7.1.18 Overdose Experience

No episodes of overdose were reported during the clinical trials; however, the effects of inadvertent intravascular injection were assessed during the pharmacokinetic study, NOVA 04-PK, in Treatment B. In this treatment arm, subjects were administered 0.4 mg of NV-101, i.e., the content of a single cartridge, intravenously as a bolus. There was no injection of local anesthetic or vasoconstrictor associated with this treatment.

Shifts in vital signs for Treatment B were similar to those seen with the other treatments. The ECG readings that were performed for 12 of 16 subjects were within normal limits.

The incidence of adverse events did not differ with Treatment B compared to the other treatments in this study. Five of the sixteen subjects experienced hypotension. Two subjects experienced bradycardia. One subject experienced a headache. One subject experienced severe injection site pain (pain above the IV site) that was considered unrelated to study-drug injection by the Investigator. All of the adverse events resolved without therapeutic intervention.

7.1.19 Postmarketing Experience

The FDA's spontaneous adverse events reports database was utilized for this analysis by the Applicant. A search was performed by the Applicant through FDA Freedom of Information Services for spontaneous adverse events utilizing the s**earch terms "Regitine" and "phentolamine." All** adverse event reports that named one of these drugs as the suspect agent were included in this analysis. No attempt was made to eliminate duplicate reports of the same case. A separate analysis was performed examining reports of fatal outcomes where phentolamine was noted by the reporter as the suspect medication.

From 1969, the time safety data was first collected by FDA through June 30, 2006, a total of 63 spontaneous reports listed Regitine/phentolamine as the suspect medication. Among these, 23 types of adverse events were reported in two or more patients. These events are listed in the table below.

Table 7-13: Adverse Events reported in ≥ 2 patients with phentolamine mesylate as the suspected medication (Table 75 from the NDA ISS)

Adverse Event	Number of Cases Reported in AERS
Angina Pectoris	2
Blood Carbon Dioxide Increased	2
Blood pH Decreased	2
Death	2
Diarrhea	3
Drug Ineffective	3
Drug interaction	2
Headache	4
Heart arrest	2
Hypertension	3
Hypotension	2

Adverse Event	Number of Cases Reported in AERS
Impotence	3
Lack of drug effect	7
Medication Error	3
Overdose NOS	2
Pain	2
Penis disorder	4
Penile pain	2
pO2 decreased	2
Priapism	23
Scar	2
Sexual Dysfunction NOS	2
Surgery	2

Among these diagnoses, priapism was the most frequent, which was most likely due to the off-label use of phentolamine for erectile dysfunction. Other diagnoses, which appeared to be related to phentolamine use for erectile dysfunction, included penis disorder, penile pain, impotence and sexual dysfunction. Based on the differences in route of administration for NV-101, these data do not appear to identify any new safety concerns.

Among the AERS diagnoses in the table above, headache and pain were reported as adverse events in the NV-101 clinical trials. To that end, these data do not identify any new safety concerns. The next **most common diagnoses – angina pectoris, heart arrest, hypertension, hypotension and diarrhea, are** all, except for angina pectoris, included in the commercial phentolamine prescribing information. These data do no appear to identify any new safety concerns for NV-101.

From the time safety data was first collected by FDA (1969) through June 30, 2006, there were a **total of three spontaneous AE reports in the FDA's database for which Regitine or phentolamine was** listed as the suspect medication and for which the patient experienced a fatal outcome. Of these three fatal outcomes, all from sources outside the US, one did not list the diagnosis and the other two are from the same individual (initial and follow-up reports) and involved a diagnosis of unstable angina, a cardiac disorder.

A review of the AERS database information for phentolamine and Regitine, by this reviewer, confirmed the findings of the Applicant.

7.2 Adequacy of Patient Exposure and Safety Assessments

The clinical evaluation of NV-101 comprised a total of nine studies, five of which involved subjects undergoing routine dental procedures (dental subjects), and four of which involved healthy subjects not undergoing dental procedures (healthy subjects). The initial studies involved assessments of safety and efficacy of varying doses of the commercially available formulation of phentolamine mesylate injected into the mandible (NOVA 02-01 and NOVA 02-02) or maxilla (NOVA 02-03) of healthy adult subjects. Following completion of the dose-

finding studies (NOVA 02-02 and NOVA 02-03), the Applicant initiated a Phase 2 (NOVA 03-001) study assessing the efficacy and safety of the to-be-marketed formulation of NV-101 for reversal of soft tissue anesthesia (STA) in adults undergoing dental procedures involving either the mandible or maxilla. Two Phase 3 studies provided the pivotal determinations of efficacy and safety of NV-101 for reversal of STA in older pediatric patients and adults undergoing dental procedures involving either the mandible (NOVA 04-100) or maxilla (NOVA 04-200). In addition, the safety and pharmacokinetics of NV-101 (NOVA 04-PK) were investigated in healthy adult subjects. Two clinical studies examined the use of NV-101 in pediatric subjects < 18 years of age. NOVA 05-PEDS evaluated safety and efficacy of NV-101 for reversal of STA in subjects 4 to 11 years of age, and NOVA 05-PEDS-PK assessed the safety and pharmacokinetics of NV-101 in subjects 3 to 17 years of age.

The formulation of NV-101 used in study NOVA 03-001 differed slightly from that used in the other studies, in that the product was filled as a 2-mL solution in vials, and delivered in 1.8-mL doses, rather than in dental cartridges designed to deliver 1.7 mL. By comparison, the commercially available phentolamine mesylate was supplied in 2-mL vials containing 5 mg of phentolamine mesylate and 25 mg of mannitol; the product was reconstituted and further diluted to the desired strengths with 0.9% sodium chloride injection for use in the clinical studies.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Safety data was derived from the clinical trials conduct by or for the Applicant. These included an adult and a pediatric PK study, dose-ranging trials involving adults who were administered local anesthetics but who did not undergo dental procedures (referred to by the Applicant as **"healthy" subject studies), and controlled studies** in adult and pediatric subjects who received local anesthetics and underwent dental procedur**es (referred to by the Applicant as "dental"** subject studies). Reversal of soft tissue anesthesia with NV-101 was assessed for a variety of local anesthetics, commonly used dental blocks, and dental procedures. The goal was to evaluate safety and efficacy under the conditions which would reflect the full range of clinical use anticipated for the drug product.

In the sections that follow, the safety database is defined in greater detail. The electronic database included with the NDA was utilized to confirm the App**licant's findings and to conduct** additional analyses. A single CRF was requested and reviewed in relationship to an apparent nerve injury sustained by a subject who was treated with NV-101 (subject 301-03-325 in study NOVA 03-001).

7.2.1.1 Study type and design/patient enumeration

The table below indicates all of the clinical trials which comprised the development plan for NV-101. Numbers of subjects and doses studied are identified for each study.

Table 7-14: Clinical trials comprising the NV-101 development plan

Subject Population Study Number (Study Type)	Population	Total Number of Subjects	Dose (mg)[B]	
Dental Subjects[A]				
NOVA 03-001 (Phase 3, randomized, double-blind, placebo-controlled, multicenter)	10 to 65 years of age; male and female	122	0 (placebo) 0.4 mg 0.8 mg	61 subjects 50 subjects 11 subjects
NOVA 04-100 (Phase 3, randomized, double-blind, placebo-controlled, multicenter)	≥ 12 years of age; male and female	244	0 (sham) 0.4 mg 0.8 mg:	122 subjects 89 subjects[G] 33 subjects[G]
NOVA 04-200 (Phase 3,randomized, double-blind, placebo-controlled)	≥ 12 years of age; male and female	240	0 (sham) 0.4 mg 0.8 mg	120 subjects 113 subjects 7 subjects
NOVA 05- PEDS (Phase 2, multicenter, randomized, double-blinded, placebo-controlled)	4 to 11 years of age; male and female; weight ≥ 15 kg	152	0 (sham) 0.2 mg 0.4 mg	56 subjects 74 subjects 22 subjects
NOVA 05-PEDS-PK (Phase 1, open-label)	3 to 17 years of age; male and female	19	0.2 mg 0.4 mg:	8 subjects 11 subjects
Healthy Subjects[C]				
NOVA 02-01 (Phase 1/2, single-center, randomized, double-blind, placebo-controlled)	18 to 65 years of age; male or female	20	0 (placebo) 0.2 mg:	10 subjects 10 subjects
NOVA 02-02 (dose-ranging, single-center, randomized, double-blind, placebo-controlled)	18 to 65 years of age; male or female	40	0 (placebo) 0.02 mg 0.06 mg 0.4 mg	10 subjects 10 subjects 10 subjects 10 subjects
NOVA 02-03 (dose-ranging, single-center, randomized, double-blind, placebo-controlled)	18 to 65 years of age; male or female	32	0 (placebo) 0.02 mg 0.08 mg 0.4 mg	9 subjects 8 subjects 7 subjects 8 subjects
III. Healthy, Other[C, D]				
NOVA 04-PK (Phase 1, open-label PK)	18 to 65 years of age; male or female	16[E]	0 mg[F] 0.4 mg 0.8 mg 0.4 mg IV	16 subjects 16 subjects 16 subjects 16 subjects

[A] Individuals undergoing dental procedures.
[B] All doses of NV-101 and phentolamine mesylate were given by intra-oral injection, except for an intravenous 0.4 mg dose in the NOVA 04-PK study.
[C] Healthy individuals not undergoing dental procedures.
[D] This study was not included in the integrated analysis.

[E] All subjects received each of the 4 treatments as prescribed by the cross-over design.
[F] Control was no injection of NV-101.
[G] Safety Analysis Set

7.2.1.2 Demographics

The subjects' demographics are divided into two groups based on whether on not the subject underwent a dental procedure as part of the study. Those subjects who underwent dental **procedures were labeled "dental subjects," and those subject**s who did not undergo dental procedures while participating in the study were **labeled "healthy subjects." The tables below** describe the demographics for each of these two sets of subjects. Each table divides subjects based on the treatment they received and the dose of NV-101 administered, if the subject was assigned to that treatment arm.

In both sets of subjects, approximately half were male and half were female. Among the dental subjects, the preponderance was white with black **and "other" comprising most of the remainder** of subjects. In the healthy subject group, the same was true. For the proposed labeled doses of 0.2-0.8 mg, the distribution of subjects by race was not sufficient to detect adverse events that may occur in a nonwhite group. However, there is no basis to suspect that race would be a risk factor for NV-101 when used in the proposed fashion. The distribution of subjects by age appeared to be adequate for the to-be-labeled dosing regimen to allow an appropriate assessment of safety. The distribution of patients by weight and height across doses of NV-101 and controls was similar and would not be expected to confound the safety analysis.

