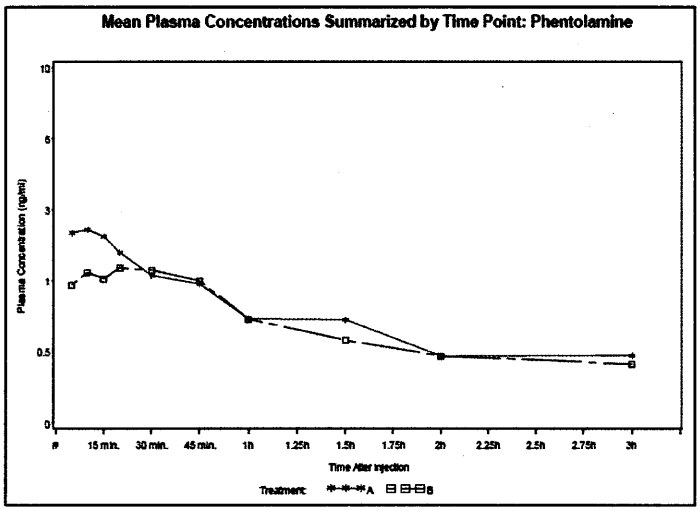
OraVerse Dose = 0.2 mg			OraVerse Dose = 0.4 mg		
Subject I.D.	Body Weight (kg)	Weight/Weight Dose (mg/kg)	Subject I.D.	Body Weight (kg)	Weight/Weight Dose (mg/kg)
01-001	20	0.0100	**03-001**	**127**	**0.0031**
01-002	17	0.0118	03-002	30	0.0133
01-003	16	0.0125	03-003	67	0.0060
01-004	25	0.0080	03-004	50	0.0080
02-001	24	0.0083	03-005	48	0.0083
02-002	21	0.0095	03-006	78	0.0051
02-003	16	0.0125	03-007	49	0.0082
03-012	26	0.0077	03-008	41	0.0098
			03-009	36	0.0111
			03-010	47	0.0085

			03-011	37	0.0108
Mean	20.625	0.0100	Mean	55.455	0.0084
Range	16-26	0.0077-0.0125	Range	**30-127**	0.0031-0.0133

The following profiles were obtained:

1) Phentolamine mean plasma concentration profile

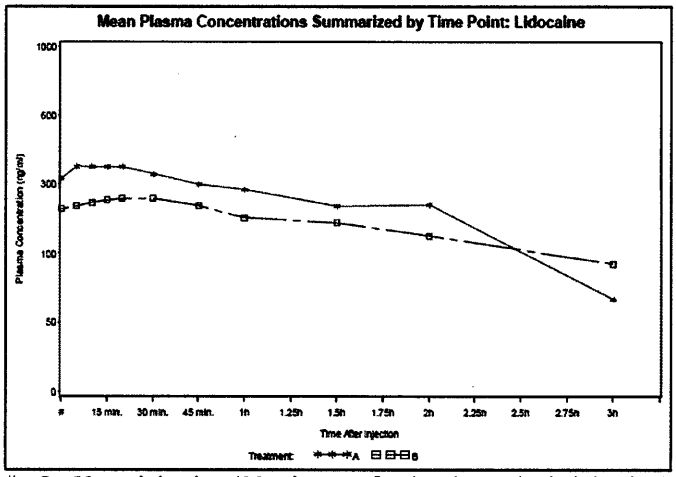
The mean phentolamine Cmax plasma concentration in the 0.4-mg dose group was nearly half the mean in the 0.2-mg group from 5 to 15 minutes after study drug administration. However, by 30 minutes after study drug administration, the mean plasma concentrations in the two groups were nearly identical and remained similar through the 2-hour sampling point.



: OraVerse injection (30 minutes after local anesthetic injection)

2) Lidocaine mean plasma concentration profile

The mean plasma concentration of lidocaine in the 0.4-mg dose group was less than the mean in the 0.2-mg group from immediately prior to OraVerse injection through the 2-hour sample. Lidocaine plasma concentrations increased after OraVerse injection, peaking at 20-30 minutes after dosing, then declined.



: OraVerse injection (30 minutes after local anesthetic injection)

The following PK parameters were obtained from the study:

PK parameters for phentolamine:

Individual PK parameters:

Subject ID	Peak Plasma Concentration (ng/mL)	Time to Peak Plasma Concentration (HH:MM)	Area under the Curve to the Last Measurable Concentration (ng.hr/mL)	Area under the Curve Extrapolated to Time Infinity (ng.hr/mL)	Elimination Half-Life (HH:MM)	Total Body Clearance (liters/hr)	Volume of Distribution (liters)
400-01-001	[redacted]	0:15	2.33	3.13	1:20	63.99	[redacted]
400-01-002		0:05	2.59	6.49	3:42	30.83	
400-01-003		0:05	1.80	2.32	1:22	86.27	
400-01-004		0:10	1.79	2.44	1:07	82.08	
400-02-001		0:15	1.13				
400-02-002		0:10	1.58	3.08	3:50	64.92	
400-02-003		0:10	3.16	4.66	1:37	42.93	
400-03-012		0:15	1.76	4.93	4:47	40.54	

b(4)

Subject ID	Peak Plasma Concentration (ng/mL)	Time to Peak Plasma Concentration (HH:MM)	Area under the Curve to the Last Measurable Concentration (ng.hr/mL)	Area under the Curve Extrapolated to Time Infinity (ng.hr/mL)	Elimination Half-Life (HH:MM)	Total Body Clearance (liters/hr)	Volume of Distribution (liters)
400-03-001	[redacted]	0:20	1.84	2.68	1:42	149.53	[redacted]
400-03-002		0:45	2.76	4.12	2:00	96.98	
400-03-003		0:20	1.95	2.59	1:39	154.17	
400-03-004		0:10	1.35	1.76	1:08	227.17	
400-03-005		0:45	2.17	6.35	5:16	62.95	
400-03-006		0:20	1.89	3.00	2:09	133.12	
400-03-007		0:30	1.87	2.93	1:52	136.63	
400-03-008		0:05	1.66	2.23	1:38	179.62	
400-03-009		0:05	1.47	2.72	1:38	147.04	
400-03-010		0:30	1.28				
400-03-011		0:10	2.18	11.57	10:51	34.56	

b(4)

Overall PK parameters:

	OraVerse Dose Group	
	0.2 mg N=8	0.4 mg N=11
Peak plasma concentration (Cmax), ng/mL		
Geometric Mean	2.60	1.47
95% CI	(1.73, 3.97)	(1.26, 1.76)
Time to peak plasma concentration (Tmax), HH:MM		
Mean (±SE)	0:10 (±0:01)	0:21 (±0:04)
95% CI	(0:07, 0:14)	(0:12, 0:31)
AUC1 to last measurable concentration (AUClast), ng hr/mL		
Geometric Mean	1.93	1.81
95% CI	(1.48, 2.55)	(1.57, 2.14)
AUC1 extrapolated to time infinity (AUCinf), ng hr/mL		
Geometric Mean	3.62	3.39
95% CI	(2.44, 5.29)	(1.88, 6.11)
Elimination half-life (t1/2), HH:MM		
Mean (±SE)	2:32 (±0:34)	2.59 (±0.56)
Median (min, max)	1:37 (1:07, 4:47)	1:47 (1:08, 10:51)
95% CI	(1:08, 3:56)	(0:51, 5:08)
Total body clearance (CL), L/hr		
Mean (±SE)	58.79 (±8.06)	132.18 (±17.59)
95% CI	(39.07, 78.52)	(92.38, 171.98)
Volume of distribution (Vd), L		
Mean (±SE)	190.56 (±35.69)	396.50 (±22.98)
95% CI	(103.23, 277.89)	(344.52, 448.49)

- This difference in dose level was not reflected in AUC values for the two groups as these parameters were approx. equal between the groups. Cmax values were, however, lower in the heavier-weight group.
- The greater mean Vd in the 0.4 mg dose group is consistent with the greater mean body weight in this dose group.
- The greater mean CL in the 0.4 mg dose group is consistent with the greater dose and similar mean AUC in this dose group.
- The mean peak plasma concentration (Cmax) of the 0.4 mg dose group was less than that of the 0.2-mg NV-101 dose group. The AUClast and AUCinf were similar in the 2 dose groups.
- The mean elimination half-life (t1/2) was similar in the 0.4-mg dose group and 0.2-mg group, and the median values in the 2 groups were nearly identical. The

mean total body clearance (CL) and mean volume of distribution (Vd) were noticeably larger in the 0.4-mg group than in the 0.2-mg group.

The following table contains incidence of treatment-related adverse events. The OraVerse appears to be tolerated in the pediatric subjects.

Incidence of Treatment-Related Adverse Events

	NV-101 Dose Group		Overall N=19
	0.2 mg N=8	0.4 mg N=11	
Number of adverse events	0	3	3
Gastrointestinal disorders	0 (0.0)	1 (9.1)	1 (5.3)
Vomiting	0 (0.0)	1 (9.1)	1 (5.3)
Injury, poisoning, and procedural complications	0 (0.0)	1 (9.1)	1 (5.3)
Oral pain	0 (0.0)	1 (9.1)	1 (5.3)
Nervous system disorders	0 (0.0)	1 (9.1)	1 (5.3)
Headache	0 (0.0)	1 (9.1)	1 (5.3)

2.2.3.3 What information is available to assess linearity?

After 0.4 and 0.8 mg OraVerse intraoral submucosal injections, the phentolamine Cmax and AUC values were dose-proportional. (Study 04)

2.2.3.4 What is the bioavailability from the local tissue injection?

The absolute bioavailability of phentolamine from OraVerse was 104% after intraoral submucosal injection compared to intravenous administration (Study 04).

2.2.3.5 What other clinical pharmacology information is available of phentolamine?

Metabolism:

According to the literature information phentolamine is extensively metabolized primarily by conjugation or by hydroxylation conjugation and excreted by urinary route. Following oral ingestion of phentolamine mesylate tablets, the reported phentolamine half-life is 5 to 7 hours and is excreted primarily in the urine (80%) and feces (20%). The main metabolite of phentolamine found in both human plasma and urine was reported to be [redacted] (Godbillon et al. 1981). b(4)

According to the Regitine Injection Labeling, phentolamine has a half-life of 19 minutes and approximately 10% to 13% of an intravenous dose is recovered in the urine unchanged.

Hepatic Impairment:

Once phentolamine reaches the general circulation, phentolamine is metabolized primarily by conjugation or by hydroxylation conjugation. It is not likely that the hepatic enzymatic system will play a role in metabolizing phentolamine. Additionally, since OraVerse will be used in a single injection setting, there will be no dosage adjustment warranted in patients with hepatic impairment.

Renal Impairment:

Phentolamine and its metabolite(s) excreted by urinary route. Since OraVerse will be used in a single injection setting, there will be no dosage adjustment in patients with renal impairment.

Elderly:

No pharmacokinetic studies were performed in elderly population. Elderly subjects may have reduced liver or kidney functions and may require reduced dose. However, as stated above, due to the single dose usage, a dose adjustment may not be necessary in elderly subjects.

There were 76 elderly subjects (55 and 21 were age 65 and over and age 75 and over, respectively) in the clinical efficacy and safety studies. There were no overall differences in effectiveness or safety was observed between elderly subjects and younger subjects.

2.3 Intrinsic Factors

2.3.1 What is the status of pediatric studies and/or any pediatric plan for study?

The Applicant requests a partial waiver to assess the safety and efficacy of OraVerse in newborn, birth to 1 month of age, 1 month to 2 years of age, in accordance with 21 CFR 314.55(c)(2). The basis for this waiver request is that studies are impossible or highly impractical because the number of pediatric patients is too small.

In general, the earliest a child has the first tooth erupt is approximately 5 months of age (The American Academy of Pediatric Dentistry, AAPD, 2003b). The range of ages when the first tooth erupts is between 4 to 13 months. The various organizations currently

recommend that children receive their first dental evaluation within the first year of life (AAPD 2003a, Erickson et al, 1997).

1. Pediatric age group(s) included in waiver request: Newborns and birth to 1 month of age

Newborns (birth to 1 month of age) have no teeth, and therefore no need for administration of a local anesthetic containing vasoconstrictor prior to a dental procedure. The number of pediatric patients in this subgroup (newborn, birth to 1 month) would be virtually non-existent.

2. Pediatric age group(s) included in waiver request: Infants (1 month to 2 years of age)

For infants with teeth up to age 2, most dental visits are "wellness visits" where no dental procedure is performed. Therefore, no local anesthetic containing a vasoconstrictor would be administered (AAPD 2004; AAPD 2005). Studies in this subgroup (infants, 1 month to 2 years) would be highly impractical due to the small number of pediatric patients.

*American Academy of Pediatric Dentistry (AAPD), American Dental Association, American Public Health Association, Association of State and Territorial Dental Directors, California Dental Association, and California Society of Pediatric Dentists

2.3.2 What factors influence phentolamine exposure?

The relationship between OraVerse exposure and the body weight was evaluated. In adults, no significant relationships were found between body weight and Cmax or AUCinf values (Study 04).

In pediatric subjects (Study 05), OraVerse was dosed based on the subject's body weight, based on the preliminary information from a Phase 2 study (Study NOVA 03-001) in which doses of 0.4 mg and 0.8 mg were administered to adults and adolescents weighing 45 to 115 kg. In Study 05, pediatric subjects weighed at least 15 kg. A significant correlation ($p < 0.01$) was found between body weight and Cmax values among subjects weighing 15 to 30 kg and dosed with 0.2 mg NV-101.

AUC values of the pediatric subjects doses with 0.2 and 0.4 mg were within the range of AUC values observed in adults dosed with 0.8 and 0.4 mg, respectively. Therefore, it is considered justified to recommend administration of 0.2 mg NV-101 for subjects > 15 kg.