Table 7-15: Demographics of dental subjects (modified Table 10 from NDA ISS, p. 51-52)

	Dose of NV-101[A]				**Control[B]**
Variable	**0.2 mg (N = 83)**	**0.4 mg (N = 284)**	**0.8 mg (N = 51)**	**Total (N = 418)**	**Total (N = 359)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex					
Male	36 (43.4)	145 (51.1)	26 (51.0)	207 (49.5)	166 (46.2)
Female	47 (56.6)	139 (48.9)	25 (49.0)	211 (50.5)	193 (53.8)
Race					
White	45 (54.2)	214 (75.4)	45 (88.2)	304 (72.7)	274 (76.3)
Black	24 (28.9)	29 (10.2)	4 (7.8)	57 (13.6)	44 (12.3)
Asian	3 (3.6)	6 (2.1)	0 (0.0)	9 (2.2)	17 (4.7)
Other	11 (13.3)	35 (12.3)	2 (3.9)	48 (11.5)	24 (6.7)
Age					
3-11 years	82 (98.8)	27 (9.5)	0 (0.0)	109 (26.1)	56 (15.6)
12-17 years	0 (0.0)	36 (12.7)	9 (17.6)	45 (10.8)	40 (11.1)
18-64 years	1 (1.2)	194 (68.3)	40 (78.4)	235 (56.2)	237 (66.0)
≥ 65 years	0 (0.0)	27 (9.5)	2 (3.9)	29 (6.9)	26 (7.2)
Height (inches)					
N	80	284	51	415	358

Variable	Dose of NV-101[A]				Control[B]
	0.2 mg (N = 83)	0.4 mg (N = 284)	0.8 mg (N = 51)	Total (N = 418)	Total (N = 359)
	N (%)	N (%)	N (%)	N (%)	N (%)
Mean (± SD)	48.5(5.8)	66.2 (5.3)	67.1 (3.5)	62.9 (8.8)	64.7 (7.0)
Median	48.8	66.1	66.9	65.0	65.6
Range	(28.0-64.0)	(47.2-80.5)	(59.8-75.2)	(28.0-80.5)	(37.8-78.0)
Weight (lbs)					
N	83	284	51	418	358
Mean (± SD)	61.4 (24.1)	167.2 (52.0)	159.4 (33.4)	145.3 (62.0)	155.7 (55.6)
Median	55.1	164.1	163.0	149.9	154.0
Range	(33.1-192.0)	(66.1-440.9)	(88.2-220.5)	(33.1-440.9)	(39.7-326.3)

[A] 0.2 mg dose was used in NOVA 05-PEDS and NOVA 05-PEDS-PK; 0.4 mg dose was used in NOVA 04-100, NOVA 04-200, NOVA 03-001, NOVA 05-PEDS and NOVA 05-PEDS-PK; and 0.8 mg doses were used in NOVA 04-100, NOVA 04-200, and NOVA 03-001. One adult subject in NOVA 03-001 received 1/2 cartridge of NV-101 and is included in the 0.2 mg group.

[B] Control was either sham injection (NOVA 04-100, NOVA 04-200, NOVA 05-PEDS) or placebo (NOVA 03-001); no control was used in NOVA 05-PEDS-PK.

Table 7-16: Demographics of healthy subjects (modified Table 11 from NDA ISS, p. 54-54)

Variable	Phentolamine Myeselate[A]						Control[B]
	0.02 mg (N = 18)	0.06 mg (N = 10)	0.08 mg (N = 7)	0.2 mg (N = 10)	0.4 mg (N = 18)	Total (N = 63)	Total (N = 29)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex							
Male	9 (50.0)	5 (50.0)	3 (42.9)	5 (50.0)	9 (50.0)	31 (49.2)	16 (55.2)
Female	9 (50.0)	5 (50.0)	4 (57.1)	5 (50.0)	9 (50.0)	32 (50.8)	13 (44.8)
Race							
White	16 (88.9)	10 (100)	7 (100)	2 (20.0)	13 (72.2)	48 (76.2)	18 (62.1)
Black	1 (5.6)	0 (0.0)	0 (0.0)	8 (80.0)	3 (16.7)	12 (19.0)	10 (34.5)
Asian	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	2 (3.2)	1 (3.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.6)	0 (0.0)
Age							
3-11 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12-17 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18-64 years	18 (100)	10 (100)	7 (100)	10 (100)	18 (100)	63 (100)	29 (100)
≥ 65 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Height (inches)							
N	18	10	7	10	18	63	29
Mean (± SD)	66.8 (3.5)	67.3 (4.7)	65.6 (3.0)	67.8 (3.1)	67.8 (4.5)	67.2 (3.9)	67.0 (3.5)
Median	67.8	66.0	65.0	68.0	67.5	67.0	67.0
Range	(59.0-72.0)	(61.5-75.9)	(62.0-71.0)	(62.0-71.0)	(62.0-78.0)	(59.0-78.0)	(60.0-74.0)
Weight (lbs)							

N	18	10	7	10	18	63	29
Mean (± SD)	158.7 (18.8)	156.7 (16.1)	145.3 (25.2)	174.5 (17.3)	162.2 (24.4)	160.4 (21.5)	167.4 (21.7)
Median	158.0	157.5	153.0	181.0	160.0	158.0	169.0
Range	(124.0-188.0)	(132.0-188.0)	(115.0-174.0)	(138.0-192.0)	(130.0-206.0)	(115.0-206.0)	(134.0-198.0)

[A] All subjects who received commercially available phentolamine mesylate; 0.02 mg was used in NOVA 02-02 and NOVA 02-03; 0.06 mg was used in NOVA 02-02; 0.08 mg was used in NOVA 02-03; 0.2 mg was used in NOVA 02-01; and 0.4 mg was used in NOVA 02-02 and NOVA 02-03.
[B] Control was placebo injection

7.2.1.3 Extent of exposure (dose/duration)

NV-101 is to be used acutely following dental procedures; therefore, duration of exposure is not relevant as a safety issue. The extent of dose exposures, for both the dental and healthy subjects, is presented in the tables in section 7.2.1.2 above.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no secondary clinical data sources related to the use of phentolamine to reverse soft tissue anesthesia.

7.2.2.1 Other studies

The studies describe above represented all the sources of data available for the assessment of safety and efficacy of NV-101 in reversing soft tissue anesthesia.

7.2.2.2 Postmarketing experience

Phentolamine mesylate is not currently and has not been marketed anywhere in the world with an indication for the reversal of soft tissue anesthesia. Phentolamine mesylate is marketed for intravenous and intramuscular use as indicated elsewhere in this review; the postmarketing experience for these indications is described in section 7.1.17 above.

7.2.2.3 Literature

There was nothing published in the literature related to the use of phentolamine to reverse the effects of local anesthetics either following dental procedures or otherwise.

7.2.3 Adequacy of Overall Clinical Experience

A total of 418 subjects undergoing dental procedures were exposed to the proposed labeled doses of NV-101. The breakdown by age of these subjects is shown in the table below. A sufficient number of exposures occurred in each age group to allow for an adequate evaluation of safety based on the known risks of phentolamine injection and the substantially reduced exposure which occurs with NV-101. The doses used for both of the pediatric subgroups, i.e., 3-11 and 12-17 years old, are consistent with the anticipated exposures for clinical practice in terms of the numbers of cartridges of local anesthetics routinely used. The distribution of the doses in the adult population also appears to reflect the anticipated clinical scenario. There are sufficient numbers of exposures to allow a safety assessment for ages 18-64 years old, and to comment on the risks for those 65 years old or older.

Table 7-17: NV-101 exposure by age groups for dental trials (from Table 8 of the NDA ISS)

	Dose of NV-101[A]				Control[B]
Age	**0.2 mg (N = 83)**	**0.4 mg (N = 284)**	**0.8 mg (N = 51)**	**Total (N = 418)**	**Total (N = 359)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
3-11 years	82 (98.8)	27 (9.5)	0 (0.0)	109 (26.1)	56 (15.6)
12-17 years	0 (0.0)	36 (12.7)	9 (17.6)	45 (10.8)	40 (11.1)
18-64 years	1 (1.2)	194 (68.3)	40 (78.4)	235 (56.2)	237 (66.0)
≥ 65 years	0 (0.0)	27 (9.5)	2 (3.9)	29 (6.9)	26 (7.2)

Data are based on the following clinical studies: NOVA 03-001, NOVA 04-100, NOVA 04-200, NOVA 05-PEDS, NOVA 05-PEDS-PK

[A] 0.2 mg dose was used in NOVA 05-PEDS and NOVA 05-PEDS-PK; 0.4 mg dose was used in NOVA 04-100, NOVA 04-200, NOVA 03-001, NOVA 05-PEDS and NOVA 05-PEDS-PK; and 0.8 mg doses were used in NOVA 04-100, NOVA 04-200, and NOVA 03-001. One adult subject in NOVA 03-001 received 1/2 cartridge of NV-101 and is included in the 0.2 mg group. Three subjects in NOVA 04-100 received 1 ½ cartridges of NV-101 and were included in the 0.8 mg group.

[B] Control was either sham injection (NOVA 04-100, NOVA 04-200, NOVA 05-PEDS) or placebo (NOVA 03-001); no control was used in NOVA 05-PEDS-PK

The nearly even exposures between male and female subjects, mandibular and maxillary dental procedures and types of dental anesthesia blocks utilized allows for a safety assessment that covers most aspects of the clinical setting. Based on the acute use and limited exposure anticipated for NV-101 in the clinical setting, the studies conducted provide sufficient data to adequately characterize the safety profile for the full range of dental patients likely to receive the drug if it is approved for marketing.

The four randomized, double-blinded, controlled, clinical trials that assessed NV-101 for safety and efficacy when used following dental procedures (NOVA 03-001, NOVA 04-100, NOVA 04-200, and NOVA 05-PEDS) were appropriately designed to achieve their stated objectives.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Applicant submitted a single-dose local tolerance study and a battery of genetic toxicology studies with phentolamine mesylate and [redacted] impurities/degradants found in the drug product, [redacted]. A Segment I male fertility study with oral administration of phentolamine mesylate was also included in the NDA. Repeat-dose toxicology, reproductive and developmental toxicology and carcinogenicity studies were not required for this 505(b)(2) application for the proposed indication. The submitted studies were deemed adequate by the Pharmacology-Toxicology team to provide relevant preclinical data not available in the Regitine label or the literature. From a clinical perspective, the local toxicology study was a key component to the safety assessment. The study adequately addressed the concerns raised regarding the effects of NV-101 on bone, tooth, nerve and gum tissues.

b(4)

7.2.5 Adequacy of Routine Clinical Testing

The key clinical testing for NV-101 involved the following:

- monitoring of vital signs and cardiac rhythm to assess for untoward effects from systemically absorbed phentolamine and phentolamine-induced release of local anesthetic and vasoconstrictor
- assessment of the oral cavity for local reactions to phentolamine or adverse interactions between phentolamine and the local anesthetic and vasoconstrictor

The clinical trials adequately monitored for each of the above safety concerns in terms of the frequency and duration of monitoring as well as the techniques employed.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No metabolic, clearance or interaction workup was required for NV-101 secondary to its acute use and the small dose requirements.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Applicant's efforts to detect adverse events specific to administration of an alpha-adrenergic blocking agent and injections in the oral mucosa in the vicinity of sensory nerves were adequate. There were no indications that NV-101 affected hemodynamic or ECG parameters to a greater extent than placebo. Adverse events related to the oral mucosa and nerves in the oral cavity occurred with similar frequencies in NV-101-treated and placebo-treated subjects. The safety concern of most importance raised by the clinical trials was the injury to the lingual nerve which may have been related to the injection of NV-101 following a dental procedure. Whether the NV-101 itself was responsible for the injury was not fully discernible, neither was the possibility that the needle used to inject the drug traumatized the nerve. The possibility also existed that the

injection of the local anesthetic or the local anesthetic itself could have produced the injury. For all these scenarios, the risk was not negligible and needed to be considered in the benefit-risk analysis.

No recommendations for future studies are indicated at this time; however, it will be important to monitor for reports of nerve injury when the product is marketed.

7.2.8 Assessment of Quality and Completeness of Data

Based on the findings of the OSI inspection and inspection of the datasets for the individual trials and the integrated summary of safety, the quality of the data and the completeness of the datasets were adequate for conducting a meaningful safety review and elucidating the risk profile for NV-101.

7.2.9 Additional Submissions, Including Safety Update

The following additional submissions were made to the NDA after the initial filing, and the clinically relevant information has been incorporated into this review:

June 8, 2007 - (0001): Requested SAS files for efficacy and safety analyses and a revised ISS Figure 2 of mean diastolic blood pressures in dental subjects were submitted.

June 22, 2007 - (0002): New patent information was provided.