2.4 Extrinsic Factors

2.4.1 Are there any lidocaine-phentolamine interaction?

Administration of phentolamine delayed lidocaine Tmax (mean values of 43 and 28 minutes for Treatments C and D, respectively). [redacted] No other parameters were affected. b(4)

2.4.2 Are there any epinephrine-phentolamine interaction?

OraVerse minimally increased epinephrine Cmax and AUC. However, this increase may not be clinically significant.

2.4.3 Are there any interactions between other local anesthetics and phentolamine expected?

For the three local anesthetics evaluated in the Phase 3 studies, no phentolamine-local anesthetic drug interaction is predicted. Phentolamine is extensively metabolized primarily by conjugation or by hydroxylation conjugation. Local anesthetics are metabolized by esterases or by oxidative N-dealkylation and hydroxylation of amide linkage.

Articaine

Articaine is unique among local anesthetics because it contains a thiophene group, and also because it contains both ester and amide groups. The major metabolism of Articaine is due to plasma and tissue esterases (e.g., pseudocholinesterase (90-95%)) follow by minimal amide group allows hepatic metabolism (5-10%).

Prilocaine

Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including ortho-toluidine and N-n-propylalanine. It is not metabolized by plasma esterases.

Mepivacaine

Mepivacaine is mostly metabolized in the liver by amidases, hydroxylation and N-demethylation, to various metabolites, e.g., to phenols, which are excreted almost exclusively as their glucuronide conjugates, and the N-demethylated compound (2',6'-pipecoloxylidide). It is not metabolized by plasma esterases.

2.5 General Biopharmaceutics – Not applicable

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Plasma samples from these studies were analyzed for phentolamine, [redacted] lidocaine, and epinephrine concentrations using validated methods by liquid chromatography/tandem mass spectroscopy (LC/MS/MS). The LC/MS/MS assay quantitation range is validated over a range from 0.2 to 500 ng/mL for phentolamine, lidocaine and [redacted] (Calibration standards for phentolamine, lidocaine, and [redacted] were 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200 and 500 ng/mL), and, range from 0.05 to 50 ng/mL for epinephrine (0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10, and 50 and 500 ng/mL). For all moieties 3 QC concentrations were prepared. b(4)

The typical results for the QC samples in human plasma are as follows:

Phentolamine

Curve number	QC at 0.6 ng/mL	QC at 12 ng/mL	QC at 238 ng/mL
Mean	0.57	12.5	253
% Dev	-4.2	5.4	6.2
CV %	7.9	4.6	1.2

lidocaine

Curve number	QC at 0.6 ng/mL	QC at 12 ng/mL	QC at 248 ng/mL
Mean	0.6	12.3	260
SD	-3.6	-0.9	4.8
CV %	15.2	8.1	7.3

[redacted] b(4)

epinephrine

Curve number	QC at 0.1 ng/mL	QC at 0.52 ng/mL	QC at 5.19 ng/mL
Mean	0.11	0.56	5.4
SD	6.2	8.6	4
CV %	2.9	-	8.3

3 Detailed Labeling Recommendations

Texts are deleted (~~crossed-out~~) and new wording added in **red** fonts, as follows:

b(4)

b(5)

[redacted]

b(4)

b(5)

[redacted]

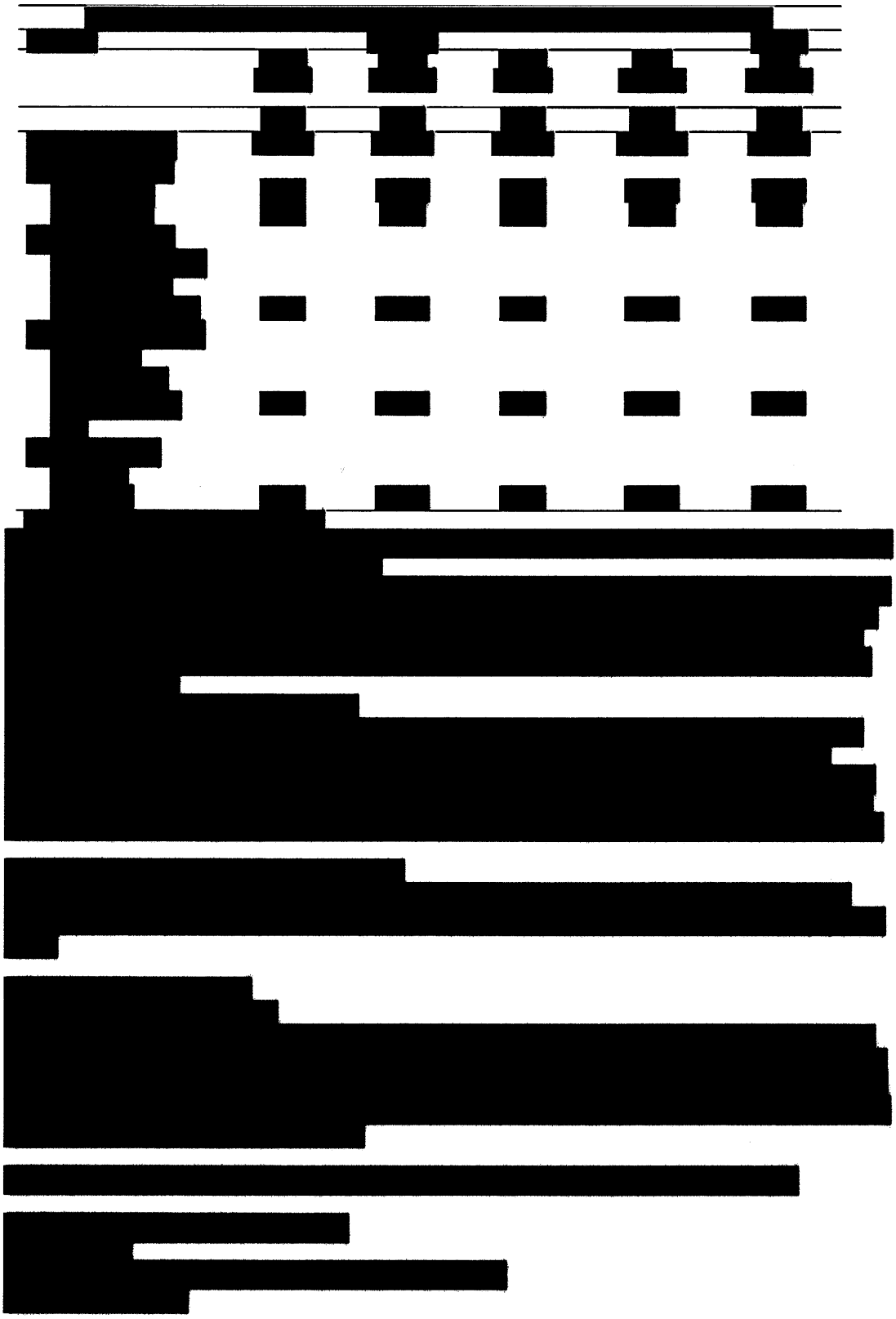
[redacted]

[redacted]

[redacted]

b(4)

b(5)



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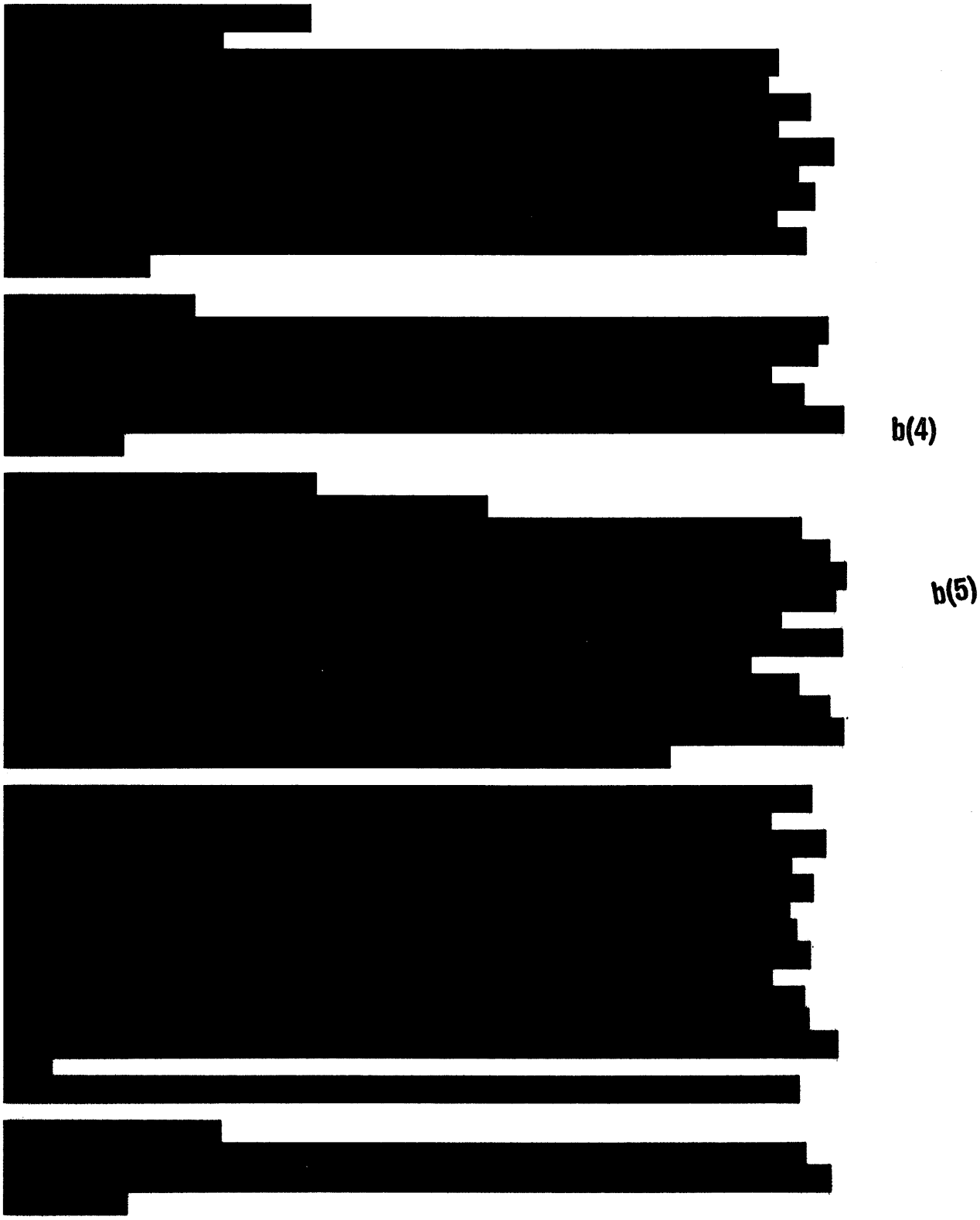
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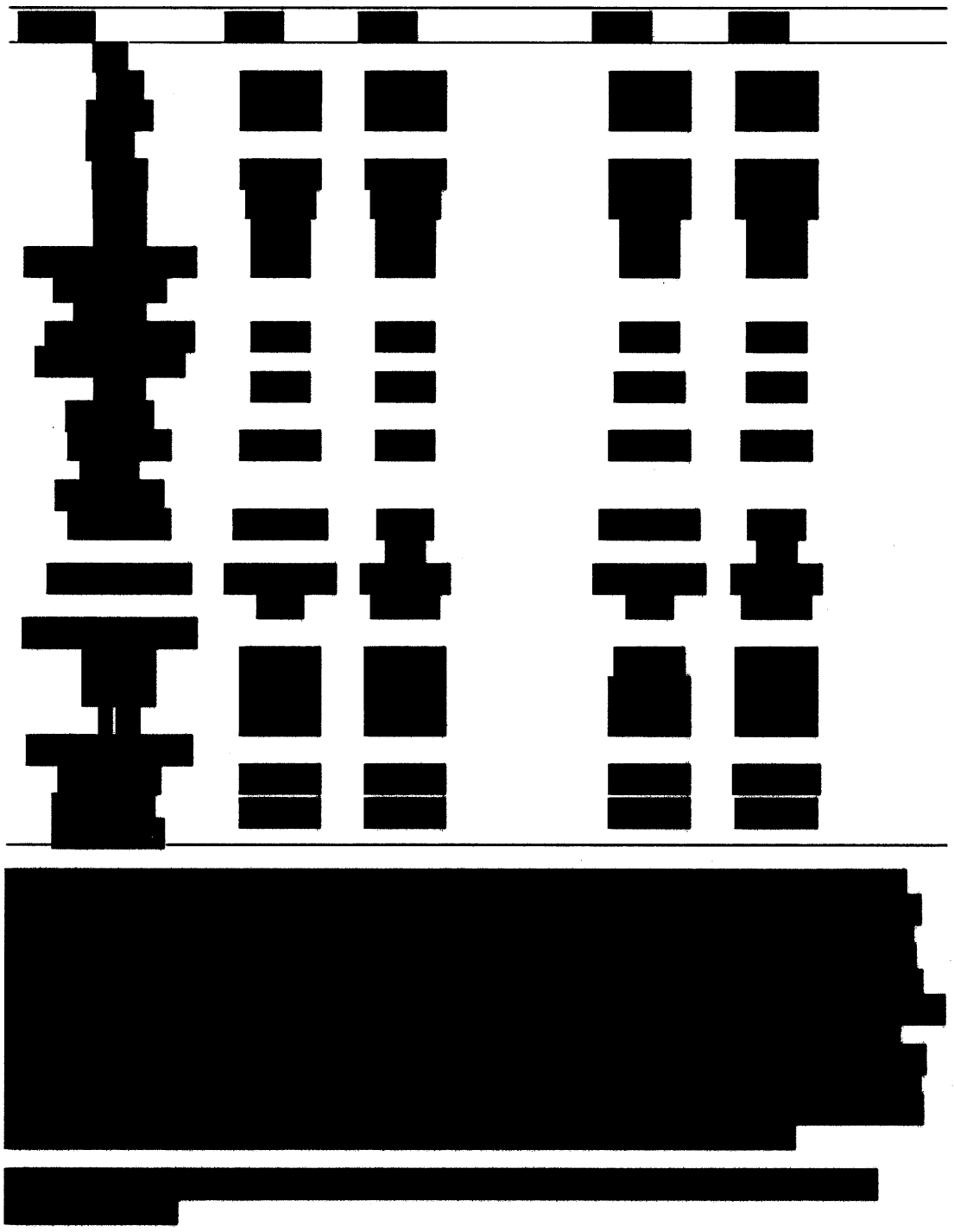