August 6, 2007 - (0003): The 120-day safety update was submitted, which indicated no new safety information had been generated and no new adverse events had been reported. Thus the ISS of the original NDA submission remained current. The submission also included an update on postmarketing experience with phentolamine mesylate for injection. Both a literature search and a review of newer AERS data did not identify any new safety concerns for NV-101.

October 19, 2007 - (0004): This submission provided a listing of all clinical trial protocol amendments and a listing of all protocol deviation for the two pivotal trials

November 9, 2007 - (0005): This submission provided a more detailed listing of the protocol deviations for the two pivotal trials.

November 14, 2007 - (0006): This submission included a modified package insert, which incorporated FDA-recommended changes, primarily grammatical in nature.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Those adverse events which occurred in ≥ 1% of the treatment groups and which occurred with greater frequency in NV-101-treated subjects then placebo- or sham-treated subjects are listed below with an assessment as to whether they are consideredNV-101 related.

- **Bradycardia – not likely related to NV-101** as alpha-adrenergic blockade would be expected to induce tachycardia.
- **Hypotension – possibly related to NV-101 al**though the incidence is low, 2%, and the extent of hypotension was similar to that seen with placebo injections.
- **Abdominal pain – possibly related although Re**gitine use is not associated with pain.
- Injection site reactions – **possibly related although** the frequency was low and comparable to that of the placebo-treated subjects.
- Injection site pain, jaw pain, oral pain, a**nd tenderness – possibly re**lated; however, it is difficult to discern to what degree the NV-101 contributes to this adverse event. For subjects exposed to sham injections as the control, 4% reported injection site pain compared to 5% of NV-101-treated subjects.
- **Lingual nerve injury – possibly related; how**ever, whether the injury was due to the needle or the drug product or possibly due to the needle or drug product for the local anesthetic was not possible to determine.

There were no limitations to the data that would impact on describing the safety profile for NV-101. Studies of NV-101 and placebo in subjects not exposed to local anesthetics may have provided a bit more information regarding the relatedness of adverse events to NV-101; however, the administration of local anesthetics and presence of numbness at the time of administration of NV-101 are requirements for the **product's use. As such, safety should be** considered in the context of the clinical setting, and in that rega**rd, the Applicant's studies were** appropriately designed.

The overall safety profile for NV-101 suggests that minimal risk is associated with the use of this drug product in healthy individuals. The adverse events that occurred in the clinical studies resolved without therapeutic intervention; although it is not clear that the patient who experienced a lingual nerve injury fully recovered as she was lost to follow-up.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence of Adverse Events

7.4.1.1 Pooled data vs. individual study data

Studies were pooled based on whether subjects underwent a dental procedure or not. Doses of NV-101 administered, type of placebo used, i.e., sham injection or normal saline injection, dental

anesthetic administered, type of dental block used, and location of dental procedure were factors that were considered individually for safety issues prior to combining the studies based on dental procedure. The pooled data, like that from individual studies, did not identify any adverse events that might be specifically tied to the use of NV-101.

7.4.1.2 Combining data

The pooling of data from the studies was performed by simply combining the adverse events based on treatment (NV-101 or placebo) and the dose of NV-101 administered.

7.4.2 Explorations for Predictive Factors

The minimal difference in adverse reactions observed with NV-101 versus placebo suggests that the systemic levels associated with acute use were either too low, too short in duration, or both to result in clinically relevant adverse findings. Regardless of the reason, there were no adverse findings that warranted explorations for predictive factors.

7.4.2.1 Explorations for dose dependency for adverse findings

No formal explorations for adverse findings related to dose dependency were conducted. The relationship between dose and adverse events is described in Section 7.1.5 of this review.

7.4.2.2 Explorations for time dependency for adverse findings

No formal explorations for adverse findings related to time dependency were conducted.

7.4.2.3 Explorations for drug-demographic interactions

No formal explorations for drug-demographic interactions were conducted.

7.4.2.4 Explorations for drug-disease interactions

No formal explorations for drug-disease interactions were conducted.

7.4.2.5 Explorations for drug-drug interactions

No formal explorations for drug-drug interactions were conducted.

7.4.3 Causality Determination

The distribution of adverse events between treatment groups was similar for each preferred term when treatment-emergent adverse events were evaluated. The requirement made by the Division of the Applicant to use a sham injection as the control for the pivotal trials allowed some discernment as to whether adverse events were associated with either the use of NV-101 or the need to introduce a needle into anesthetized tissues, with its concomitant risks, to administer the drug.

There was only one adverse event, a lingual nerve injury, where causality may have been more likely due to the injection rather than the injectate, which in this case was NV-101. Although the drug itself may not have been responsible, and there is no way to fully exonerate the NV-101, the need to inject it was considered, by this reviewer, as part of the treatment and, therefore, the resultant injury was attributed **to "treatment with NV-101."**

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The following are the dosing regimen and administration instructions proposed by the Applicant:

- 1/2 cartridge (0.2 mg) of NV-101 when 1/2 cartridge of local anesthetic has been administered.
- 1 cartridge (0.4 mg) of NV-101 when 1 cartridge of local anesthetic has been administered.
- 2 cartridges (0.8 mg) of NV-101 when 2 cartridges of local anesthetic have been administered.

NV-101 is administered using the same location(s) and same techniques(s) (infiltration or block injection) used for the administration of local anesthetic.

The dose-ranging studies conducted by the Applicant provide adequate support for the efficacy of the 0.4- and 0.8-mg doses in adult patients. The dose response trials, NOVA 02-02 and NOVA 02-03, demonstrated increased efficacy with increasing dose. In NOVA 02-02, it was demonstrated that only the 0.4-mg dose of NV-101 significantly reduced the time for reversal of soft tissue anesthesia in the chin, lip and tongue. In NOVA 02-03, the 0.4-mg dose of NV-101 significantly reduced the time for reversal of soft tissue anesthesia in the lip but not the nose. The safety profiles did not differ substantially between doses for either the mandibular or maxillary use of NV-101.

The assessment of efficacy in pediatric patients was performed in NOVA 05-PEDS, which showed that there was more rapid return to normal sensation of the lip and tongue with both 0.2- and 0.4-mg doses of NV-101, used to reverse ½ and 1 cartridge of local anesthetic with vasoconstrictor, respectively, than with placebo. However, the pediatric studies were limited by the unproven validity of the palpation technique for assessing return of sensation.

Summary reviews of the aforementioned trials can be found in Section 10.1 of this review. Dose modification for special populations was not assessed. The only limit placed on timing of administration of NV-101 in the clinical trials was that the lip had to be numb at the time of administration.

8.2 Drug-Drug Interactions

Drug-drug interactions were not assessed for NV-101. Due to the low systemic levels of phentolamine observed following intraoral administration and the lack of a clinically significant hemodynamic effect observed compared to placebo, it is not likely that NV-101 poses a significant risk to patients. The limited safety data from subjects taking vasoactive drugs,

including sympathomimetics, did not indicate a safety issue existed that would require either a dose adjustment of NV-101 or contraindicate its use.

8.3 Special Populations

The only consideration for dose adjustments in special populations involved the use of NV-101 in pediatric patients. [redacted] Use in pediatric patients under [redacted] years of age or <15 kg was not evaluated and, therefore, is not recommended. b(4)

Although geriatric patients were not evaluated separately, it was noted that 55 subjects from all the clinical trials were age 65 and over, while 21 were age 75 and over. There were no overall differences in safety or effectiveness observed between these patients and their younger cohorts.

8.4 Pediatrics

On October 30, 2003, the Division and the Sponsor met for an End-of-Phase 2 meeting at which the Sponsor posed the following question:

> **"Children ages 10-17 were include**d in the Phase 2 study (Study No. NOVA 03-001) (N=24), and are proposed [redacted] Does the Division concur with this approach, and does the Division have a minimum number of subjects in this age group that should **be included in the Phase 3 study?"** b(4)

The Division's response, submitted prior to the meeting, was as follows:

> **"The label will reflect the population**s studied. Off-label use is a consideration in the overall benefit/risk analysis for the drug.
>
> We strongly encourage you to evaluate, at some point, the use of phentolamine in children of all ages who may benefit from reversal of local anesthetic.
>
> Approximately 100 children with an adequate age distribution should provide a sufficient safety database. Adequacy of the database size will depend in large part upon clinical findings, dosing, and demographic **considerations."**

At the meeting, the Division questioned the age cutoff of [redacted] years old as it considered a younger population more likely to be at risk for injury from biting an anesthetized tongue or lip. The Sponsor indicated that it would be difficult to test the product in a young population due to concerns about the ability of the younger patients to reliably provide efficacy data, such as the information used in the STAR questionnaire. The Sponsor indicated that the collection of safety data in this population was less likely to be problematic. The Division stated it might be acceptable to look primarily at safety data in children, but that if the Sponsor wished to do so, they would need to provide adequate justification or evidence that it would be appropriate to extrapolate efficacy from older children and adults. The Division advised the Sponsor to talk with pediatric dentists about the use of this drug in the pediatric population. The Sponsor agreed and asked whether a pediatric study could be a post marketing commitment. The Division stated that this should be addressed at the time of the NDA filing.

b(4)

The NDA submission included a Request for Partial Pediatric Waiver for the following two groups:

1. **Newborns (birth to 1 month of age) – The** Applicant cited literature which indicated that the first tooth erupts between 4 and 13 months of age and argued that there is minimal, if any, need for administration of a local anesthetic containing a vasoconstrictor prior to a dental procedure. The Applicant also indicated that the limited availability of patients in this age group would preclude the conduct of a meaningful clinical trial.

2. **Infants (1 month to 2 years of age) – The** Applicant again cited literature which indicated that the first teeth have just begun to erupt in this age group and, therefore, there is minimal, if any, need for administration of a local anesthetic containing a vasoconstrictor prior to a dental procedure. It was also stated that children receive their first dental evaluation within the first year of life, and that for those infants with teeth up to age 2 **years old, most dental visits are "wellness visits" where no dental procedure is** performed. Thus, there is a limited need for NV-101 in this age group and, at best, a limited availability of patients in this age group for the conduct of a meaningful clinical trial.

The Applicant has provided sufficient justification for the waiver, and this reviewer recommends that it be granted.

The Applicant has not provided sufficient clinical data to fully assess safety and efficacy in the pediatric patient population aged 3-5 years old. In Section 9.3.2, Required Phase 4 Commitments, recommendations are made that will address the shortcomings of the development program for this population and provide the data to allow an appropriate benefit-risk analysis for this age group.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was held regarding the development program, safety or efficacy for NV-101. Although the indication sought for this product is novel, the Applicant has

established a means of assessing clinical relevance for the use of NV-101 and demonstrated a sufficiently favorable benefit-risk ratio for the product that the need for Advisory Committee input was not warranted.

8.6 Literature Review

A review of the literature revealed no information related to the use of phentolamine in the oral cavity or elsewhere for the reversal of local anesthesia. A broader review of the literature did not reveal any phentolamine-related safety issues that have not been described in the Regitine label or noted in the AERS database.

8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan was not required for NV-101 and none was submitted by the Applicant.

8.8 Other Relevant Materials

The Division of Scientific Investigations was asked to inspect the four clinical sites which generated more than half of the efficacy data for the pivotal trials. There were a substantial number of protocol deviations associated with these trials, and an inspection was requested to **assess the Investigators' level of** adherence to the study protocols. The inspection of these sites were not impeded in any way and resulted in a finding of no significant regulatory violations. The data from these sites appeared to the inspector to be acceptable in support of the respective indication.