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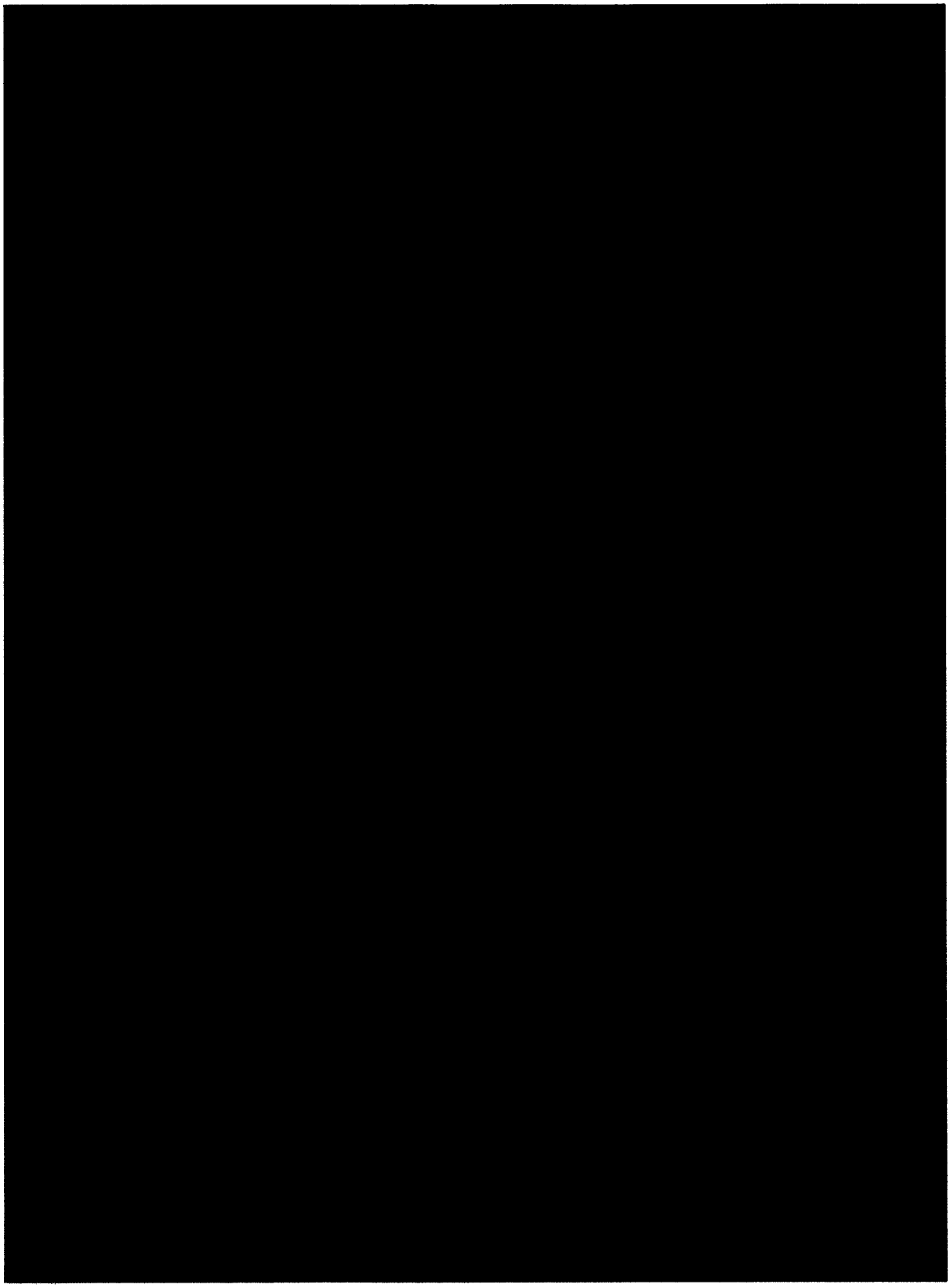

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4.2 Individual study review

Study NOVA 04-PK

Title: A Phase 1, Open-Label Study of NV-101 for Pharmacokinetics, Pharmacodynamics, and Safety in Healthy Adult Volunteers

Study Objectives:

1) to determine the PK of phentolamine administered by intraoral and intravenous (IV) injections; (2) to determine the effects of NV-101 by intraoral injection on the PK of lidocaine and epinephrine administered by intraoral injection; (3) to evaluate the pharmacodynamics (PD) of NV-101 as measured by time to normal sensation of the lip(s) in Treatments A, C, and D; and (4) to evaluate the safety and tolerability of NV-101.

Study Design: This was a single center, open-label, 4-treatment, 4-period, crossover study designed to evaluate the PK, PD, and safety of HV-101 when administered as an intraoral injection following local anesthesia with 2% lidocaine HCI with 1:100,000 epinephrine and when administered as an IV injection over 1 minute.

Sequence #	First Period	Second Period
1	AD	BC
2	CB	DA
3	DA	CB
4	BC	AD

1) Sixteen healthy adult volunteers were enrolled. Subjects received 2 of the 4 treatments during each of 2 Clinic admissions.
2) Each admission lasted for 2 full days (2 overnights). Subjects were admitted to the clinical testing facility (Clinic) on the first morning of each 2-day visit and remained in the Clinic until the morning after the second treatment. An interval of at least 24 hours separated each treatment.
3) Subjects were contacted by telephone 2 days after discharge from each Clinic admission (Day 4, where Day 1 = the first day of that Clinic admission) to inquire about adverse events and concomitant medication use.
4) Each subject received all 4 treatments (A, B, C, and D) in 1 of 4 sequences. The 4 treatments were the following:

	2% lido/epi*	NV-101	Comments
Treatment A	1 cartridge, 1.8 mL	1 cartridge, 0.4 mg phentolamine	- Lido/epi given as a supraperiosteal infiltration over the first molar in the maxilla. - NV-101 injected 30 minutes later where anesthetic was given.
Treatment B		1 cartridge as Intravenous	
Treatment C	4 cartridges, 7.2 mL	2 cartridges 0.8 mL phentolamine	- 2 cartridges of lido/epi as an inferior alveolar nerve block; 2 cartridges of lido/epi as a supraperiosteal infiltration over the first motar in the maxilla. These injections were administered in the same side of the face. - 2 cartridges of NV-101 injected (one cartridge at each site) 30 minutes later where anesthetic was given
Treatment D	4 cartridges, 7.2 mL		Same as Treatment C, without NV-101

Notes:
1. 1 cartridge 2% lidocaine HCI with 1:100,000 epinephrine - 1.8 mL
2. 1 cartridge NV-101: 0.4 mg phentolamine in 1.7 mL

Thus, the following comparison is carried out: Compare A vs. B, Compare A vs. C, and Compare C vs. D

Study Population and Criteria for Inclusion/Exclusion: Healthy subjects, between the ages of 18 to 65 years.

Inclusion criteria:

1. Male or female between 18 and 65 years of age; 2. Body weight between 55 to 120 kg; 3. Subjects were to be healthy as determined based on medical history, physical examination, and vital signs; 4. Subjects were to have white blood count and prothrombin time within normal limits; 5. Subjects were to have no

clinically significant abnormalities of hemoglobin, platelets, albumin, BUN, creatinine, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, calcium, phosphorus, or thyroid stirnulating hormone (TSH); 6. Female subjects of childbearing potential were to have negative urine pregnancy tests. (Women of childbearing potential included all women except for those whose menstrual periods had not occurred for >1 year after menopause, who were surgically sterilized, or who had had a hysterectomy.); 7. Subjects were to have electrocardiogram results within normal limits; 8. Subjects were to be able to understand and sign the informed consent document, and be able to communicate with the investigator, understand, and comply with, the requirements of the protocol.

Exclusion criteria:

1. History or presence of any condition that would contraindicate the use of lidocaine or epinephrine; 2. Clinically relevant surgical history, e.g., maxillofaciaf procedures that would alter blood supply or innervation; 3. Subjects who took concomitant medications including nonselective beta blockers (e.g., propranolol) or tricyclic antidepressants; or used opioid or opioid-like analgesics within 52 hours of the procedure; 4. Subjects with any of the following concurrent conditions: cardiac arrhythmias, unstable angina, uncontrolled hypertension, uncontrolled hyperthyroidism, significant infection or inflammatory process (systemic or oral cavity requiring prescribed treatment), or acute gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea); 5. History of alcoholism and/or drug abuse within the last five years; 6. Allergy or intolerance to lidocaine, epinephrine, sulfites, phentolamine, or topical benzocaine; 7. Use of any investigational drug and/or participation in any clinical trial within 30 days of study drug administration; 8. Participation in any previous trial of phentolamine for reversal of local anesthesia; 9. Pregnant or lactating women; or women who were attempting to conceive (who were unwilling to use an effective method of contraception or abstinence for 2 days after study drug); 10. Subject with any condition that in the opinion of the investigator increased the risk to the subject of participating in this trial or decreased the likelihood of compliance with the protocol.

Treatments: NV-101 was manufactured by [redacted]) as a sterile, pyrogen-free, isotonic solution for administration in glass dental cartridges that delivered 0.4 mg phentolamine mesylate in 1.7 mL (per cartridge). The concentration of the active ingredient (phentolamine mesylate) in NV-101 was 0.235 mg/mL. The lot number of NV-101 used for this study was 3067. Local anesthetic was obtained by the site from a commercial supplier. b(4)

Pharmacokinetics (PK): Blood samples were drawn to assay for phentolamine, lidocaine, epinephrine, [redacted] Blood samples were drawn for PK analysis, starting immediately prior to first injection of local anesthetic (if given) or injection of NV-101, and ending 8.5 hours after the first injection of local anesthetic (if given) and/or 8 hours after injection of NV-101. Per protocol, only selected samples were assayed for epinephrine. PK parameters were estimated based on non- compartmental methods. b(4)

Samples:

• Treatment A: immediately prior to injection of anesthetic and at 5, 10, 20, 30 minutes (just prior to injection of f4V-101), at 35, 40, 50 minutes, and at 1.0, 1.5, 2.0, 2.5, 4.5, and 8.5 hours after injection of anesthetic (14 samples; 126 mL blood).

• Treatment B: immediately prior to IV injection of NV-101, at 1 minute (at the end of injection), at 5, 10, 20, 30 minutes, and at 1.0, 1.5, 2.0, 4.0, and 8.0 hours after injection of NV-101 (11 samples; 99 mL blood).

• Treatment C: immediately prior to the first injection of anesthetic, at 5, 10, 20, 30 minutes (just prior to injection of NV-101), at 35, 40, 50 minutes, and at 1.0, 1.5, 2.0, 2.5, 4.5, and 8.5 hours after the first injection of anesthetic (14 samples; 126 mL blood).

• Treatment D: immediately prior to first injection of anesthetic, at 5, 10, 20, 30, 35, 40, 50 minutes, and at 1.0, 1.5, 2.0, 2.5, 4.5, and 8.5 hours after the first injection of anesthetic (14 samples; 126 mL blood).

Assay:
The methods for the assay of phentolamine, lidocaine, epinephrine, [redacted]

b(4)

Pharmacodynamics (PD): The PD endpoints were the times to normal sensation in the upper lip, lower lip, and tongue in subjects who experienced numbness and/or tingling in these sites.

Safety: Safety assessments included adverse events, changes in vital signs (temperature, respirations, blood pressure, and pulse), clinically significant changes in cardiac rhythm as measured by Holter monitor recordings, and clinically significant changes in oraf cavity examinations.

Statistical Methods: Safety, PK, and PD data were summarized in tabular and/or graphical format by treatment.

1) The effect of NV-101 on the PK parameters of lidocaine and epinephrine was compared with an ANOVA model. A linear mixed effect model was used to analyze the data, where sequence, treatment, and period effects were deemed fixed, and subject effect (within sequence) was considered random. Restricted Maximum Likelihood Estimates (REML) was utilized as the estimation method, and the covariance matrix was assumed to have a standard variance components structure.
2) The comparison between **Treatment C and Treatment D** was made using the "ESTIMATE" statement of the SAS MIXED procedure performed on the log-transformed variables, and was based on the difference of Least-Square (LS) adjusted means and the standard error associated with this difference. The null hypothesis that the PK parameters of lidocaine and epinephrine were the same with and without subsequent treatment with NV-101 (comparing lidocaine and epinephrine PK after **Treatments C and D) was tested via the use of the "ESTIMATE" statement on log-transformed Cmax,** AUClast, and AUCinf. Treatment C and Treatment D were compared with respect to lidocaine and epinephrine Cmax, AUClast, and AUCinf, and by a 90% confidence interval on the ratio of geometric means by first constructing on the log scale a confidence interval on the difference of LS adjusted means, and then transforming the endpoints by anti-logarithm back to the original scale. For these 3 PK parameters, if the lower and upper limits of the confidence interval for the ratio of geometric means (C/D: expressed in %) were both within the interval [80%, 125%], it was concluded that there was no statistically significant difference between the treatments.
3) The comparisons between Treatment C and Treatment D for PK parameters other than C and AUC **were performed via the use of the "ESTIMATE" statement and were based on the difference of LS** adjusted means (C-D) and the standard error associated with this difference. For these comparisons, if the lower and upper limits of the 95% confidence interval on the difference in LS means included 0, it was concluded that there was no statistically significant difference between the treatments.
4) For lidocaine and epinephrine Cmax and AUC, LS adjusted geometric means, and the 90% confidence interval for the true mean ratio are presented. For other lidocaine and epinephrine PK parameters, the adjusted means and the 95% CI for the true difference in means are presented.
5) Descriptive statfstics, including arithmetic mean, median, standard deviation (SD), coefficient of variation (%CV), and range are also presented on the original (untransformed) scale.