The Study Endpoints and Label Development (SEALD) team was asked to determine whether the Applicant had provided adequate validation of the metrics it developed, i.e., the STAR questionnaire and the FAB test, to assess the clinical relevance of reversal of soft tissue anesthesia. They were also asked to determine whether the lip and tongue palpation tests for efficacy assessments and use of the STAR questionnaire and the FAB test were valid in the pediatric population. Based on the content of the submission, the SEALD team made the following comments:

- Novalar has not included information to ascertain that the lip/tongue palpation tests can be adequately completed by the pediatric population (<12 years of age). It has not been determine if children can comprehend the instructions, questions, and responses. The large number of efficacy assessments excluded from analysis due to lack of patient comprehension (n=37) in Study NOVA-05-PEDS, suggests that the instruments are not appropriate for this age group.
- Although Novalar selected 3 domains: sensory, perception, and function, in order to evaluate the local dental anesthetic effects in their pivotal clinical studies in patients > 12 years of age, in the study involving children 4-12 years of age, Study NOVA-05-PEDS,

only the domain of sensation was evaluated. Justification has not been submitted to suggest that the omitted perception and function assessments are not important measurements for this pediatric population. In order to adequately assess the efficacy of NV-101 in reversing the effects of dental anesthesia in the pediatric population, it is recommended that Novalar develop age-appropriate instruments which measure the sensation, perception, and function outcomes.

- The use of the 7 questions from the Soft Tissue Anesthesia Recovery (STAR) Questionnaire as a composite score to measure the impact of local dental anesthesia in adults is supported by the instrument development/validation plan submitted. Therefore, the STAR Questionnaire is an acceptable endpoint as utilized in the pivotal clinical trials for evaluating perceived clinical benefit from reversal of dental anesthesia in adults.
- The data from Study NOVA 05-SQV do not support the content validity of the STAR Questionnaire for use in patients 12-17 years of age. In study NOVA 05-SQV, several items rated by the target population in terms of commonality, obtained mean patient rated scores of <1 (1 = somewhat common). Based upon the results of this study, the STAR Questionnaire may need to be revised for use in this age group of patients.
- Novalar has not provided any information concerning the development of the Functional Assessment Battery (FAB) in order to ascertain its content validity. Therefore, SEALD cannot determine the adequacy of this instrument in terms of measuring function as a result of dental anesthesia.

DMETS and DDMAC had no objections to the use of the proposed proprietary name, OraVerse, at the time of the mid-cycle review. A re-review of the name before the NDA approval to rule out any objections based upon approvals of other proprietary and/or established names since the mid-cycle review found no basis for objecting to the proposed proprietary name.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant has adequately demonstrated that NV-101 significantly reduces the duration of soft tissue anesthesia in adults following the most commonly performed dental blocks using the most commonly administered local anesthetic-vasoconstrictor combination products. This reduction in anesthesia duration was substantial, on the order of an hour to an hour and a half. The recovery of normal sensation was accompanied by both a perceived and a demonstrated ability to eat, drink, smile, speak and not drool. Safety and efficacy have been adequately assessed in clinical trials involving multiple dental procedures and assessing the use of NV-101 for procedures involving teeth in either the maxilla or the mandible. The risk from NV-101 does not differ substantially from placebo. The greatest concern for safety raised by the clinical development program was the possibility of a nerve injury resulting from the trauma of injection of NV-101 into anesthetized tissues in the vicinity of sensory nerves. The injury may also have been caused by the injection of the local anesthetic thereby complicating the risk assessment for NV-101.

Safety and efficacy of NV-101 have also been demonstrated in portions of the pediatric population. In pediatric patients ages 6-17 years old, the Applicant has demonstrated that NV-101 significantly reduces the time to return of normal sensation in the lip compared to sham. The magnitude of the effect of NV-101 in this patient population was similar to that observed in adults and was sufficiently large compared to the minimal level of risk observed to generate a favorable benefit-risk ratio. The Applicant collected additional data, which demonstrated a significantly reduced time for the return of normal sensation in the tongue and similarly reduced times for the perception of return to normal function, for the actual return of such function, and for the relief of concern for self-inflicted injury (biting the tongue, lip or cheek), for patients 12-17 years of age thereby providing further evidence of a clinical benefit for NV-101. Although the Applicant has not provided such evidence in the younger patients, the combination of the magnitude of the effect of NV-101 and the increased risk in younger patients for self-inflicted injury while the soft tissues are anesthetized was sufficient to outweigh the small level of risk associated with its use.

Efficacy of NV-101 was not assessed in pediatric patients who were 3-5 years old; however, safety was evaluated and did not appear to differ from that with use in adults. As this age group is more vulnerable than their older counterparts for self-inflicted injury, there is a clear indication for further study of safety and efficacy in this subgroup.

9.2 Recommendation on Regulatory Action

It is recommended that NV-101 be approved for the indication of reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection

of a local anesthetic containing a vasoconstrictor. At this time, the product should be approved for use only in adult patients and pediatric patients ages 6-years old and older.

9.3 Recommendation on Postmarketing Actions

The only postmarketing-action recommendation is that the Applicant conducts the necessary studies to satisfy the required Phase 4 commitments listed in section 9.3.2 below in order to achieve compliance with PREA.

9.3.1 Risk Management Activity

No postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

The Applicant was advised during the End of Phase 2 meeting that use of NV-101 in pediatric patients was likely to occur in the clinical setting and that the product offered a potential benefit to this population in terms of safety, e.g., reduce the incidence of biting the lip, tongue or cheek, and in terms of patient satisfaction. The Applicant has provided adequate justification for not evaluating pediatric patients ages 0-2 years old, and has provided safety data for the pediatric population ages 3-18 years of age. Assessments of efficacy in pediatric patients 12-17 years of age were also made in the two pivotal trials, and the Applicant has demonstrated a clinical benefit to the markedly diminished duration of anesthesia in this population. As it is likely that:

- the return to normal sensation in patients 3-5 years old may be accelerated to the same degree as adults and older children
- the safety profile does not differ substantially in this age group than in the others, and
- a safety benefit may be had in the reduction of self-inflicted injuries

it is recommended that the Applicant commit to the following:

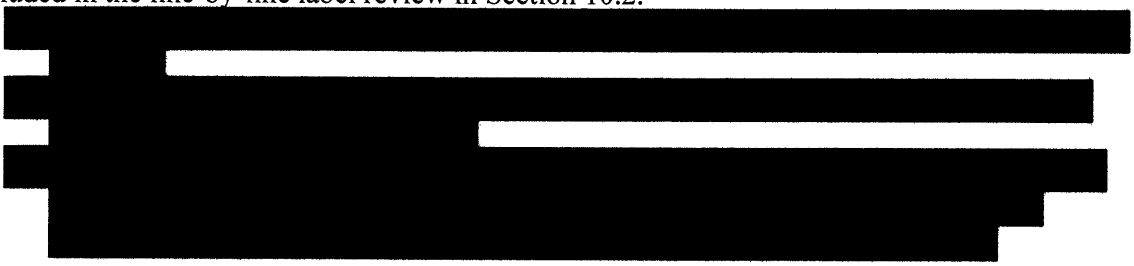
1. Develop and, if necessary, validate a technique for assessing return of sensation in pediatric patients 3-5 years of age following soft tissue anesthesia.
2. Conduct clinical trial(s) designed to demonstrate whether a significant and substantial reduction in the return of normal soft tissue sensation occurs in pediatric patients ages 3-5 years old following the administration of NV-101 compared to a sham injection. One trial may be sufficient in light of the data already obtained in this population provided the means of assessing return of normal sensation are valid for the entire age group.

9.3.3 Other Phase 4 Requests

No Phase 4 requests are recommended from a clinical perspective.

9.4 Labeling Review

The major changes need in the propose label are listed below; the specific edits to the label are included in the line-by-line label review in Section 10.2.



b(4)

The Division of Medication Errors and Technical Support (DMETS) provided a review of the proposed trade name, OraVerse, and had no objection to its use.

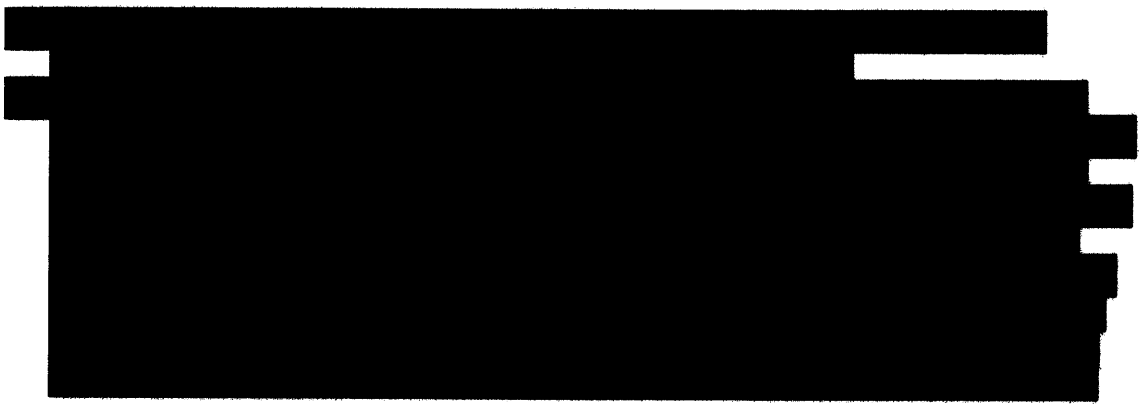
There is no need for a Mediation Guide or Patient Package Insert based on the findings for the safety and efficacy profiles.

9.5 Comments to Applicant

The following comments to the Applicant are recommended based on previous discussions of pediatric evaluations and the results of the pediatric trials.

You were advised during the End-of-Phase-2 meeting that the use of NV-101 in pediatric patients was likely to occur in the clinical setting and that the product offered a potential benefit to this population in terms of safety, e.g., reduce the incidence of biting the lip, tongue or cheek, and in terms of patient satisfaction.

In the NDA, you have provided adequate justification for not evaluating pediatric patients ages 0-2 years old and have provided safety data for the pediatric population ages 3-18 years of age. However, the primary outcome for efficacy in pediatric patients has only been assessed in patients 6-17 years of age. Therefore, it is recommended that the following commitments be made:



b(4)

b(4)

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 NOVA 04-100

> **"A Phase 3, Multicenter, Randomized, B**linded, Controlled Study of NV-101 for Efficacy, Pharmacodynamics and Safety in Dental Patients Undergoing Mandibular **Procedures"**

NOVA 04-100 was submitted to DAARP on September 13, 2005, for review as a Special Protocol Assessment (IND 65,095 N-049-SM). On October 26, 2005, DAARP issued a letter to the Sponsor indicating its agreement that the design and planned analysis of the study were acceptable as modified and clarified. The protocol was initiated on February 10, 2006 with the randomization of the first subject and was terminated on May 26, 2006, when the last subject completed the study. The final study report was dated October 25, 2006, and indicated that the study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study.

10.1.1.1 Objectives

Primary Objective

- To determine if NV-101 accelerated time to normal sensation of the lower lip compared to control, as measured by a standardized palpation procedure.

Secondary Objectives

- To determine if NV-101 accelerated the time to STAR-7 score of zero as measured by the soft tissue anesthesia recovery (STAR) questionnaire;
- To determine if NV-101 accelerated the time to normal function as measured by a functional assessment battery (FAB);
- To determine if NV-101 accelerated the time to normal sensation of the tongue as measured by standardized palpation procedure;
- To characterize the pharmacodynamic profile of NV-101 as measured by onset and offset of treatment effect; and
- To evaluate the safety and tolerability of NV-101 as measured by the incidence, severity, and duration of adverse events and intraoral pain as measured by the H-P VAS, analgesic requirements for the treatment of intraoral pain, clinically significant findings in oral cavity assessments and changes in vital signs.

10.1.1.2 Study Design

This study was Phase 3, multicenter, randomized, blinded, and placebo-controlled clinical study in design. It was intended to evaluate the efficacy, pharmacodynamics, and safety of NV-101 when used for the reversal of soft tissue anesthesia (STA), i.e., anesthesia of the lip and tongue, in subjects undergoing restorative or periodontal maintenance procedures involving the mandible. The procedures evaluated were to have required local anesthesia with an anesthetic agent containing a vasoconstrictor. Subjects were to have been randomized with respect to both the type of anesthetic/vasoconstrictor and the study treatment (NV-101 or sham injection). The study was planned to randomize approximately 240 subjects (120 subjects per treatment group).

10.1.1.3 Study Population

Inclusion Criteria

1. Male or female, ≥12 years of age;
2. Sufficiently healthy to receive routine dental care, as determined by the Investigator;
3. Underwent a restorative procedure involving the mandible such as cavity preparation, restoration/filling, or crown or a periodontal maintenance procedure, such as teeth cleaning (non-surgical scaling and/or root planing) on one side of the lower mouth;
4. Treated with 1 or 2 cartridges of local anesthetic/vasoconstrictor administered by one of the following intraoral injection techniques:
   - inferior alveolar nerve block,
   - Gow-Gates nerve block,
   - Vazirani-Akinosi block,
   - mental-incisive block,
   - supraperiosteal injection;
5. Underwent dental procedure that was completed within 60 minutes of the first administration of local anesthetic
6. Normal lower lip and tongue sensations at baseline prior to administration of local anesthetic;
7. Experienced numbness in the lower lip on the side of the procedure at the completion of the dental procedure;
8. STAR-7 score of zero prior to anesthetic;
9. FAB, as scored by subject and observer, was normal prior to anesthetic;
10. Negative urine pregnancy test at screening for females of childbearing potential past menarche (including all females except those whose menstrual periods had not occurred for ≥1 year after menopause or who were surgically sterilized or had a hysterectomy);
11. Understood and gave written informed consent;
12. For subjects 12 to 17 years of age, gave written assent and parent(s) or legal guardian(s) gave written informed consent; and
13. Was able to communicate with the Investigator and study staff, and understand and comply with the requirements of the protocol.

Exclusion Criteria

1. History or presence of any condition that contraindicated routine dental care;
2. Required more than 2 cartridges of local anesthetic (excluding supplemental injections) or use of nitrous oxide or sedatives to perform the scheduled dental procedure;
3. Scheduled dental procedure required > 60 minutes to complete;
4. Was unable to tolerate 1 liter of water over 5 hours;
5. Had any of the following concurrent incapacitating medical conditions:
   - unstable angina,
   - uncontrolled cardiac arrhythmias,
   - uncontrolled hypertension,
   - uncontrolled hyperthyroidism,
   - significant infection or inflammatory process of the oral cavity;
6. Used any of the following concomitant medications: opioid or opioid-like analgesic (e.g., codeine, tramadol, pentazocine) within 24 hours prior to administration of anesthetic;
7. Allergy or intolerance to lidocaine, articaine, prilocaine, mepivacaine, epinephrine, levonordefrin, sulfites, phentolamine or topical benzocaine;
8. Had used any investigational drug and/or participated in any clinical study within 30 days of study drug administration;
9. Had participated in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia (STA); or
10. Had any condition which in the opinion of the Investigator increases the risk to the subject of participating in this study or decreases the likelihood of compliance with the protocol.

Criteria for Removal of Subjects from the Study

1. Significant protocol violation on the part of the Investigator;
2. Significant noncompliance on the part of the subject;
3. Withdrawal of consent (refusal of the subject to continue treatment or observations);
4. Adverse event or unacceptable toxicity;
5. Decision by the Investigator that termination is in the subject's **best medical interest;**
6. Unrelated medical illness or complication; or
7. Lost to follow up.

For subjects removed from the study, the dates and reasons for subject withdrawal were to have been recorded, and in addition, all evaluations specified for the end of the observation period (5 hours after administration of study drug) were to have been performed, if feasible, at the time of withdrawal.

10.1.1.4 Efficacy Endpoints (details of tests are provided in Appendix 1)

1. Observed soft tissue sensation in the lower lip and tongue
2. Perception of function/sensation assessed by the Soft Tissue Anesthesia Recovery questionnaire (STAR-7),

3. Observed functions of smiling, speaking, drinking and drooling evaluated using the Functional Assessment Battery(FAB), and
4. Pharmacodynamics

The following sequence was to have been used for efficacy assessments:

1. lip and tongue palpation
2. STAR questionnaire
3. FAB

When a time point did not require the STAR assessment, the lip and tongue sensation ratings were to be done first, followed by the FAB.

10.1.1.5 Methods

The protocol involved two randomizations. The first randomization was to have been performed to assign the local anesthetic for the dental procedure, and the second randomization was to have been performed for the assignment of study treatment, as described below.

Randomization to local anesthetic was to have been performed prior to the start of the dental procedure. Subjects were to be randomized, in a 2:1 ratio, to either 2% lidocaine with 1:100,000 epinephrine or another anesthetic containing a vasoconstrictor. The 2:1 ratio was used as 2% lidocaine with 1:100,000 epinephrine is the most commonly used anesthetic in dental practice. The other anesthetic/ vasoconstrictor combinations were to include:

1) 4% articaine with 1:100,000 epinephrine
2) 4% prilocaine with 1:200,000 epinephrine
3) 2% mepivacaine with 1:20,000 levonordefrin

These were to have been randomly assigned in a 1:1:1 allocation ratio, resulting in a 6:1:1:1 overall ratio. No stratification factors were used for randomization to anesthetic.

Following completion of the dental procedure, subjects who met all eligibility criteria were to have been randomized to receive NV-101 or sham (control) in a 1:1 allocation ratio using a dynamic (adaptive) randomization scheme. The Applicant indicated that this scheme was utilized to balance important stratification factors across treatment groups including study center, anesthetic, the number of cartridges of anesthetic administered (1 or 2), and subject age (12-17 years, 18-64 years, 65 years or older) using an algorithm designed to minimize numerical imbalance within each stratum. Subjects who received a single cartridge of anesthetic were to have received a single injection of NV-101 or a single sham injection; subjects who received two cartridges of anesthetic were to have received two injections of NV-101 or two sham injections. Sham injections were to mimic the time, preparation and application of NV-101, through the use of a syringe with a capped needle that did not allow tissue penetration.

The Investigator who administered the anesthetic was also to have administered the NV-101 or sham and was not to have been blinded. The subject was to have been blinded to the study

treatment. A visual barrier was to have been used to obstruct the subject's view of the preparation and administration of study drug. A separate member of the investigative team, who was blinded to the treatment assignment, was to have performed subsequent assessments during the 5-hour observation period.

Study personnel who were to be involved in assessments following administration of study drug were not to have been present at the time of the preparation and administration of study drug, but were to have been informed about the site(s) of anesthetic and study drug administration and the site of the procedure.

The efficacy assessment were to have comprised the following variables: observed soft tissue sensation in the lower lip and tongue, perception of function/sensation (STAR-7), observed functions of smiling, speaking, drinking and drooling (FAB), and pharmacodynamics. The following sequence was to have been used for efficacy assessments:

1. lip and tongue palpation
2. STAR questionnaire
3. functional assessment battery (FAB)

When a time point did not require the STAR assessment, the lip and tongue sensation ratings were to be done first, followed by the FAB.

Recovery from soft tissue anesthesia (STA) in the lower lip and tongue was to have been determined by palpation every 5 minutes for 5 hours after completion of study drug administration starting at 10 minutes after study drug administration. Palpation was to have consisted of soft tapping of the lower lip and tongue with the subject's index or middle finger. Subjects were to have rated the degree of lip and tongue numbness as "numb", "tingling", or "normal". Tingling was to have been defined as a sensation of "pins and needles." Prior to the start of the dental procedure, subjects were to have received training on the required lip and tongue palpation technique according to standardized instructions.

The time to recovery of normal sensation for both the lip and tongue was to have been calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation. The recovery of normal sensation was also to have been considered to occur if the sensation test was rated normal at the subject's final evaluation and the rating from the preceding assessment was other than normal (i.e., not done, numb, or tingling). Subjects who did not meet these criteria before the end of the 5-hour observation period were to have been right-censored at the time of the subject's last sensation rating. No imputation was to have been used for missing sensation data.

The STAR scoring was to have been based on the STAR-7 questionnaire, which was to have been self-administered every 30 minutes during the 5-hour observation period after the administration of study drug.

Smiling, speaking, drinking and drooling were to have been assessed by both the subject and the observer using the FAB tool. A subject was to have been considered to have "abnormal function" if one or more functions were deemed abnormal. The tests were to have been

conducted in the following sequence: (1) smiling, (2) speaking, (3) drinking, and (4) drooling. Initially, assessments of smiling, speaking, and drooling, but not drinking, were to have been done every 5 minutes starting at 10 minutes after study drug administration until the results were found to be normal by both the subject and the observer. The drinking assessment was then to have been started, and all four functions were then to be tested every 5 minutes until all four functions were normal on two consecutive assessments by both subject and observer ratings. Thereafter, the frequency of testing was to have been decreased to every 30 minutes for the remainder of the 5-hour observation period.

The onset (recovery from STA) and possible offset (re-emergence of numbness or tingling) of the NV-101 treatment effect were to have been determined during the 5-hour observation period using the standardized palpation procedure. Pharmacodynamic effects were to have been determined for both the lower lip and the tongue based on this technique.

The safety and tolerability of NV-101 was to have been evaluated based on the following parameters:

- Incidence, severity, and duration of intraoral pain as measured by the Heft-Parker Visual Analog Scale (H-P VAS)
- Clinically significant findings from oral cavity assessments
- Analgesic requirements for the treatment of intraoral pain
- Changes in vital signs (blood pressure, pulse, respiration, and temperature)
- Incidence, severity, and duration of adverse events

General and specific oral cavity assessments (OCA) were to have been performed to evaluate complications of the intraoral submucosal injection(s) used in the study. The general oral cavity assessment was to have consisted of a broad evaluation of the mouth. The specific oral cavity assessments were to have consisted of evaluations of oral tissues at the injection site(s) and procedural site(s). The general OCA was to have been done before anesthetic administration, before randomization, and prior to discharge. The specific OCA was to have been done immediately after anesthetic and study drug administration, every 15 minutes after administration of study drug for the first hour and hourly thereafter. Clinically significant abnormal OCA findings were to have been recorded as adverse events on the appropriate CRF.

The use of analgesics for intraoral pain was to have been evaluated following the dental procedure throughout the study. Subjects who requested an analgesic for intraoral or mouth pain were to have been given ibuprofen. Subjects who were intolerant or allergic to ibuprofen were to be given acetaminophen.

Blood pressure and pulse were to have been assessed before and after administration of anesthetic and study drug, either in the supine or sitting position, or after standing for one minute, as follows. Blood pressure and pulse were to have been determined before administration of anesthetic, before randomization, every 15 minutes after study drug administration during the first hour, hourly thereafter, and prior to discharge. Standing (for one minute) blood pressure and pulse were to have been determined before administration of anesthetic, and within 5 minutes and between 10 and 20 minutes of study drug administration.

Temperature and respiration were to have been determined immediately prior to local anesthetic administration, within 15 minutes after administration of study drug and prior to discharge.

All AEs occurring after the study drug administration were to have been recorded on the CRF and reviewed by the Medical Monitor. All adverse events were to have been followed until resolution.