Results

1. Demographic and Additional Baseline Characteristics

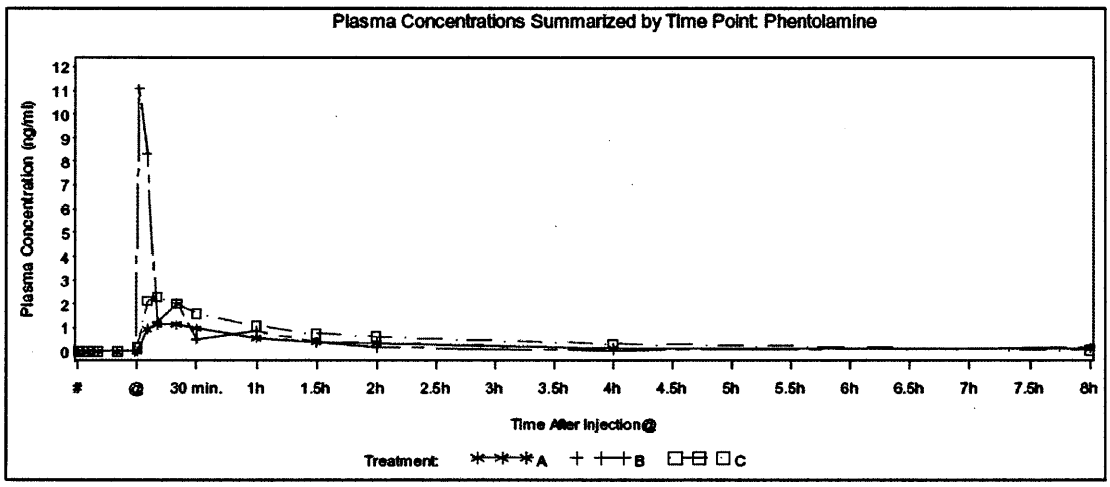
	Overall
Number of Subjects	16
Gender	
Male	7
Female	9
Race:	
White	16
Age (years):	
Mean (±SD)	24.3 (±7.6)
Range	18.0 – 50.0
Height:(inches)	
Mean ± SD	68.6 ±3.6
Range	63.0 – 76.0
Weight (lbs):	
Mean ± SD	163.2 ±21.4
Range	119.0 – 200.4

SD = Standard Deviation.

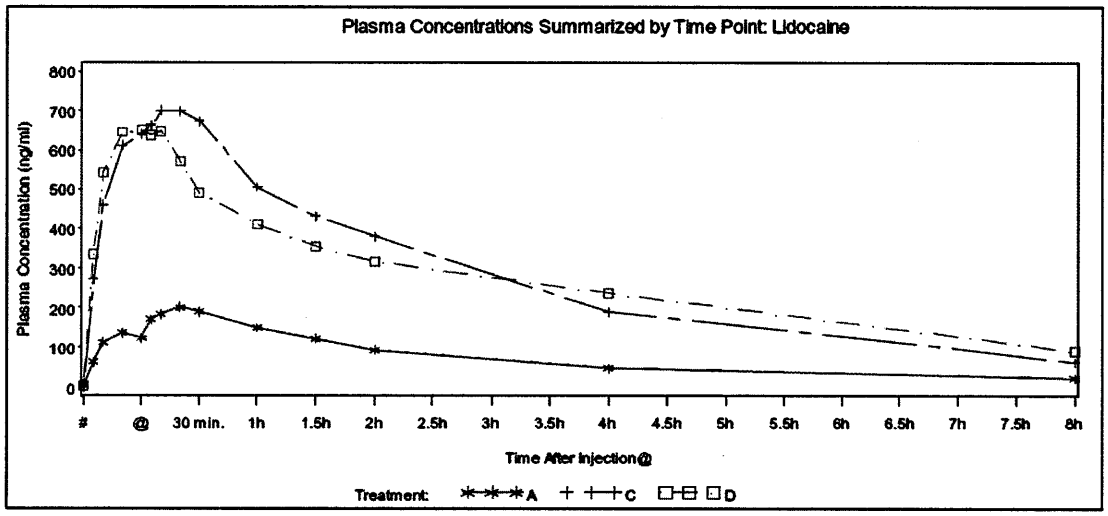
2. PK figures and tables

A. Profiles

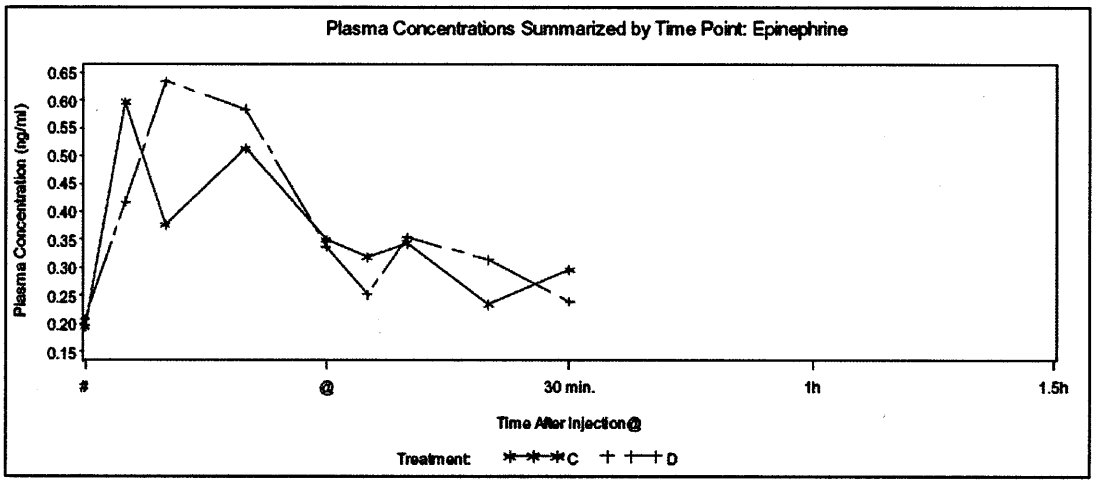
1) Phentolamine mean plasma concentration profile



2) Lidocaine mean plasma concentration profile



3) Epinephrine mean plasma concentration profile



[redacted] b(4)

Note: The plasma concentrations of [redacted] were almost entirely below the limit of quantitation. Therefore, PK parameters were not estimated for [redacted] b(4)

B. PK parameters:

Table 3: Pharmacokinetic Parameters of Phentolamine, Lidocaine, and Epinephrine in Study NOVA 04-PK

Parameter	Phentolamine[a]			Lidocaine[b]			Epinephrine[b]	
	A	B	C	A	C	D	C	D
C_{max} (ng/mL)								
Adjusted geometric mean	1.34	10.98	2.73	212.26	799.82	716.67	0.95	0.75
90% CI for C/D					(77.76, 103.24)		(89.17, 183.77)	
AUC_{last} (ng.hr/mL)								
Adjusted geometric mean	1.69	1.71	3.29	639.15	2371.71	2137.11	0.27	0.26
90% CI for C/D					(78.95, 102.85)		(71.37, 152.09)	
AUC_{inf} (ng.hr/mL)								
Adjusted geometric mean	2.88	2.76	4.58	736.46	2602.95	2533.72	0.55	0.41
90% CI for C/D					(81.84, 115.78)		(55.59, 328.19)	
T_{max} (hr:min)								
Adjusted mean (± SE)	00:15 (±00:02)	00:07 (±00:03)	00:11 (±00:01)	00:50 (±00:03)	00:43 (±00:04)	00:28 (±00:03)	00:22 (±00:05)	00:20 (±00:05)
95% CI for C/D					(00:03, 00:25)		(-00:08, 00:12)	
$t_{1/2}$ (hr:min)								
Adjusted mean (± SE)	03:08 (± 00:55)	02:24 (± 00:38)	02:14 (± 00:25)	02:42 (± 00:15)	02:21 (± 00:16)	03:02 (± 00:15)	00:27 (±00:15)	00:29 (±00:16)
95% CI for C/D					(-01:26, 00:03)		(-01:40, 01:36)	
Cl (L/hr)								
Adjusted mean (± SE)	160.93 (± 24.02)	175.49 (± 30.36)	203.64 (± 36.21)	50.34 (± 4.49)	56.45 (± 4.70)	60.10 (± 4.50)	147.92 (± 27.81)	206.33 (±28.30)
95% CI for C/D					(-16.85, 9.54)		(-107, -9.44)	
Vd (L)								
Adjusted mean (± SE)	470.61 (± 62.72)	441.99 (± 83.68)	499.68 (± 60.08)	182.16 (± 13.77)	191.62 (± 14.24)	236.70 (± 13.80)	76.06 (±20.79)	97.06 (±22.50)
95% CI for C/D					(-76.51, -13.66)		(-151, 109.2)	

Source: Table 26, Table 27.1, Table 27.2, and Table 27.3 in CSR NOVA 04-PK, Section 5.3.3.1

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; Cl, clearance; C_{max}, maximum concentration; SE, standard error; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vd, volume of distribution

[a] No NV-101 was administered in treatment D.

[b] No local anesthetic/vasoconstrictor was administered in treatment B.

Notes: Unadjusted mean values are presented for phentolamine; adjusted LS means are presented for lidocaine and epinephrine. The 4-hour phentolamine value of [redacted] for treatment B for subject PK-01-16 and the 30-minute epinephrine value of [redacted] for treatment D for subject PK-01-19 were regarded as outliers and treated as missing in the PK calculations, figures, and parameter estimates. Estimation of phentolamine pharmacokinetic parameters using log concentrations was also performed to see if there was a marked effect of the sharp peak in phentolamine concentration.

	Study Treatment (Phentolamine*)				Study Treatment (Lidocaine*)			Study Treatment (Epinephrine*)	
	A	B	B (Log)	C	A	C	D	C	D
Number of Subjects	16	16	16	15	16	15	16	15	16
C_{max} – ng/mL									
Adjusted Geometric mean	1.34	10.98	10.98	2.73	212.26	799.82	716.67	0.95	0.75
90% CI for C/D						(77.76, 103.24)		(89.17, 183.77)	
AUC_{last} – ng*hr/mL									
Adjusted Geometric mean	1.69	1.71	1.59	3.29	639.15	2371.71	2137.11	0.27	0.26
90% CI for C/D						(78.95, 102.85)		(71.37, 152.09)	
AUC_{inf} – ng*hr/mL									
Adjusted Geometric mean	2.88	2.76	2.59	4.58	736.46	2602.95	2533.72	0.55	0.41
90% CI for C/D						(81.84, 115.78)		(55.59, 328.19)	
T_{max} – HH:MM									
Adjusted Mean (±SE)	00:15 (±00:02)	00:07 (±00:03)	00:07 (±00:03)	00:11 (±00:01)	00:50 (±00:03)	00:43 (±00:04)	00:28 (±00:03)	00:22 (±00:05)	00:20 (±00:05)
95% CI for C-D						(00:03, 00:25)		(-00:08, 00:12)	
$t_{1/2}$ – HH:MM									
Adjusted Mean (±SE)	03:08 (±00:55)	02:24 (±00:38)	02:24 (±00:38)	02:14 (±00:25)	02:42 (±00:15)	02:21 (±00:16)	03:02 (±00:15)	00:27 (±00:15)	00:29 (±00:16)
95% CI for C-D						(-01:26, 00:03)		(-01:40, 01:36)	
CL – liters/hr									
Adjusted Mean (±SE)	160.93 (±24.02)	175.49 (±30.36)	184.99 (±31.30)	203.64 (±36.21)	50.34 (±4.49)	56.45 (±4.70)	60.10 (±4.50)	147.92 (±27.81)	206.33 (±28.30)
95% CI for C-D						(-16.85, 9.54)		(-107, -9.44)	
Vd – liters									
Adjusted Mean (±SE)	470.61 (±62.72)	441.99 (±83.68)	463.39 (±84.89)	499.68 (±60.08)	182.16 (±13.77)	191.62 (±14.24)	236.70 (±13.80)	76.06 (±20.79)	97.06 (±22.50)
95% CI for C-D						(-76.51, -13.66)		(-151, 109.2)	

[a] no phentolamine was administered in Treatment D

[b] no local anesthetic was administered in Treatment B

Unadjusted mean values are presented for phentolamine; adjusted LS means are presented for lidocaine and epinephrine.

Estimation of phentolamine PK parameters using log concentrations was also performed to see if there was a marked effect of the sharp peak in phentolamine concentration.

The Hour 4 phentolamine value of [redacted] for treatment B for subject PK-01-16 and the Minute 30 epinephrine value of [redacted] for treatment D for subject PK-01-19 were regarded as outliers and treated as missing in the PK calculations, figures, and parameter estimates.

b(4)

1) PK parameters for phentolamine

Table 26. Pharmacokinetic Parameter Estimates: Phentolamine

Parameter Statistic	Study Treatment A	B	B (Log)	C	D
Number of subjects - no.	16	16	16	15	NA
Peak plasma concentration - ng/mL					
Observed Mean (±SE)	1.32 (±0.13)	15.57 (±3.70)	15.57 (±3.70)	2.63 (±0.25)	NA
Geometric mean	1.34	10.98	10.98	2.73	NA
Area under the curve to the last measurable concentration - ng.hr/mL					
Observed Mean (±SE)	1.82 (±0.26)	2.42 (±0.54)	2.20 (±0.46)	3.54 (±0.51)	NA
Geometric mean	1.69	1.71	1.59	3.29	NA
Area under the curve extrapolated to time infinity - ng.hr/mL					
Observed Mean (±SE)	3.41 (±0.62)	3.45 (±0.76)	3.19 (±0.68)	5.26 (±0.82)	NA
Geometric mean	2.88	2.76	2.59	4.58	NA
Time to peak plasma concentration - HH:MM					
Observed Mean (±SE)	00:15 (±00:02)	00:07 (±00:03)	00:07 (±00:03)	00:11 (±00:01)	NA
Elimination half-life - HH:MM					
Observed Mean (±SE)	03:08 (±00:55)	02:24 (±00:38)	02:24 (±00:38)	02:14 (±00:25)	NA
Total body clearance - liters/hr					
Observed Mean (±SE)	160.93 (±24.02)	175.49 (±30.36)	184.99 (±31.30)	203.64 (±36.21)	NA
Volume of distribution - liters					
Observed Mean (±SE)	470.61 (±62.72)	441.99 (±83.68)	463.39 (±84.89)	499.68 (±60.08)	NA

2) PK parameters for lidocaine

Table 27.1. Pharmacokinetic Parameter Estimates: Lidocaine

Parameter Statistic	Study Treatment A	B	C	D
Number of subjects - no.	16	NA	15	16
Peak plasma concentration - ng/mL		NA		
Observed Mean (±SE)	218.19 (±10.26)		823.33 (±52.42)	767.93 (±71.93)
Adjusted geometric mean	212.26	NA	799.82	716.67
90% CI for C/D		NA	(77.76, 103.24)	
Area under the curve to the last measurable concentration - ng.hr/mL		NA		
Observed Mean (±SE)	644.49 (±26.69)		2397.52 (±121.15)	2249.71 (±138.65)
Adjusted geometric mean	639.15	NA	2371.71	2137.11
90% CI for C/D		NA	(78.95, 102.85)	
Area under the curve extrapolated to time infinity - ng.hr/mL		NA		
Observed Mean (±SE)	771.75 (±74.66)		2619.77 (±137.87)	2679.00 (±161.71)
Adjusted geometric mean	736.46	NA	2602.95	2533.72
90% CI for C/D		NA	(81.84, 115.78)	
Time to peak plasma concentration - HH:MM		NA		
Observed Mean (±SE)	00:50 (±00:05)		00:44 (±00:02)	00:29 (±00:02)
Adjusted mean (±SE)	00:50 (±00:03)	NA	00:43 (±00:04)	00:28 (±00:03)
95% CI for C-D		NA	(00:03, 00:25)	
Median		NA	00:49	00:30
P-value*		NA	0.0013	
Elimination half-life - HH:MM		NA		
Observed Mean (±SE)	02:42 (±00:20)		02:20 (±00:04)	03:05 (±00:14)
Adjusted mean (±SE)	02:42 (±00:15)	NA	02:21 (±00:16)	03:02 (±00:15)
95% CI for C-D		NA	(-01:26, 00:03)	
Total body clearance - liters/hr		NA		
Observed Mean (±SE)	50.75 (±3.18)		57.27 (±3.21)	59.01 (±6.35)
Adjusted mean (±SE)	50.34 (±4.49)	NA	56.45 (±4.70)	60.10 (±4.50)
95% CI for C-D		NA	(-16.85, 9.54)	
Volume of distribution - liters		NA		
Observed Mean (±SE)	180.56 (±9.75)		191.27 (±10.22)	236.74 (±17.86)
Adjusted mean (±SE)	182.16 (±13.77)	NA	191.62 (±14.24)	236.70 (±13.80)
95% CI for C-D		NA	(-76.51, -13.66)	

3) PK parameters for epinephrine

Table 27.2. Pharmacokinetic Parameter Estimates: Epinephrine

Parameter Statistic	Study Treatment A	B	C	D
Number of subjects - no.	NA	NA	15	16
Peak plasma concentration - ng/mL	NA	NA		
Observed Mean (±SE)			1.05 (±0.13)	0.90 (±0.17)
Adjusted geometric mean	NA	NA	0.95	0.75
90% CI for C/D	NA	NA	(89.17, 183.77)	
Area under the curve to the last measurable concentration - ng.hr/mL	NA	NA		
Observed Mean (±SE)			0.36 (±0.07)	0.38 (±0.09)
Adjusted geometric mean	NA	NA	0.27	0.26
90% CI for C/D	NA	NA	(71.37, 152.09)	
Area under the curve extrapolated to time infinity - ng.hr/mL	NA	NA		
Observed Mean (±SE)			0.78 (±0.13)	1.08 (±0.50)
Adjusted geometric mean	NA	NA	0.55	0.41
90% CI for C/D	NA	NA	(55.59, 328.19)	
Time to peak plasma concentration - HH:MM	NA	NA		
Observed Mean (±SE)			00:21 (±00:05)	00:20 (±00:03)
Adjusted mean (±SE)	NA	NA	00:22 (±00:05)	00:20 (±00:05)
95% CI for C-D	NA	NA	(-00:08, 00:12)	
Elimination half-life - HH:MM	NA	NA		
Observed Mean (±SE)			00:31 (±00:10)	00:39 (±00:16)
Adjusted mean (±SE)	NA	NA	00:27 (±00:15)	00:29 (±00:16)
95% CI for C-D	NA	NA	(-01:40, 01:36)	
Total body clearance - liters/hr	NA	NA		
Observed Mean (±SE)			113.25 (±19.20)	169.50 (±36.38)
Adjusted mean (±SE)	NA	NA	147.92(±27.81)	206.33(±28.30)
95% CI for C-D	NA	NA	(-107.39, -9.44)	
Volume of distribution - liters	NA	NA		
Observed Mean (±SE)			72.17 (±16.46)	85.12 (±22.55)
Adjusted mean (±SE)	NA	NA	76.06(±20.79)	97.06(±22.50)
95% CI for C-D	NA	NA	(-151.19, 109.21)	

C. Discussion

1). Phentolamine PK parameters:

a) Treatments A, B, and C were evaluated for phentolamine PK parameters.
b) The phentolamine Cmax values for Treatments A and C were dose-proportional. The phentolamine Cmax value for Treatment B (iv injection) was 8 times larger than the value for Treatment A.
c) The phentolamine AUClast and AUCinf values were dose proportional, with Treatments A and B similar in value, and Treatment C approximately twice the value of Treatments A and B.
d) The phentolamine Tmax was earlier for Treatment B (7 minutes) than for Treatments A (15 minutes) or C (11 minutes).
e) The phentolamine t1/2, CL, and Vd values were similar for Treatments A, B, and C.
f) Phentolamine was completely bioavailable after intraoral injection (Treatment A) (104% or 111%, using linear or log trapezoidal methods, respectively, for AUC calculation, compared to its bioavailability after intravenous injection (Treatment B).

2) Lidocaine PK parameters:

a) Treatments A, C, and D were evaluated for lidocaine PK parameters.
b) The lidocaine Cmax, AUClast and AUCinf values were all dose proportional, with similar values for Treatments C and D, and values for Treatment A that were approximately one-fourth the values of Treatments C and D.
c) The lidocaine t1/2 and CL values were similar for Treatments A, C, and D.
d) The lidocaine Vd value was statistically significantly smaller in Treatment C than in Treatment D.
e) The observed difference in lidocaine Vd, 192 liters in Treatment C and 237 liters in Treatment D, **although statistically significant, is not clinical)y meaningful because neither C ,nor AUC values** differed significantly between these two treatments.
f) The phentolamine-induced delay of the lidocaine Tmax in Treatment C, relative to Treatment D, is **a demonstration of phentolamine's abi lity to** accelerate the clearance of lidocaine from oral tissues into the circulatory system.

3) Epinephrine PK parameters:

a) Treatments C and D were evaluated for epinephrine PK parameters. (No local anesthesia was administered in Treatment B, and it was felt that the epinephrine concentrations resulting from the injections in Treatment A might be so low that they would not be discernable from endogenous epinephrine.)
b) The epinephrine Cmax, Tmax, AUClast, AUCinf, t1/2 and Vd values were all similar among treatment groups.
c) The epinephrine CL for Treatment C was statistically significantly smaller than the epinephrine CL for Treatment D. The decreased CL of epinephrine in Treatment C relative to Treatment D, although statistically significant, is not considered to be clinically meaningful. Epinephrine clearance could be calculated for only 8 of the 16 subjects and might thus be a biased estimate of epinephrine clearance.
d) [redacted] PK parameters: The plasma concentrations of [redacted] were almost entirely below the limit of quantitation. Therefore, PK parameters were not estimated for [redacted]. b(4)

3. Pharmacodynamics:

1) The sensation rating for the upper lip was evaluated for Treatments A (maxillary injection), C (both mandibular and maxillary injections), and D (both mandibular and maxillary injections). Only subjects who experienced numbness and/or tingling in their upper lip were evaluable for return of normal sensation in the upper lip. For treatments A, S, and C, the time to return of normal sensation was calculated relative to the time of NV-101 injection. For Treatment D, NV-101 was not administered. Thus, for this treatment, the time to **normal sensation ("adjusted time") was calculated** relative to the injection time of the local anesthetic plus a constant equal to the mean time between the first injection of local anesthetic and first injection of NV-101 for Treatment C.
    a. **By 60 minutes after injection of NV-101 for Treatments A and C or "adjusted time" for** Treatment D, the percentage (%) of evaluable subjects with normal sensation in the upper lip was markedly greater with Treatments A and C than with Treatment D.
    b. By 90 minutes after injection of NV-101 for Treatment C, all evaluable subjects had normal sensation in the upper lip, with maintenance of normal upper lip sensation through the rest of the 5-hour follow-up period.
    c. After Treatment A, all evaluable subjects had normal upper lip sensation by 170 minutes after injection of NV-101.
    d. **In contrast, with Treatment D, not until 230 minutes "adjusted time" did all evaluable subjects** regain normal upper lip sensation. Consistent with these findings, the median time to normal sensation of the upper hp for Treatment D was approximately twice as long as the median time for Treatments A or C.
2) The sensation rating for the lower lip was evaluated for Treatments C and D (both mandibular and maxillary injections), but not for Treatments A (maxillary injection) and B (IV injection). Only subjects who experienced numbness and/or tingling in their lower lip were evaluable for return of normal sensation in the lower lip.
    a. All evaluable subjects regained normal lower lip sensation after Treatment C by 170 minutes after dosing with NV-101.
    b. **In contrast, with Treatment D, at the 170 minute "adjusted time" time point only** approximately 10% of evaluable subjects had regained normal lower lip sensation, and by 250 **minutes "adjusted time" to the end of the 300- minute "adjusted-time" follow-up period, only** approximately 80% of evaluable subjects had regained normal lower lip sensation.
    c. Consistent with these findings, the median time to normal sensation of the lower lip for Treatment D was approximately twice as long as the median time for Treatment C.

3) The sensation rating for the tongue was evaluated for Treatments C and D (both mandibular and maxillary injections), but not for Treatments A (maxillary injection) and B (IV injection). Only subjects who experienced numbness and/or tingling in their tongue were evaluable for return of normal sensation in the tongue.

a. All evaluable subjects regained normal tongue sensation after Treatment C by 160 minutes **after dosing with NV-101. In contrast, with Treatment D, at the 160 minute "adjusted-time"** time point only approximately 25% of evaluable subjects had regained normal tongue **sensation, and from 260 minutes "adjusted time" to the end of the 300-minute "adjusted-time"** follow-up period, approximately 95% of evaluable subjects had regained normal tongue sensation. Consistent with these findings, the median time to normal sensation of the tongue for Treatment D was approximately twice as long as the median time for Treatment C.

4. Safety:

1) There were no deaths or serious adverse events reported during this study.
2) No subjects discontinued due to adverse events.
3) Overall, the most frequent all-causalities adverse event was hypotension, which was defined in the protocol as systolic blood pressure <100 mm Hg. Hypotension was most frequent after Treatment D, in which no NV-101 was administered. Either all or a majority of the episodes of hypotension were judged to be treatment-related after Treatments A, B, and C. All episodes of hypotension were mild and asymptomatic. Other frequent adverse events included bradycardia, headache, and paraesthesia (an anticipated side effect of anesthetic), for which either no or no more than half of the episodes were judged to be treatment-related after treatment. A11 episodes of bradycardia, which was defined in the protocol as pulse <50 beats per minute (bpm), were also asymptomatic.
4) All adverse events in this study were listed as resolved.

All causalities (treatment-related) Treatment-Emergent AEs occurring in at least 2 subjects after at least 1 treatment (number of subjects):

Adverse Event	Study Treatment			
	A N = 16	B N = 16	C N = 16	D N = 16
(Preferred Term)				
Hypotension	5 (3*)	5 (3*)	2 (2*)	9 (3*)
Bradycardia	4 (2*)	2 (1*)	0 (0*)	0 (0*)
Headache	2 (1*)	1 (0*)	3 (1*)	0 (0*)
Paraesthesia	0 (0*)	0 (0*)	2 (1*)	4 (0*)
Facial pain	1 (0*)	0 (0*)	2 (0*)	0 (0*)
Dizziness	0 (0*)	0 (0*)	0 (0*)	2 (0*)
Pain in jaw	0 (0*)	0 (0*)	2 (0*)	0 (0*)

A = 1 cartridge of local anesthetic and 1 cartridge of NV-101; B = 1 cartridge of IV injection of NV-101;
C = 4 cartridges of local anesthetic and 2 cartridges of NV-101; D = 4 cartridges of local anesthetic.
***Treatment-related = related to study injection.**

5) **Other Safety Parameters – Vital Signs:**
   a. The mean changes from baseline were small for all treatment groups at all time points: between +4 mm Hg and -8 mm Mg for systolic and diastolic blood pressure and between +12 beats per minute (bpm) and -13 bpm for pulse rate.
   b. Oral Assessments: Oral assessments were performed for Treatments A, C, and D. No abnormalities from the oral cavity assessment were reported for Treatment C. Very few abnormalities were reported for Treatments A and D, and none of these abnormalities were considered clinically significant. A total of 4 of the 16 subjects had abnormal assessments including abnormal oral cavity assessment (mucosa), abnormal condition of soft tissue at maxillary injection (hyperemic, edema, and pale), and abnormal condition of soft tissue at mandibular injection (edema). There were no clinically significant abnormalities from oral cavity assessments with an onset either before or after injection of NV-101 reported for any subject.
   c. Holter Monitor Readings: Holter monitor readings were performed for 12 of 16 subjects for Treatment A, for 12 of 16 subjects for Treatment B, for 11 of 36 subjects for Treatment C, and for 15 of 16 subjects for Treatment D. The results of all Holter monitor readings were normal.