On completion of the study, a final quality audit was to have been performed before locking the database. All variables received for a random sample of 10% of all subjects were to have been audited against the CRFs. The 10% of subjects were randomly selected. The acceptable error rate was deemed $\leq 0.05\%$, excluding text and dictionary fields. In the case of an error rate > 0.05%, data for an additional 10% of subjects were to have been audited. In the case that the error rate for the second group also was > 0.05%, all data for all subjects were to have been audited. Any error found was to have been corrected. Additionally, the database was to have been audited against the CRFs for the following semicritical variables using a separate random sample of 10% of subjects: inclusion/exclusion criteria, subject demographics, tongue palpation, STAR questionnaire, FAB, adverse events, anesthetic and study drug administration, and end-of-study record. The acceptable error rate was to have been $\leq 0.01\%$. Additional audits were to have been performed as described above using the error rate cutoff of $\leq 0.01\%$.

Finally, lip palpation data, which were used for determination of the primary efficacy endpoint (critical variable), were audited for all subjects. Any error that was found was to be corrected in the database. Once the error rates for the database audits were within acceptable limits and approval was received from Novalar, the database lock process was to be initiated.

10.1.1.6 Schedule

Table 10-1: Schedule of Study Assessments (Table 9-1 from Final Study Report)

Assessment	Period 1	Period 2	Period 3	Period 4	Period 5
	Screening Day -14 to Day 1	Dental Procedure Day 1	Study Drug Day 1	Observation Day 1	Follow-Up Day 2 to Day 3
Informed Consent/Assent & Assign Screening Number	X				
Medical/dental history/Concurrent Illness	X[A]				
Demographics (incl. ht. & wt.)	X				
Urine pregnancy test, if applicable	X				
Training: lip & tongue palpation, STAR, FAB, H-P VAS	X				
BP & pulse (after standing for 1 min.)		X[C]		X[J]	
BP & pulse (supine or sitting)		X[C]	X[E]	X[J]	
Temperature & respirations		X[C]		X[J]	
Confirm Baseline Criteria	X[B]				

Assessment	Period 1	Period 2	Period 3	Period 4	Period 5
	Screening Day -14 to Day 1	Dental Procedure Day 1	Study Drug Day 1	Observation Day 1	Follow-Up Day 2 to Day 3
Randomization to Anesthetic		X			
Apply Topical Anesthetic, if needed		X[C]			
Administer Local Anesthetic & record time		X			
Dental Procedure & record time		X			
Confirm Selection Criteria			X[F]		
Randomize to Study Drug - record time & assign Subject ID #			X		
Place Visual Barrier for Blinding			X[G]		
Administer Study Drug & record time			X		
Remove Visual Barrier				X	
Lip & tongue palpation	X		X[E]	X[J]	
STAR Questionnaire	X		X[E]	X[J]	
FAB	X		X[E]	X[J]	
H-P VAS – anesthetic injection(s)		X[D]			
H-P VAS - study drug injection(s)				X[H]	
H-P VAS - on side of dental procedure			X[E]	X[J]	
General Oral Cavity Assessment		X[C]	X[E]	X[J]	
Specific Oral Cavity Assessments (Injection/Procedure Sites)		X[D]		X[J]	
Concomitant Medications	X[I]	X	X	X[J]	X
Adverse Events				X[J]	X
Schedule/Telephone Follow-Up				X	X
Discharge subject (record time)				X	

[A] Update during Baseline Evaluation on Day 1 if different from day of Initial Screening of Selection Criteria

[B] Normal lower lip and tongue sensation, STAR-7 score is zero, FAB by subject and observer rating is normal, no opioids or opioid-like analgesics within 24 hours, pregnancy criteria/negative pregnancy test, if applicable

[C] Immediately prior to administration of local anesthetic

[D] Immediately after administration of local anesthetic

[E] Prior to randomization to NV-101 or sham

[F] Subject has numbness of the lower lip and tongue on the side of the dental procedure at completion of dental procedure, dental procedure was completed within 60 minutes of first administration of local anesthetic, not more than 2 cartridges of local anesthetic (excluding supplemental buccal or lingual infiltrations) were used, no nitrous oxide, sedatives, opioid or opioid-like analgesics were used to perform the dental procedure

[G] Prior to preparation and administration of study drug

[H] Immediately after administration of study drug

[I] Record concomitant medications taken within 24 hours of local anesthetic administration

[J] Post study drug:

Efficacy Assessments

Lip & tongue palpation every 5 minutes for 5 hours after completion of study drug administration starting at 10 minutes after study drug administration

STAR questionnaire every 30 minutes after administration of study drug for 5 hours

FAB smiling/speaking/drooling every 5 minutes until normal by both subject and observer ratings starting at 10 minutes after study drug administration; then add drinking and continue to test every 5 minutes until all 4 functions are normal on 2 consecutive assessments by both subject and observer ratings; thereafter, decrease the frequency of testing to every 30 minutes for the remainder of 5-hour observation period.

Safety Assessments

All were performed within a 15-minute window, unless specified otherwise.

H-P VAS for pain in the mouth on the side of the procedure every 30 minutes post study drug for the first 2 hours and hourly for the next 3 hours; and prior to analgesics, as needed

BP and pulse after standing for 1 minute within 5 minutes and between 10 and 20 minutes of study drug administration

BP and pulse in supine or sitting position every 15 minutes during the first hour, then hourly during the first quarter of the hour and prior to discharge

Temperature and respirations within 15 minutes post study drug and prior to discharge

Specific oral cavity assessments of the injection and procedure site(s) after study drug, every 15 minutes for the first hour, and hourly thereafter during the fourth quarter of the hour.

General oral cavity assessment prior to discharge

Adverse events during the 5-hour observation period; in addition, question the subject hourly for adverse events

Concomitant medications taken during the observation period, including any analgesics taken for intraoral pain, medications previously prescribed (subjects will supply their own medications), and medications required to treat an adverse event

10.1.1.7 Amendments to the Protocol

The protocol was amended once on November 9, 2005, which was prior to the randomization date of the first subject, February 10, 2006. The amendment included the transfer of certain Sponsor obligations for the conduct of the trial to [redacted] These obligations included the following: b(4)

- Selecting monitors as defined under CFR 312.53 (d).
- Monitor the progress of all clinical investigations conducted under this IND as defined under 21 CFR §312.56 (a).
- Maintain complete and accurate records showing financial interest as defined under CFR §312.57 (b and c).
- Permit FDA inspection and access to, and copy, and to verify any records and reports relating to the clinical investigation as defined under CFR §312.58 (a).

In addition, the Investigator's Brochure was revised to include information from previous studies.

10.1.1.8 Post Hoc Changes

The following additions were made to the analysis plan:

1. Correlation Among Time-to-Event Efficacy Endpoints
   The timing and correlation of STAR-7 with other time-to-event efficacy endpoints was investigated to determine wh**ether subjects' perception of** recovery (STAR-7) occurred before actual recovery (sensation of lip and tongue or the FAB). This analysis used the

Weibull AFT data for each time-to-event endpoint (recovery of normal lower lip sensation, normal tongue sensation, normal FAB, and STAR-7 score of zero). Correlations between all possible pairs of time-to-event endpoints were also examined for the randomized treatment groups.

2. Use of a Secondary As-Treated Efficacy Analysis
   A secondary as-treated analysis of the primary endpoint was performed to determine the dose-response relationship for NV-101. The as-treated analysis used the number of cartridges of study drug as a stratification factor and differed from the primary ITT efficacy analysis, which used the number of cartridges of anesthetic as the stratification factor, because 6 subjects received a different number of cartridges of anesthetic and study drug.

3. Determination of Numbers of Cartridges of Anesthetic or Study Drug
   Some subjects received 1.5 cartridges of anesthetic or study drug, rather than 1 or 2 cartridges as specified by the protocol. In all analyses, these subjects were counted as having received 2 cartridges.

10.1.1.9 Results as Reported by the Sponsor

Patient Demographics

The subject population was balanced with respect to sex, race, age, height, and weight. Nearly equal numbers of males and females were enrolled. The majority (approximately 80%) of all subjects was white, approximately 9% were black, and the rest were of other races. The mean age for the overall group was 37 ± 19 years, with similar means for each treatment group. While the majority (76%) of subjects were between the ages of 18 and 64 years, the study also enrolled 31 children and adolescents between the ages of 12 and 17 (12% of all subjects), and 27 adults ≥ 65 years of age (11% of all subjects). Because of the stratification used for randomization, the treatment groups were comparable with respect to the numbers of subjects in each age group.

Patient Exposures and Treatment Arm Characteristics

The number of subjects included in each analysis data set is shown in Table 10-4. The data set for the primary ITT analysis of efficacy differed from that used for the analysis of safety, due to deviations in the administration of either the anesthetic or the study drug that caused six subjects to receive different numbers of cartridges of anesthetic and study drug. Stratification for number of cartridges in the analysis of efficacy was based on the number of cartridges of anesthetic, as specified in the protocol and SAP. A secondary as-treated analysis of efficacy based on the number of cartridges of study drug was performed to investigate dose-response effects. The analysis of safety was based on the number of cartridges of study drug received.

Baseline characteristics related to the dental procedure and the anesthetic used for the ITT population are shown in the table below. The majority of subjects (68%) underwent cavity preparation, restoration, and/or filling, while 30% underwent periodontal maintenance procedures. Only three subjects (all randomized to sham) had crown procedures. The type of

procedure was relatively well balanced between the treatment groups. Slightly more than half of all subjects (N = 131; 54%) underwent procedures involving the lower left mandible, while the remainder (N = 113; 46%) underwent procedures involving the lower right mandible.

In addition to being stratified by subject age group, study drug randomization also was stratified by the previously assigned anesthetic/vasoconstrictor combination and by the number of cartridges of anesthetic used. Thus, the NV-101 and sham groups were comparable with respect to these stratification factors. As described above, because of the 6:1:1:1 randomization ratio, lidocaine was used for 67% of subjects, articaine was used by 12% of subjects, prilocaine was used for 11% of subjects, and mepivacaine was used for 11% of subjects. The majority (N = 182; 75%) of subjects required injection of a single cartridge of anesthetic, and the remaining subjects (N = 62; 25%) required injection of two cartridges of anesthetic. Nearly all subjects received the primary injection of anesthetic and the study drug injection by either inferior alveolar nerve block (80%), or mental-incisive nerve block (18%). Fifty-nine subjects (24%; 30 randomized to NV-101; 29 randomized to sham) required supplemental injections of anesthetic. These supplemental injections were comprised of up to one-half cartridge (0.9 mL) given as buccal or sublingual infiltrations.

Table 10-2: Dental procedures and anesthesia (Table 11-3 from the final study report)

Variable	NV-101	Sham	Total
	N=122	N=122	N=244
	N (%)of Subjects	N (%) of Subjects	N (%) of Subjects
Dental Procedure			
Cavity[a]	88 (72.1)	79 (64.8)	167 (68.4)
Crown	0 (0.0)	3 (2.5)	3 (1.2)
Periodontal maintenance[b]	34 (27.9)	40 (32.8)	74 (30.3)
Mouth Quadrant[c]			
Right Lower	54 (44)	59 (48)	113 (46)
Left Lower	68 (56)	63 (52)	131 (54)
Type of Anesthetic[d,e]			
Lidocaine	82 (67)	81 (66	163 (67)
Other	40 (33)	41 (34)	81 (33)
Articaine	16 (13)	12 (10)	28 (12)
Prilocaine	13 (11)	14 (12)	27 (11)
Mepivacaine	11 (9)	15 (12)	26 (11)
Number of Cartridges of Anesthetic[d]			
1	91 (75)	91 (75)	182 (75)
2	31 (25)	31 (25)	62 (25)
Primary Injection Type			
Inferior Alveolar Nerve Block	96 (79)	98 (80)	194 (80)
Mental-Incisive Block	21 (17)	24 (20)	45 (18)
Supraperiosteal Injection	5 (4)	0 (0)	5 (2)
Secondary Injection Type			
Inferior alveolar nerve block	31 (25)	30 (25)	61 (25)
Mental-incisive block	0 (0.0)	1 (0.8)	1 (0)
Supplemental Injections			

Variable	NV-101	Sham	Total
	N=122	N=122	N=244
	N (%)of Subjects	N (%) of Subjects	N (%) of Subjects
Half Cartridge (0.9 mL)	30 (25)	29 (24)	59 (24)
Buccal Infiltrations[f]	30 (25)	28 (23)	58 (24)
Sublingual infiltrations[g]	0 (0)	2 (2)	2 (1)

[a] Preparation, restoration, and/or filling
[b] E.g., teeth cleaning (non-surgical scaling and/or root planing)
[c] Quadrant for anesthetic injection, study drug injection, and dental procedure
[d] Randomization to treatment was stratified by this variable
[e] Anesthetic/vasoconstrictor combinations used were 2% lidocaine with 1:100,000 epinephrine; 4% articaine with 1:100,000 epinephrine; 4% prilocaine with 1:200,000 epinephrine; and 2% mepivacaine with 1:20,000 levonordefrin.
[f] Five subjects received 2 buccal infiltrations
[g] One subject received both a buccal infiltration and a sublingual infiltration, and 1 subject received 2 sublingual infiltrations

Efficacy Results

The Applicant reported that the results of the data quality audit procedures revealed no errors in critical or semi-critical variables. Based on these data, the following findings were reported.