CONCLUSIONS:

• After intraoral injection of NV-101, the PK properties for phentolamine were the following: Tmax was short (11-15 minutes after injection), Cmax, AUClast, and AUCinf were roughly dose proportional, CL was rapid (approximately 160-200 L/hr), Vd large (approximately 470-500 L), and t<m brief (approximately 2-3 hours).

• After IV injection of NV-101, the PK properties for phentolamine were the following: Tmax was earlier (7 minutes after injection) than the values observed after intraoral injection, Cmax was approximately 8 times that after intraoral injection, and AUClast, AUCinf, CL, Vd, and t1/2 were similar to the values seen with intraoral injection,

• Phentolamine was completely bioavailable after intraoral injection.

• Administration of phentolamine as HV-101 significantly delayed lidocaine Tmax (mean values of 43 and 28 minutes for Treatments C and D, respectively).

The phentolamine-induced delay of the lidocaine Tmax in Treatment C is a demonstration of **phentolamine's ability to accelerate the clearance of lidocai**ne from oral tissues into the circulatory system.

• NV-101 administration did not affect the pharmacokinetics of epinephrine in a clinically meaningful manner.

• Intraoral treatments of NV-101 substantially accelerated the return of normal sensation to the upper lip (Treatments A and C vs. Treatment D), the lower lip (Treatment C vs. Treatment 13), and the tongue (Treatment C vs. Treatment D).

• Treatment with both intraoral and IV NV-101 was well-tolerated.

Study NOVA 05-PEDS-PK

Title: A Phase 1, Open Label Study of NV-101 to Evaluate the Pharmacokinetics and Safety in Pediatric Dental Patients

Study Objectives:

Primary Objective: To evaluate the pharmacokinetics (PK) of NV-101 (phentolamine) in pediatric dental patients who were undergoing dental procedures under general anesthesia or conscious sedation, to the extent possible with blood sampling limited to the duration of the intravenous (IV) access line after NV-101 administration.

Secondary Objective: To evaluate the safety of NV-101 in pediatric dental patients as measured by the incidence and severity of adverse events and concomitant medications.

Study Design: This was a multicenter, open label study of NV-101 to evaluate the PK and safety of NV-101 in pediatric dental patients who were undergoing a dental

procedure under general anesthesia or conscious sedation and required an IV line. All subjects were administered local anesthetic consisting of 2% lidocaine with 1:100,000 epinephrine. All subjects were monitored at the site for at least 2 and up to 3 hours after the administration of study drug (NV-101) to perform safety assessments and for venous blood sampling.

NV-101 was administered by submucosal injection approximately 30 minutes after the injection of local anesthetic (2% lidocaine with 1:100,000 epinephrine) and completion of the dental procedure using the same location and same technique used for the administration of local anesthetic.

The doses of local anesthetic and study drug (NV-101) depended upon the weight of the subject. See Treatment section.

Note: If additional injections of local anesthetic were required for dental procedures elsewhere in the oral cavity, additional injections of 2% mepivacaine with 1:20,000 levonordefrin or 3% mepivacaine were permitted. There were 5 subjects in the 3 – 6 year group who received additional local anesthetics. See Results section.

Schedule of study assessments and procedures:

Event/Assessment	Period 1 Screening Day -14 to Day 1	Period 2 Anesthetic/ Dental Procedure Day 1	Period 3 NV-101 Day 1	Period 4 Observation Day 1	Period 5 Telephone Follow-Up Day 1; Day 2 - 3
Informed Consent/Assent	X				
Preoperative evaluation including limited physical examination	X				
Medical/Dental History/Concurrent Illness	X[a]	X[d]			
Demographics (including height, weight & grade level)	X				
Urine pregnancy test, if applicable	X[b]				
BP & pulse (supine)		X[e, f]	X[h]	X[i]	
Temperature & respirations		X[e]		X[i]	
Administer general anesthesia or conscious sedation with IV line in place		X			
Administer 2% lidocaine with 1:100,000 epinephrine (record time and type of injection)		X			
Dental Procedure (record time completed)		X			
Assign Subject ID #	X[b]				
Obtain PK samples at specified times			X[h]	X[i]	
Administer NV-101 (record time completed)			X		
General Oral Cavity Assessments		X[e]		X[i]	
Specific Oral Cavity Assessments (Injection/Procedure Sites)		X[g]		X[i]	
Concomitant Medications	X[c]	X	X	X	X[j]
Adverse Events				X	X[j]
Schedule/Telephone Follow-Up				X	X[k]
Discharge subject (record time)				X	

Study Population and Criteria for Inclusion/Exclusion:

Inclusion criteria:
Both male and female subjects age 3 to 17 years were eligible for study entry; sufficiently healthy as determined by the Investigator to receive dental care under general anesthesia or conscious sedation requiring an indwelling IV catheter; a negative urine pregnancy test in all females of childbearing potential (past menarche).

Exclusion criteria:
Weight less than 15 kg; history or presence of any condition that contraindicated dental care under general anesthesia or conscious sedation; allergy or intolerance to phentolamine, epinephrine, sulfites, or relevant local and general anesthetics and conscious sedation agents; use of any investigational drug and/or participation in any clinical study within 30 days of study drug administration; participation in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia; or any condition which in the opinion of the Investigator increased the risk to the subject of participating in this study or decreased the likelihood of compliance with the protocol.

Treatments: NV-101 was manufactured by [redacted] b(4)
as a sterile, pyrogen-free, isotonic solution for administration in glass dental cartridges that delivered 0.4 mg phentolamine mesylate in 1.7 mL (per cartridge). The

concentration of the active ingredient (phentolamine mesylate) in NV-101 was 0.235 mg/mL. The lot/batch number was 51115.

	2% lido/epi*	NV-101	Comments
Treatment A ≥15 kg and <30 kg	1/2 cartridge 0.9 mL	1/2 cartridge 0.2 mg phentolamine	NV-101 was administered by submucosal injection approximately 30 minutes after the injection of local anesthetic (2% lidocaine with 1:100,000 epinephrine) and completion of the dental procedure using the same location and same technique used for the administration of local anesthetic.
Treatment B ≥30 kg	1 cartridge 1.8 mL	1 cartridge 0.4 mg phentolamine	

Notes:
1. 1 cartridge 2% lidocaine HCl with 1:100,000 epinephrine - 1.8 mL
2. 1 cartridge NV-101: 0.4 mg phentolamine in 1.7 mL

The Applicant stated that these doses were selected based on an analysis of the mg/kg dose of phentolamine received by subjects in the Phase 2 study (NOVA 03-001):

- 0.0053 ± 0.0014 mg/kg (mean ± S.E.) for those given one cartridge of NV-101
- 0.0121 ± 0.002 mg/kg (mean ± S.E.) for those given two cartridges of NV-101

The highest weight/weight doses given any subject in this study were:

- 0.0088 mg/kg to those given one cartridge of NV-101
- 0.0166 mg/kg to those given two cartridges of NV-101

In NOVA 04-PK, the mean NV-101 dose of phentolamine was 0.0055 ± 0.0008 mg/kg (mean ± S.E.) with one cartridge of NV-101 and 0.011 ± 0.0016 mg/kg (mean ± S.E.) with two cartridges of NV-101.

Thus, general scheme is:

Body Weight		Dosing Scheme		
lbs.	kg	Fraction of Cartridge	Phentolamine Dose (mg)	Phentolamine Dose (mg/kg)
33	15	1/2	0.2	0.013
44	20	1/2	0.2	0.010
55	25	1/2	0.2	0.008
66	30	1	0.4	0.013
88	40	1	0.4	0.010
110	50	1	0.4	0.008

Pharmacokinetics (PK): Blood samples were drawn to assay for phentolamine and lidocaine. Blood samples were drawn for PK analysis, starting immediately prior to first injection of local anesthetic (if given) or injection of NV-101, and 5, 10, 15, 20, 30, and 45 minutes, and at 1.0, 1.5, 2.0 and 3.0 hours post study drug administration.

The following pharmacokinetic parameters were estimated for phentolamine: peak plasma concentration (Cmax), time to peak plasma concentration (Tmax), the area under the plasma disposition curve from 0 to the last time-point with measurable concentration (AUClast), the area under the plasma concentration-time curve from time 0 to infinity (AUCinf), elimination half-life ($t_{1/2}$), clearance (CL), and the volume of distribution (Vd). PK parameters were estimated based on non- compartmental methods.

The Applicant stated that the lidocaine PK parameters were not estimated. No explanation was provided in the study report.

Assay:
Plasma concentrations of phentolamine and lidocaine were assayed with a validated LC/MS/MS method. Plasma samples were shipped frozen on dry ice for overnight delivery to [redacted], for assay with the method, [redacted] b(4)

Safety: Safety assessments included adverse events, vital signs (temperature, respirations, blood pressure and pulse), oral cavity examinations and use of concomitant medications.

Statistical Methods:

General:
Inferential testing was not planned. The results of the analyses were presented by rotocol-specified time points and by dose level of NV-101 (0.2 mg and 0.4 mg). Continuous variables were summarized using descriptive statistics, including N (sample size), mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized using frequency count and percentage.

Pharmacokinetics:
Pharmacokinetic parameters for phentolamine were determined using the non-compartmental model with extravascular input in WinNonlin 2.1. Plasma concentrations below the limit of quantitation were treated as zero for the calculation of pharmacokinetic parameters. The calculation of pharmacokinetic parameters was based on the protocol-planned nominal sampling times.

Plasma concentration data for phentolamine and lidocaine were presented graphically as treatment means (0.2 mg and 0.4 mg dose groups) and for individual subjects. Descriptive statistics including N (sample size), mean (geometric mean for AUC and

Cmax), median, standard deviation, minimum, and maximum, were employed to describe the results for phentolamine by dose group (0.2 mg and 0.4 mg).

Safety:
The subject incidence of treatment-emergent adverse events was tabulated by system organ class (SOC), preferred term, and dose group. SOCs and preferred terms were coded from the reported adverse event terms using the Medical Dictionary for Regulatory Activities (MedDRA®), version 8.2. The severity of each adverse event was graded according to the World Health Organization (WHO) criteria. In addition, subjects with serious adverse events were summarized by dose group. Subject incidence of severity of treatment-emergent adverse events was tabulated by SOC, preferred term, and dose group. These summary tables were presented for all-causality and treatment-related adverse events. The administration of concomitant medications, including analgesic medications for intraoral pain, was tabulated by medication class (WHO Anatomic Therapeutic Chemical Classification System), drug dictionary preferred term, and NV-101 treatment (0.2 and 0.4 mg) according to the WHO Drug dictionary. Medications taken within 24 hours of first anesthetic administration were reported. In addition, medications taken from discharge to telephone follow-up on Day 1 and Day 2 to 3 were also reported.
Vital signs were listed but not summarized, as the effects of study medication on vital signs would be confounded with the effects of the medications administered to produce general anesthesia or conscious sedation in all subjects. Similarly, oral cavity assessments were listed but not summarized, as it was anticipated that oral cavity assessments might be abnormal in many subjects because no restrictions were placed on the dental procedures to be performed.

Results

1. Demographic and Additional Baseline Characteristics

Subject Disposition
The number of subjects in the 3-6 years, 7-11 years, and 12-17 years age groups was 6, 6, and 7, respectively. All of the 3-6 year old subjects were in the 0.2 mg dose group, and all of the 12-17 year old subjects were in the 0.4 mg dose group. Of the 7-11 year old subjects, 2 were in the 0.2 mg dose group and 4 were in the 0.4 mg dose group. All of the enrolled subjects were treated and all completed the study assessments.