The median time to recovery of normal sensation in the lip was reduced by 85 minutes (55%) by NV-101; median times were 70 minutes for subjects randomized to NV-101 and 155 minutes for subjects randomized to sham. Results of the Cox proportional hazards model predicted a hazard ratio of 3.2 for NV-101 versus sham, indicating that subjects treated with NV-101 were 3.2 times more likely than subjects treated with sham to achieve normal lower lip sensation during the 5-hour observation period ($p < 0.0001$). Results of the Weibull AFT model predicted an event time ratio of 0.57 for NV-101 versus sham, indicating that NV-101 accelerated the time to recovery of normal sensation in the lower lip by 43%. The Cox model also showed no treatment group interaction effect of anesthetic or number of cartridges on the primary endpoint comparison.

Consistent differences between the treatment groups were observed for subsets of subjects treated with lidocaine, articaine, prilocaine or mepivacaine, for subjects treated with either 1 or 2 cartridges/sham injections, for subjects in the 3 age groups (12 to 17 years of age, 18 to 64 years of age and ≥ 65 years of age), for subjects treated with either inferior alveolar block or mental-incisive block, for subjects undergoing cavity preparation/restoration/filling or periodontal maintenance, and for both males and females. Reduction factors ranged from 37% to 68%.

Statistically significant differences between subjects randomized to NV-101 and subjects randomized to sham also were observed for all 3 secondary endpoints: perceived recovery from anesthesia according to STAR-7; normalization of function according to the FAB; and recovery of normal tongue sensation. STAR-7 recovery occurred after recovery of other endpoints for the majority of subjects in both treatment groups. These results indicated that perceived recovery of normal sensation in the lip and tongue did not occur earlier than actual recovery. The table below summarizes both the primary and the secondary endpoint findings.

Table 10-3: Summary of efficacy findings as reported by the sponsor

Time-to-Event Endpoint	NV-101		Sham		P value	Time Difference (min.)	Reduction Factor With NV-101 (%)
	N	Time (min.) [median (95% CI)]	N	Time (min.) [median (95% CI)]			
Normal Lip Sensation	122	70 (65-80)	122	155 (140-165)	< 0.0001	85	55
STAR-7 = 0	118	90 (60-90)	121	150 (120-150)	< 0.0001	60	40
Normal FAB	103	60 (50-75)	103	120 (110-130)	< 0.0001	60	50
Normal Tongue Sensation	93	60 (55-70)	103	125 (110-135)	< 0.0001	65	52

An offset of the treatment effect (i.e., re-emergence of numbness in either the lower lip or tongue) was observed in four subjects: two subjects had offset in the lip; one subject had offset in the tongue; and one subject had offset in both. In three subjects treated with NV-101, the recurring numbness was of short duration and normal sensation returned within 10 to 30 minutes; in one subject, treated with sham, the period of recurrent numbness was 65 minutes.

In an effort to assess the impact of protocol deviations on the conclusions reached using the protocol-specified primary efficacy analysis, additional analyses of the primary and secondary endpoints were conducted using all available data. The results from these analyses of subpopulations are shown in the table below.

Table 10-4: Comparison of Efficacy Endpoints on Subpopulations (Table 11-17 in final report)

Subset Population	NV-101		Sham	
	N	Median (mins.)	N	Median (mins.)
Lower Lip Sensation Recovery				
Primary: ITT	122	70	122	155
Secondary: ITT excluding "tingling"	122	70	121	155
Secondary: As-treated[A]	122	70	122	155
STAR-7 Normalization				
Primary: mITT	118	90	121	150
Secondary: ITT	122	75	122	150
FAB Normalization				
Primary: mITT	103	60	103	120
Secondary: ITT	122	55	122	115
Secondary: Imputation[B]	103	60	103	120
Tongue Sensation Recovery				
Primary: mITT (numb at baseline)	93	60	103	125

Subset Population	NV-101		Sham	
	N	Median (mins.)	N	Median (mins.)
Secondary: mITT (numb or tingling at baseline)	100	57.5	108	125
Secondary: ITT	122	50	122	112.5

Note: All results are based on Kaplan-Meier analyses.
[A] Based on the number of cartridges of study drug (safety analysis data set)
[B] Analysis was conducted using imputed FAB time to correct for protocol deviations.

For the recovery of normal sensation in the lower lip, analyses including and excluding the subject who experienced tingling, rather than numbness prior to randomization to study drug, **were compared. In addition, an "as-treated" an**alysis with stratification by the number of cartridges of study drug was performed for recovery of lower lip sensation. For STAR-7 and FAB, analyses using the respective mITT population and the ITT population were compared. For the recovery of normal sensation in the tongue, mITT analyses including and excluding subjects who experienced tingling, rather than numbness prior to randomization to study drug, were compared to analysis using the ITT population. Additionally, an analysis using imputed FAB time to correct for protocol deviations was performed to assess the effect of FAB deviations on outcome. Results from these alternative analyses indicated that the conclusions reached by the primary efficacy analysis using Kaplan-Meier methods were reported to be robust.

The table below presents the efficacy results based on different clinically important subgroupings. Based on the reduction factors, each of the subgroups demonstrates a substantial reduction in recovery times following treatment with NV-101. The two lowest reduction factors were associated with the local anesthetic-vasoconstrictor used. There was a 43% reduction in the recovery time associated with mepivacaine and levonordefrin and a 37% reduction in the recovery time associated with prilocaine and epinephrine. It is not clear why the differences were less with these two agents, but there was a clear difference in the right direction; however, the small numbers of subjects in each group must also be taken into consideration.

Table 10-5: Subset Analysis of Time to Recovery of Normal Sensation in the Lower Lip (Table 11-9 from final study report)

Subgroup	NV-101		Sham		Reduction Factor for (%)
	N	Median Time (minutes)	N	Median Time (minutes)	
Overall	122	70.0	122	155.0	54.8
Number of Cartridges					
1	91	65.0	91	155.0	58.1
2	31	85.0	31	155.0	45.2
Anesthetic					
Lidocaine	82	67.5	81	145.0	53.5
Other	40	90.0	41	165.0	45.5
Articaine	16	100	12	192.5	48.1
Prilocaine	13	80	14	127.5	37.3
Mepivacaine	11	115	15	200	42.5
Age Group					
12 to 17 years	16	62.5	15	170.0	63.2
18 to 64 years	93	75.0	93	155.0	51.6
≥ 65 years	13	60.0	14	120.0	50.0
Type of Injection					
Inferior Alveolar Nerve	96	80.0	97	160.0	50.0
Block					
Mental-Incisive Block	21	35.0	24	110.0	68.2
Type of Procedure					
Cavity[A]	88	75.0	79	160.0	53.1
Periodontal maintenance[B]	34	60.0	40	132.5	54.7
Sex					
Male	66	75	54	162.5	53.8
Female	56	70	68	145	51.7

[A] Preparation, restoration, and/or filling
[B] E.g., teeth cleaning (non-surgical scaling and/or root planing)

Summary of Applicant-Reported Safety Results

A total of 63 subjects reported 77 adverse events (AEs) (NV-101: 44 AEs in 34 subjects; sham: 33 AEs in 29 subjects). None of the AEs were serious or severe, and no subject was discontinued because of an AE. The most frequently reported study drug-related, mild or moderate AEs were injection site pain (6% of all subjects) and post-procedural pain (6% of all subjects). Headaches associated with study drugs were reported in 3% of all subjects. Other study-drug related events occurred in less than 2% of subjects. The overall frequency of study drug-related AEs appeared similar in the two treatment groups (NV-101: 20%; sham: 16%), as did the incidence of the most frequently reported AEs: injection site pain (NV-101: 7%; sham: 6%; post-procedural pain (NV-101: 3%; sham: 5%); and headaches (NV-101: 3%; sham: 2%).

The frequency of study drug-related AEs also appeared similar for subjects treated with 1 cartridge (19%) or 2 cartridges (23%) of NV-101. No relationship was apparent between the types of AEs and age group.

No clinically significant changes in vital signs were observed in association with administration of NV-101. Some subjects (NV-101: 4%; sham: 7%) experienced clinically significant orthostatic changes in vital signs (baseline taken with subjects sitting or supine; post-treatment taken after subjects stood for 1 minute). There were no apparent differences for subjects who received 1 or 2 cartridges of NV-101 or 1 or 2 sham injections.

Results from the H-P VAS pain assessment indicated that the majority of subjects in both treatment groups experienced only mild oral pain, with less than 10% of subjects in each group reporting moderate oral pain. In general, the occurrence of any oral pain (mild or moderate) appeared to be somewhat more frequent in subjects who received 2 cartridges of NV-101 or 2 sham injections than in subjects who received 1 cartridge/sham injection.

Results of the specific OCAs showed minor abnormalities that were not clinically significant in most subjects. Only 4 subjects (NV-101: 3; sham: 1) had clinically significant abnormalities (minimal bleeding, paleness, and petechia) at the injection or procedure site. All abnormal findings were resolved by the end of the 5-hour observation period (minimal bleeding, paleness) or by the time of the telephone follow-up (petechia).

Analgesics were used by only 14 subjects (NV-101: 8; sham: 6) for the management of oral pain either during the 5-hour observation period or during the 24-hour period following discharge.

Summary

The Applicant summarized the conclusions of this study as follows:

1. The primary efficacy endpoint, time to recovery of normal sensation in the lower lip, was reduced by 85 minutes (55%) for 122 subjects randomly assigned to NV-101 compared with an equal number of subjects assigned to sham injection. This reduction in recovery time would likely be clinically meaningful to dental patients.
2. The secondary endpoints of time to perception of normal sensation/function (STAR-7 score of zero), time to observed recovery of normal function (FAB), and time to recovery of normal sensation in the tongue were all significantly reduced in the NV-101 group.
3. NV-101 was well tolerated in this study of dental patients as there were no deaths, or other serious or severe AEs, and no subject was discontinued due to an AE.
4. Twenty percent of NV-101 and 16% of sham-injected patients experienced treatment-related, transient, mild to moderate adverse events, all of which resolved within the study period.
5. NV-101 did not affect vital signs or oral pain experienced by subjects.

10.1.1.10 Discussion of Results

The protocol as submitted on September 13, 2005, and clarified in an e-mail on October 13, 2005 and further clarified in an e-mail on October 20, 2005, was reviewed by the Division as a Special Protocol Assessment. In a letter issued by the Division on October 26, 2005, the Sponsor was notified of the Division's agreement that the design and planned analysis of the study adequately addressed all issues raised by the Division and the study could proceed as proposed. Administrative changes were made in the single amendment to the protocol which also included a revised Investigator's brochure. The amendments were made before the first patient was enrolled in the trial and would not be expected to alter either the conduct of the study or the results.