Characteristic	NV-101 Dose Group		Overall N=19
	0.2 mg N=8	0.4 mg N=11	
Number of subjects, n (%)			
Gender			
Male	5 (62.5%)	8 (72.7%)	13 (68.4%)
Female	3 (37.5%)	3 (27.3%)	6 (31.6%)
Ethnicity			
Hispanic or Latino	4 (50.0%)	8 (72.7%)	12 (63.2%)
Not Hispanic or Latino	4 (50.0%)	3 (27.3%)	7 (36.8%)
Race			
White	6 (75.0%)	3 (27.3%)	9 (47.4%)
Other	2 (25.0%)	8 (72.7%)	10 (52.6%)
Age, years			
Mean (±SE)	5.4 (0.6)	12.5 (0.8)	9.5 (1.0)
Median (minimum, maximum)	5.0 (3, 8)	13.0 (8, 16)	9.0 (3, 16)
Height, cm			
Mean (±SE)	109.4 (6.5)	157.4 (4.7)	142.4 (6.8)
Median (minimum, maximum)	104.0 (94, 130)	160.0 (133, 185)	148.0 (94, 185)
Weight, kg			
Mean (±SE)	20.6 (1.4)	55.5 (8.3)	40.8 (6.2)
Median (minimum, maximum)	20.5 (16, 26)	48.0 (30, 127)	36.0 (16, 127)
≥15 kg and ≤30 kg	8 (100.0%)	0 (0.0%)	8 (42.1%)
≥30 kg	0 (0.0%)	11 (100.0%)	11 (57.9%)

Subject Disposition Summarized by Age Group and Treatment

	AGE Group						Overall N=19
	3 – 6 years		**7 – 11 years**		**12 – 17 years**		
NV-101 Dose Group	0.2 mg N=6	0.4 mg N=0	0.2 mg N=2	0.4 mg N=4	0.2 mg N=0	0.4 mg N=7	
Number of subjects							
Enrolled subjects	6	-	2	4	-	7	19
Treated subjects	6	-	2	4	-	7	19

2. Dose administered

Phentolamine dose:

With an even distribution of body weights of children, the target average dose was expected to be 0.010 mg/kg. The mean dose in the lighter-weight group (0.0100 mg/kg) was on target but the mean dose of the larger children (0.0084 mg/kg) was slightly below the target. The following table shows doses administered in each group:

OraVerse Dose = 0.2 mg			OraVerse Dose = 0.4 mg		
Subject I.D.	Body Weight (kg)	Weight/Weight Dose (mg/kg)	Subject I.D.	Body Weight (kg)	Weight/Weight Dose (mg/kg)
01-001	20	0.0100	**03-001**	**127**	**0.0031**
01-002	17	0.0118	03-002	30	0.0133
01-003	16	0.0125	03-003	67	0.0060
01-004	25	0.0080	03-004	50	0.0080
02-001	24	0.0083	03-005	48	0.0083
02-002	21	0.0095	03-006	78	0.0051
02-003	16	0.0125	03-007	49	0.0082
03-012	26	0.0077	03-008	41	0.0098
			03-009	36	0.0111
			03-010	47	0.0085
			03-011	37	0.0108
Mean	20.625	0.0100	Mean	55.455	0.0084
Range	16-26	0.0077-0.0125	Range	**30-127**	0.0031-0.0133

Local anesthetics

There were subjects who received additional local anesthetics. The additional local anesthetics were injected in elsewhere and do not obstruct with the overall findings.

	AGE Groups						**Overall**	
	3 - 6 years		**7 - 11 years**		**12 - 17 years**			
NV-101 Dose Group	**0.2 mg N=6**	**0.4 mg N=0**	**0.2 mg N=2**	**0.4 mg N=4**	**0.2 mg N=0**	**0.4 mg N=7**	**0.2 mg N=8**	**0.4 mg N=11**
General anesthesia or conscious sedation								
General anesthesia	6 (100.0)	-	1 (50.0)	0 (0.0)	-	0 (0.0)	7 (87.5)	0 (0.0)
Conscious sedation	0 (0.0)	-	1 (50.0)	4 (100.0)	-	7 (100.0)	1 (12.5)	11 (100.0)
Total volume of local anesthetica administered								
0.85 mL (1/2 cartridge)	6 (100.0)	-	2 (100.0)	0 (0.0)	-	0 (0.0)	8 (100.0)	0 (0.0)

1.7 mL (1 cartridge)	0 (0.0)	-	0 (0.0)	4 (100.0)	-	7 (100.0)	0 (0.0)	11 (100.0)
Number of subjects who received additional local anesthetic		-			-			
Yes	5 (83.3)	-	1 (50.0)	1 (25.0)	-	2 (28.6)	6 (75.0)	3 (27.3)
No	1 (16.7)	-	1 (50.0)	3 (75.0)	-	5 (71.4)	2 (25.0)	8 (72.7)
Additional local anesthetic								
2% mepivacaine	**2 (33.3)**	**-**	**1 (50.0)**	**1 (25.0)**	**-**	**2 (28.6)**	**3 (37.5)**	**3 (27.3)**
3% mepivacaine	**3 (50.0)**	**-**	**0 (0.0)**	**0 (0.0)**	**-**	**1 (14.3)**	**3 (37.5)**	**1 (9.1)**

Table I: NV-101 Administration

	Age Group							
	3-6 years		7-11 years		12-17 years		Overall	
NV-101 Dose Group	0.2 mg N=6	0.4 mg N=0	0.2 mg N=2	0.4 mg N=4	0.2 mg N=0	0.4 mg N=7	0.2 mg N=8	0.4 mg N=11
Total volume of NV-101 administered		-			-			
0.85 mL (1/2 cartridge)	6 (100.0)	-	2 (100.0)	0 (0.0)	-	0 (0.0)	8 (100)	0 (0.0)
1.7 mL (1.0 cartridge)	0 (0.0)	-	0 (0.0)	4 (100.0)	-	7 (100.0)	0 (0.0)	11 (100.0)
Elapsed time between injections of local anesthetic and NV-101		-			-			
25 to 29 minutes	2 (33.3)	-	2 (100.0)	0 (0.0)	-	1 (14.3)	4 (50.0)	1 (9.1)
30 to 34 minutes	2 (33.3)	-	0 (0.0)	4 (100.0)	-	5 (71.4)	2 (25.0)	9 (81.8)
35 to 39 minutes	1 (16.7)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (12.5)	0 (0.0)
40 to 44 minutes	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	0 (0.0)
other	1 (16.7)	-	0 (0.0)	0 (0.0)	-	1 (14.3)	1 (12.5)	1 (9.1)
N	6	-	2	4	-	7	8	11
Mean (SE)	28.3 (2.2)	-	28.5 (0.5)	31.8 (0.8)	-	33.0 (2.3)	28.4 (1.6)	32.5 (1.4)
Median	27.5	-	28.5	31.0	-	30.0	28.5	31.0
Range	(22.0, 37.0)	-	(28.0, 29.0)	(31.0, 34.0)	-	(29.0, 46.0)	(22.0, 37.0)	(29.0, 46.0)

For the total volume of NV-101 administered and the elapsed time between injections of local anesthetic and NV-101, the table entries are the number of subjects (n) and the percentage of subjects meeting the stated criteria.

Source: Table 7

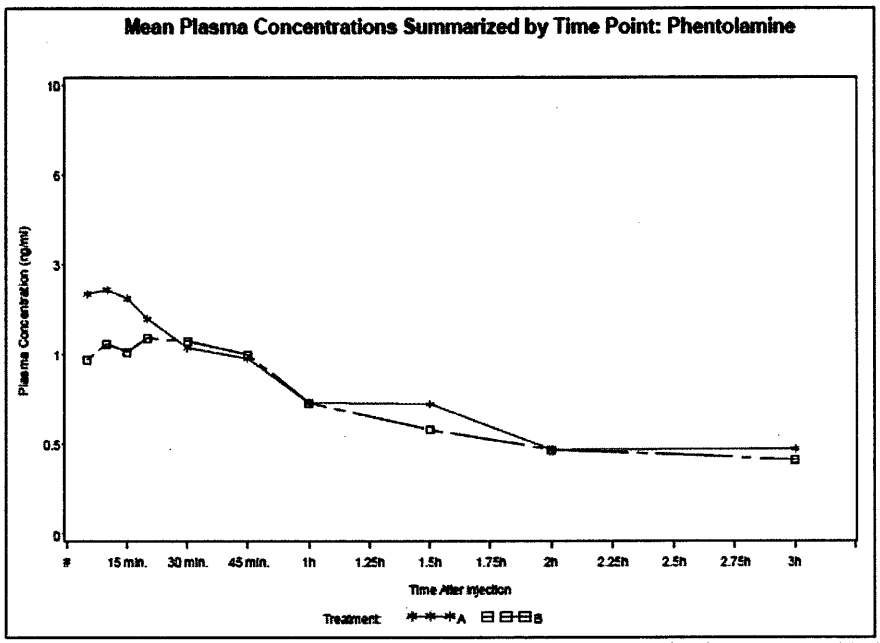
3. PK figures and tables

1) Phentolamine mean plasma concentration profile

Only one subject in the 0.2 mg group contributed a sample at the 3-hour time point.

The mean plasma concentration of phentolamine in the 0.4-mg dose group was nearly half the mean in the 0.2-mg group from 5 to 15 minutes after study drug administration.

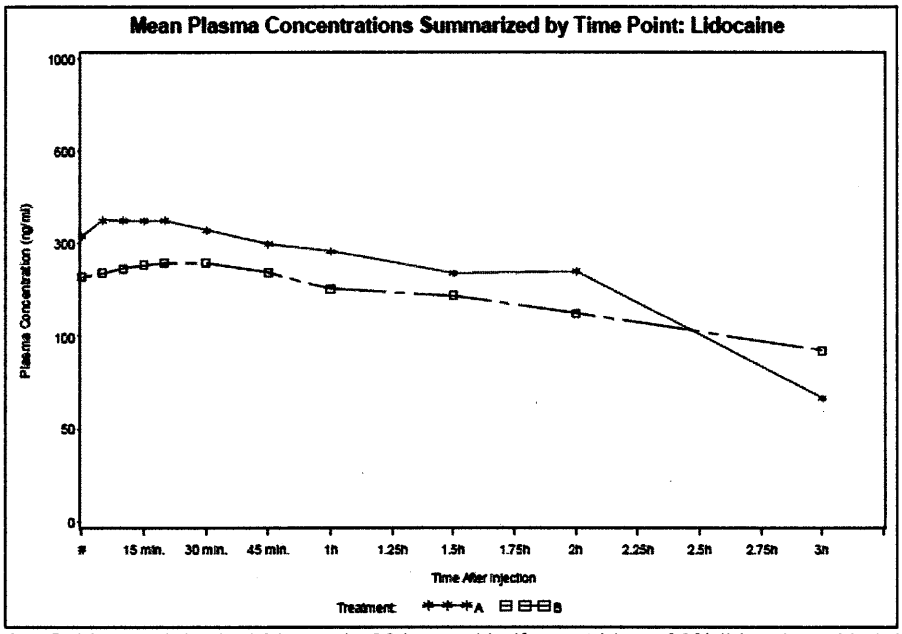
By 30 minutes after study drug administration, the mean plasma concentrations in the two groups were nearly identical and remained similar through the 2-hour sampling point.



A = Subject weighed ≥15 kg and <30 kg, and half a cartridge of 2% lidocaine with 1:100,000 epinephrine and half a cartridge of NV-101 (0.2 mg) were administered.
B = Subject weighed ≥30 kg, and a whole cartridge of 2% lidocaine with 1:100,000 epinephrine and a whole cartridge of NV-101 (0.4 mg) were administered.
# = prior to study drug administration.
For the 0.2 mg dose group, only 1 data point was used to calculate the 3-hour value.

2) Lidocaine mean plasma concentration profile

The mean plasma concentration of lidocaine in the 0.4-mg dose group was less than the mean in the 0.2-mg group from immediately prior to NV-101 injection through the 2-hour sample. Lidocaine plasma concentrations increased after NV-101 injection, peaking at 20-30 minutes after dosing, then declined.



A = Subject weighed ≥15 kg and <30 kg, and half a cartridge of 2% lidocaine with 1:100,000 epinephrine and half a cartridge of NV-101 (0.2 mg) were administered.
B = Subject weighed ≥30 kg, and a whole cartridge of 2% lidocaine with 1:100,000 epinephrine and a whole cartridge of NV-101 (0.4 mg) were administered.
# = prior to study drug administration.
For the 0.2 mg dose group, only 1 data point was used to calculate the 3-hour value.

B. PK parameters:

PK parameters for phentolamine:

	NV-101 Dose Group	
	0.2 mg N=8 **15 – 30 kg wt**	0.4 mg N=11 > 30 kg wt
Peak plasma concentration (Cmax), ng/mL		
Geometric Mean	2.60	1.47
Median (min, max)	2.45 (1.50, 5.30)	1.60 (0.90, 2.20)
95% CI	(1.73, 3.97)	(1.26, 1.76)
Time to peak plasma concentration (Tmax), HH:MM		
Mean (±SE)	0:10 (±0:01)	0:21 (±0:04)
Median (min, max)	0:10 (0:05, 0:15)	0:20 (0:05, 0:45)
95% CI	(0:07, 0:14)	(0:12, 0:31)
AUC1 to last measurable concentration (AUClast), ng hr/mL		
Geometric Mean	1.93	1.81
Median (min, max)	1.79 (1.13, 3.16)	1.87 (1.28, 2.76)
95% CI	(1.48, 2.55)	(1.57, 2.14)
AUC1 extrapolated to time infinity (AUCinf), ng hr/mL		
Geometric Mean	3.62	3.39
Median (min, max)	3.13 (2.32, 6.49)	2.82 (1.76, 11.57)
95% CI	(2.44, 5.29)	(1.88, 6.11)
Elimination half-life (t1/2), HH:MM		
Mean (±SE)	2:32 (±0:34)	2.59 (±0.56)
Median (min, max)	1:37 (1:07, 4:47)	1:47 (1:08, 10:51)
95% CI	(1:08, 3:56)	(0:51, 5:08)
Total body clearance (CL), L/hr		
Mean (±SE)	58.79 (±8.06)	132.18 (±17.59)
Median (min, max)	63.99 (30.83, 86.27)	141.84 (34.56, 227.17)
95% CI	(39.07, 78.52)	(92.38, 171.98)
Volume of distribution (Vd), L		
Mean (±SE)	190.56 (±35.69)	396.50 (±22.98)
Median (min, max)	164.59 (100.76, 359.91)	371.67 (280.77, 541.37)
95% CI	(103.23, 277.89)	(344.52, 448.49)

This difference in dose level was not reflected in AUC values for the two groups as these parameters were remarkably equal between the groups. Cmax values were, however, lower in the heavier-weight group.

The greater mean Vd in the 0.4 mg dose group is consistent with the greater mean body weight in this dose group.

The greater mean CL in the 0.4 mg dose group is consistent with the greater dose and similar mean AUC in this dose group.

The mean peak plasma concentration (Cmax) of the 0.4 mg dose group was less than that of the 0.2-mg NV-101 dose group. The AUClast and AUCinf were similar in the 2 dose groups.

The mean elimination half-life (t1/2) was similar in the 0.4-mg dose group and 0.2-mg group, and the median values in the 2 groups were nearly identical. The mean total body clearance (CL) and mean volume of distribution (Vd) were noticeably larger in the 0.4-mg group than in the 0.2-mg group.

Subject ID	Peak Plasma Concentration (ng/mL)	Time to Peak Plasma Concentration (HH:MM)	Area under the Curve to the Last Measurable Concentration (ng.hr/mL)	Area under the Curve Extrapolated to Time Infinity (ng.hr/mL)	Elimination Half-Life (HH:MM)	Total Body Clearance (liters/hr)	Volume of Distribution (liters)
400-01-001	[redacted]	0:15	2.33	3.13	1:20	63.99	[redacted]
400-01-002		0:05	2.59	6.49	3:42	30.83	
400-01-003		0:05	1.80	2.32	1:22	86.27	
400-01-004		0:10	1.79	2.44	1:07	82.08	
400-02-001		0:15	1.13				
400-02-002		0:10	1.58	3.08	3:50	64.92	
400-02-003		0:10	3.16	4.66	1:37	42.93	
400-03-012		0:15	1.76	4.93	4:47	40.54	

b(4)

Subject ID	Peak Plasma Concentration (ng/mL)	Time to Peak Plasma Concentration (HH:MM)	Area under the Curve to the Last Measurable Concentration (ng.hr/mL)	Area under the Curve Extrapolated to Time Infinity (ng.hr/mL)	Elimination Half-Life (HH:MM)	Total Body Clearance (liters/hr)	Volume of Distribution (liters)
400-03-001	[redacted]	0:20	1.84	2.68	1:42	149.53	[redacted]
400-03-002		0:45	2.76	4.12	2:00	96.98	
400-03-003		0:20	1.95	2.59	1:39	154.17	
400-03-004		0:10	1.35	1.76	1:08	227.17	
400-03-005		0:45	2.17	6.35	5:16	62.95	
400-03-006		0:20	1.89	3.00	2:09	133.12	
400-03-007		0:30	1.87	2.93	1:52	136.63	
400-03-008		0:05	1.66	2.23	1:38	179.62	
400-03-009		0:05	1.47	2.72	1:38	147.04	
400-03-010		0:30	1.28				
400-03-011		0:10	2.18	11.57	10:51	34.56	

b(4)

3. Safety:

Overall, there were a total of 5 adverse events experienced by 4 subjects in the 0.4 mg NV-101 dose group and zero adverse events in the 0.2 mg NV-101 dose group. There were no severe adverse events or serious adverse events (SAEs) and there were no

subjects who discontinued due to adverse events. A total of 3 treatment-related adverse events were experienced by 2 subjects.

Incidence of Treatment-Emergent Events

	NV-101 Dose Group		Overall N=19
	0.2 mg N=8	0.4 mg N=11	
Number of adverse events	0	5	5
Number of subjects with adverse events, n (%)	0 (0.0)	4 (36.4)	4 (21.1)
Gastrointestinal disorders	0 (0.0)	1 (9.1)	1 (5.3)
Vomiting	0 (0.0)	1 (9.1)	1 (5.3)
Injury, poisoning, and procedural complications	0 (0.0)	3 (27.3)	3 (15.8)
Oral pain	0 (0.0)	1 (9.1)	1 (5.3)
Post-procedural pain	0 (0.0)	2 (18.2)	2 (10.5)
Nervous system disorders	0 (0.0)	1 (9.1)	1 (5.3)
Headache	0 (0.0)	1 (9.1)	1 (5.3)

Incidence of Treatment-Related Adverse Events

	NV-101 Dose Group		Overall N=19
	0.2 mg N=8	0.4 mg N=11	
Number of adverse events	0	3	3
Number of subjects with adverse events, n (%)	0 (0.0)	3 (18.2)	2 (10.5)
Gastrointestinal disorders	0 (0.0)	1 (9.1)	1 (5.3)
Vomiting	0 (0.0)	1 (9.1)	1 (5.3)
Injury, poisoning, and procedural complications	0 (0.0)	1 (9.1)	1 (5.3)
Oral pain	0 (0.0)	1 (9.1)	1 (5.3)
Nervous system disorders	0 (0.0)	1 (9.1)	1 (5.3)
Headache	0 (0.0)	1 (9.1)	1 (5.3)

CONCLUSIONS:

The pharmacokinetics of phentolamine after intraoral injection in pediatric dental patients indicates that systemic exposure is brief and at low levels, consistent with the low incidence of safety findings in this study.

NV-101 was well-tolerated at the doses administered in this study.

4.3 Consult Review (including Pharmacometric Reivews) – **Not applicable**

4.4 Cover Sheet and OCPB Filing/Review Form

New Drug Application Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	**22-159**	Brand Name	OraVerse®	
OCP Division	II	**Generic Name**	**Phentolamine mesylate**	
Medical Division	HFD-170	Drug Class	Anesthesia	
OCPB Reviewer	David Lee	Indication(s)	Reversal of tissue anesthesia	
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Intravenous injection solution	
		Dosing Regimen	Single dose	
Date of Submission	4/9/07	Route of Administration	Intravenous injection	
Estimated Due Date of OCP Review		Sponsor	Novalar, Inc.	
Medical Division Due Date		Priority Classification	Standard	
PDUFA Due Date	2/9/08			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
Single dose:	X	2		
Multiple dose:	X			Duration 7 days with WO of 14 days
Dose proportionality	X			
Patients-				
Single dose:				
Multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

100
0

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x			**Full Waiver – "No incidence in ped. population"**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	X			
Phase 1:				
Phase 2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x			Phentolamine IV
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total number of studies		2		

Filability and QBR comments		
	"X" if yes	Comments Related IND:
Application filable ?	X	Yes. As a 505(b)(2) application, the Applicant submitted relative BA, multiple dose and dose proportionality (looking at the maximum likely dosing scheme) information.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Lee
12/17/2007 10:39:44 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
12/17/2007 11:42:46 AM
BIOPHARMACEUTICS

New Drug Application Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	**22-159**	Brand Name	-
OCP Division	II	**Generic Name**	**Phentolamine mesylate**
Medical Division	HFD-170	Drug Class	Anesthesia
OCPB Reviewer	David Lee	Indication(s)	Reversal of tissue anesthesia
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Intravenous injection solution
		Dosing Regimen	Single dose
Date of Submission	4/9/07	Route of Administration	Intravenous injection
Estimated Due Date of OCP Review	-	Sponsor	Novalar, Inc.
Medical Division Due Date	/ /	Priority Classification	Standard
PDUFA Due Date	/ /		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
Single dose:	X	2		
Multiple dose:	X			Duration 7 days with WO of 14 days
Dose proportionality	X			
Patients-				
Single dose:				
Multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	X			
Phase 1:				
Phase 2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x			Phentolamine IV
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total number of studies		2		
Filability and QBR comments				
	"X" if yes	Comments Related IND:		
Application filable ?	X	Yes. As a 505(b)(2) application, the Applicant submitted relative BA, multiple dose and dose proportionality (looking at the maximum likely dosing scheme) information.		

Clinical Pharmacology summary presented by the Applicant:

This New Drug Application (NDA) is a 505(b)(2) application for approval of NV-101 (phentolamine mesylate) Injection. Phentolamine mesylate has been marketed in the U.S.

since 1952 [Regitine® is the reference listed drug (RLD)] and is currently marketed as generic phentolamine mesylate by Bedford Laboratories.

Proposed Indication
NV-101 (phentolamine mesylate) Injection is being developed for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

Pharmacological Class of Medicinal Product
Phentolamine mesylate is a sympatholytic competitive a-adrenergic blocker that nonselectively antagonizes both a_1 and a_2 receptors. The anatomical therapeutic chemical (ATC) code of phentolamine is C04AB01 (cardiovascular system, peripheral vasodilators, peripheral vasodilators, imidazoline derivatives).

To-be-marketed formulation of NV-101 was used in Phase 1 PK studies (NOVA 04-PK in Section 5.3.3.1 and NOVA 05-PEDS-PK in Section 5.3.3.2):

Table 2: Comparison of NV-101 Formulations

Ingredient	Initial Formulation (per mL)[a]	Final formulation (per mL)[b]
Phentolamine mesylate, USP		
EDTA Na_2, USP		
D-mannitol, USP		
Sodium acetate trihydrate, USP		
Acetic acid, USP		
Sodium hydroxide, NF		

b(4)

Abbreviations: EDTA, ethylenediaminetetraacetic acid; NA, not applicable; NF, National Formulary; q.s., quantity sufficient; USP, United States Pharmacopoeia; n

[a] Formulation used in NOVA 03-001 ; 1.8 mL (0.4 mg) was delivered for each injection

[b] Formulation used in NOVA 04-100, NOVA 04-200, NOVA 04-PK, NOVA 05-PEDS, and NOVA 05-PEDS-PK ; 1.7 mL (0.4 mg) was delivered per cartridge

Study synopses

Study ID	No. of Study Centers / Locations	Status / Total Enrollment/ Enrollment Goal	Study Design and Type of Control	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm / Entered/ Completed	Duration	Gender M/F / Median Age (Range)	Diagnosis / Inclusion Criteria	CTD Location
NOVA 04-PK	1 U.S.	Completed 16/16	Open label, 4 treatment, 4 period, crossover	NV-101 0.4, 0.8 mg intraoral submucosal NV-101, 0.4 mg IV	PK, safety	16/16	Single dose	7/9 23 (18-50)	Healthy subjects aged 18-65 years	NOVA 04-PK in Section 5.3.3.1
NOVA 05-PEDS-PK	3 U.S.	Completed 19/19	Open label	NV-101 0.2 mg 0.4 mg Intraoral submucosal	PK, safety	8/8 11/11	Single dose	13/6 9 (3-16)	Subjects aged 3-17 years undergoing dental procedures	NOVA 05-PEDS-PK in Section 5.3.3.2

Study No.	Study Design	Subjects (No. (M/F) Type Age: Median (Range)	Treatments (Dose, Dosage Form, Route) [Product ID]	Phentolamine - Mean Parameters (± SE)						
				C_{max} (ng/mL)[d]	AUC_{last} (ng.hr/mL)[d]	AUC_{inf} (ng.hr/mL)[d]	T_{max} (hr:min)[e]	$t_{1/2}$ (hr:min)[e]	Cl (L/hr)[e]	Vd (L)[e]
NOVA 04-PK	Open label, 4 treatment, 4 period, crossover	16 (7/9) Healthy subjects 23 (18-50)	NV-101, 0.4 mg intraoral submucosal[a] [3067]	1.34	1.69	2.88	00:15 ± 00:02	3:08 ± 0:55	160.93 ± 24.02	470.61 ± 62.72
			NV-101, 0.8 mg intraoral submucosal[b] [3067]	2.73	3.29	4.58	00:11 ± 00:01	02:14 ± 00:25	203.64 ± 36.21	499.68 ± 60.08
			NV-101, 0.4 mg IV [3067]	10.98	1.71	2.76	00:07 ± 00:03	2:24 ± 0:38	175.49 ± 30.36	441.99 ± 83.68
NOVA 05-PEDS-PK	Open label	8 (5/3) Pediatric subjects undergoing dental procedures 5 (3-8)	NV-101, 0.2 mg intraoral submucosal [51115][f]	2.60	1.93	3.62	0:10 ± 0:01	2:32 ± 0:34	58.79 ± 8.06	190.56 ± 35.69
		11 (8/3) Pediatric subjects undergoing dental procedures 13 (8-16)	NV-101, 0.4 mg intraoral submucosal [51115][c]	1.47	1.81	3.39	0:21 ± 0:04	2:59 ± 0:56	132.18 ± 17.59	396.50 ± 22.98

Request for Waiver of In Vivo Bioavailability Studies

The Applicant requests a waiver per 21 CFR 314.90 for the requirement stated in the Guidance for Industry: Applications Covered by Section 505(b)(2), dated October 1999, on page 8, that one of the items that should be included in a 505(b)(2) application is, "A Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any)" for the NV-101 NDA 22-159 submitted in accordance with 505(b)(2) of the Food, Drug and Cosmetic Act and 21 CFR 314.50 and 21 CFR 314.54. Regitine® is listed in the FDA Orange Book as the reference listed drug (RLD) for phentolamine mesylate. Regitine (NDA 8-278) was approved in January 1952 for and marketed by Ciba (now Novartis). A generic version of Regitine was approved (ANDA 40-235) on March 11, 1998. The ANDA contained a waiver request of *in vivo* bioequivalance for its 5 mg/vial product based upon 21 CFR 320.22 which was granted by FDA. This generic version is currently marketed in the U.S. The Applicant believes it is justified for FDA to grant a waiver for evidence of *in vivo* bioavailability comparing NV-101 to Regitine, the reference listed drug because: 1) the RLD, Regitine, is not currently marketed in the U.S. and is unavailable; 2) the bioavailability of intraoral submucosal NV-101 was evaluated, and the absolute bioavailability is 104% when compared to IV administration of NV-101 (as determined by AUC); 3) the recommended clinical dose of NV-101 is several fold lower than that of the RLD recommended dose, and the C_{max} levels when NV-101 was administered IV were 8 times higher than the C_{max} of NV-101 administered by intraoral submucosal injection; 4) the NV-101 NDA 22-159 contains clinical data in over 400 NV-101 treated dental subjects for use in evaluating the safety and efficacy of NV-101.

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/s/

David Lee
6/8/2007 11:55:51 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/12/2007 12:16:09 PM
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