Of the 244 subjects randomized, all completed the study; however, one subject (100-05-014) reported "tingling" in the lower lip at the completion of the dental procedure rather than the required "numbness" but was enrolled and included in the primary analysis of efficacy. One hundred thirty five of the randomized subjects were found to have a total of 229 protocol deviations; the distribution between treatment groups was similar: 69 (57%) who received NV-101 and 66 (54%) who received sham treatment. All but 15 of the deviations involved study procedures; ten of which were related to administration of study drug. Just over half of the 214 deviations involving study procedures involved administration of the FAB tool (110 deviations; 51%). The deviations are summarized in the table below.

Table 10-6: Summary of Protocol Deviations (Table 10-4 from final study report)

Category	NV-101		Sham		Total	
	N (%) of all deviations	N (%) of study procedure deviations	N (%) of all deviations	N (%) of study procedure deviations	N (%) of all deviations	N (%) of study procedure deviations
All	119 (100)		110 (100)		229 (100)	
Inclusion/Exclusion Criteria	0 (0)		1 (1)		1 (0)	
Study Drug	6 (5)		4 (3)		10 (4)	
Randomization	0 (0)		0 (0)		0 (0)	
Study Procedure	111 (91)		103 (94)		214 (93)	
Sensation Rating		11 (10)		12 (12)		23 (11)
STAR-7		8 (7)		10 (10)		18 (8)
FAB		60 (54)		50 (49)		110 (51)
OCA		6 (5)		8 (8)		14 (6)
Vital Signs		8 (7)		7 (7)		15 (7)
H-P VAS		7 (6)		4 (4)		11 (5)
Telephone Follow-up		9 (8)		11 (11)		20 (9)
Informed Consent		2 (2)		1 (1)		3 (1)
Blinding	2 (2)		2 (2)		4 (2)	

The Applicant noted that two subjects, 100-12-001 and 100-23-001, had deviations in the planned lower lip and tongue assessment schedules that had the potential to affect the primary endpoint and the secondary endpoint of tongue sensation. Both of these patients were in the sham-treatment groups. The Sponsor provided the following description and assessment for the deviations in the final study report.

> **"For subject 100-12-001, the frequency of** the assessments was switched to every 30 minutes instead of every 5 minutes after the subject achieved normal sensation in both the lip and tongue. This deviation would not affect the calculation of the median time to normal sensation in either the lip or tongue. In Subject 100-23-001, the frequency of the assessments was switched to every 30 minutes instead of every 5 minutes after the 180-minute time point, at which time the subject had already achieved normal sensation in the tongue but had not yet achieved normal sensation in the lower lip. This subject subsequently met the protocol definition of normal lip sensation at the 300-minute time point. Because the deviation occurred after the normalization of tongue sensation and at a time point later than the sham group median time for normalization of lip sensation (155 minutes), this **deviation had no impact on the study results."**

A review of the data indicated the Sponsor's conclusions regarding these two patients were correct.

A review of the comments on the protocol deviations as extracted from the CRFs and included in section 16.4, listing 5, of the final study report revealed that most deviations related to inappropriate timing of FAB assessments or inappropriate timing for adding drinking to the FAB assessment based on previous FAB assessments. It appeared that the investigators did not fully comprehend the protocol regarding the use of this tool and when it was appropriate to allow patients to attempt to drink water. Based on the listing, it appears that 90 subjects had deviations **related to timing of FAB – missed, too frequent**, too infrequent, and extra assessments, and 72 subjects had deviations related **to adding drinking to the FAB assessment – both too soon and too** delayed. The sites with the most study procedure deviations were #13 (14/26 subjects), #18 (8/26 subjects) and #22 (12/26 subjects). Each of these sites was among the four chosen for routine inspection by the Division of Scientific Investigations due to the relatively large numbers of patients enrolled at them. Due to the importance of the FAB assessment results for determining the clinical relevance dental soft tissue anesthesia reversal, the statistics review team reanalyzed the FAB data excluding patients for whom there were FAB-related protocol deviations. The results of this analysis are shown in the table below and indicate that the data were quite robust as the two treatment arms still differed at a level of $p < 0.0001$.

Table 10-7: Reanalysis of FAB assessment results based on protocol deviations

Parameter	All Subjects		Subjects without FAB-related protocol deviations	
	Sham (N=103)	NV-101 (N=103)	Sham (N=71)	NV-101 (N=64)
Time to recovery of normal FAB				
Median (minutes)	120	60	120	55
95% confidence limits (minutes)	110-130	50-75	110-130	45-75
Log-rank *p* value	< 0.0001		< 0.0001	

10.1.1.11 Conclusions

The study was conducted in accordance with the protocol approved by the Division under the Special Protocol Assessment. The study demonstrated a marked reduction in the time for soft tissue recovery from anesthesia following the injection of NV-101. The reduction in this time to recovery was accompanied by similar reductions in both the times at which patients perceived their recovery to be complete and the times at which their recoveries were demonstrated to be complete as assessed by the STAR-7 questionnaire and the FAB assessments, respectively. Thus, the study satisfied the requirements of the SPA agreement and successfully demonstrated efficacy in the populations and clinical scenarios studied.

10.1.2 NOVA 04-200

"A Phase 3, Multicenter, Randomized, Blinded, Controlled Study of NV-101 for Efficacy, Pharmacodynamics and Safety in Dental Patients Undergoing Maxillary **Procedures"**

NOVA 04-200 was submitted to DAARP on September 13, 2005, for review as a Special Protocol Assessment (IND 65,095 N-049-SM). On October 26, 2005, DAARP issued a letter to the Sponsor indicating its agreement that the design and planned analysis of the study were acceptable as modified and clarified. The protocol was amended on November 9, 2005, to include an additional analysis which assessed the timing and correlation of STAR-7 with other **time-to-event efficacy endpoints to determine whether subjects' perception of recovery (STAR-**7) occurred before actual recovery (as assessed by return of sensation in the lip and FAB score). The protocol was initiated on February 10, 2006 with the randomization of the first subject and was terminated on June 2, 2006, when the last subject completed the study. The final study report was dated November 17, 2006, and indicated that the study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study.

10.1.2.1 Objectives

Primary Objective

- To determine if NV-101 accelerated time to normal sensation of the upper lip compared to control, as measured by a standardized palpation procedure.

Secondary Objectives

- To determine if NV-101 accelerated the time to STAR-7 score of zero as measured by the soft tissue anesthesia recovery (STAR) questionnaire;
- To determine if NV-101 accelerated the time to normal function as measured by a functional assessment battery (FAB);
- To characterize the pharmacodynamic profile of NV-101 as measured by onset and offset of treatment effect; and
- To evaluate the safety and tolerability of NV-101 as measured by the incidence, severity, and duration of adverse events and intraoral pain as measured by the H-P VAS, analgesic requirements for the treatment of intraoral pain, clinically significant findings in oral cavity assessments and changes in vital signs.

10.1.2.2 Study Design

This study was designed as a Phase 3, multicenter, randomized, blinded, and placebo-controlled clinical trial. It was intended to evaluate the efficacy, pharmacodynamics, and safety of NV-101

when used for reversal of soft tissue anesthesia (STA), i.e., anesthesia of the upper lip, in subjects undergoing restorative or periodontal maintenance procedures involving the maxilla. Procedures evaluated were to have required local anesthesia with an anesthetic agent containing a vasoconstrictor. Subjects were to have been randomized with respect to both the type of anesthetic/vasoconstrictor used and the study treatment (NV-101 or sham injection) administered. The study was planned to randomize approximately 240 subjects (120 subjects per treatment group).

10.1.2.3 Study Population

Inclusion Criteria

1. Male or female, ≥12 years of age;
2. Sufficiently healthy to receive routine dental care, as determined by the Investigator;
3. Underwent a restorative procedure involving the maxilla such as cavity preparation, restoration/filling, or crown or a periodontal maintenance procedure, such as teeth cleaning (non-surgical scaling and/or root planing) on one side of the upper mouth;
4. Treated with 1 or 2 cartridges of local anesthetic/vasoconstrictor administered by one of the following intraoral injection techniques:
   - supraperiosteal injection,
   - superior anterior alveolar nerve block,
   - infraorbital nerve block;
5. Underwent dental procedure that was completed within 60 minutes of the first administration of local anesthetic;
6. Normal sensation in upper lip at baseline, prior to administration of local anesthetic;
7. Numbness in the upper lip on the side of the procedure at the completion of the dental procedure;
8. STAR-7 score of zero prior to anesthetic;
9. FAB, as scored by subject and observer was normal prior to anesthetic;
10. Negative urine pregnancy test at screening for females of childbearing potential past menarche (included all females except those whose menstrual periods had not occurred for ≥1 year after menopause, who were surgically sterilized or had a hysterectomy);
11. Understood and gave written informed consent;
12. For subjects 12 to 17 years of age, gave written assent and parent(s) or legal guardian(s) gave written informed consent; and
13. Was able to communicate with the Investigator and study staff, and understand and comply with the requirements of the protocol.

Exclusion Criteria

1. History or presence of any condition that contraindicated routine dental care;
2. Required more than 2 cartridges of local anesthetic (excluding supplemental injections) or use of nitrous oxide or sedatives to perform the scheduled dental procedure;
3. Scheduled dental procedure required > 60 minutes to complete;
4. Was unable to tolerate 1 liter of water over 5 hours;
5. Had any of the following concurrent incapacitating medical conditions:

- unstable angina,
- uncontrolled cardiac arrhythmias,
- uncontrolled hypertension,
- uncontrolled hyperthyroidism,
- significant infection or inflammatory process of the oral cavity;

6. Used any of the following concomitant medications: opioid or opioid-like analgesic (e.g., codeine, tramadol, pentazocine) within 24 hours prior to administration of anesthetic;
7. Allergy or intolerance to lidocaine, articaine, prilocaine, mepivacaine, epinephrine, levonordefrin, sulfites, phentolamine or topical benzocaine;
8. Had used any investigational drug and/or participated in any clinical study within 30 days of study drug administration;
9. Had participated in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia (STA); or
10. Had any condition which in the opinion of the Investigator increases the risk to the subject of participating in this study or decreases the likelihood of compliance with the protocol.

Criteria for Removal of Subjects from the Study

1. Significant protocol violation on the part of the Investigator;
2. Significant noncompliance on the part of the subject;
3. Withdrawal of consent (refusal of the subject to continue treatment or observations);
4. Adverse event or unacceptable toxicity;
5. Decision by the Investigator that termination is in the subject's **best medical interest;**
6. Unrelated medical illness or complication; or
7. Lost to follow up.

For subjects removed from the study, the dates and reasons for subject withdrawal were to have been recorded, and in addition, all evaluations specified for the end of the observation period (5 hours after administration of study drug) were to have been performed, if feasible, at the time of withdrawal.

10.1.2.4 Efficacy Endpoints (details of tests are provided in Appendix 1)

1. Observed soft tissue sensation in the upper lip
2. Perception of function/sensation assessed by the Soft Tissue Anesthesia Recovery questionnaire (STAR-7),
3. Observed functions of smiling, speaking, drinking and drooling evaluated using the Functional Assessment Battery(FAB), and
4. Pharmacodynamics

The following sequence was to have been used for efficacy assessments:

1. lip palpation

2. STAR questionnaire
3. FAB

When a time point did not require the STAR assessment, the lip sensation rating was to be done first, followed by the FAB.

10.1.2.5 Methods

The protocol involved two randomizations. The first randomization was to have been performed to assign the local anesthetic for the dental procedure, and the second randomization was to have been performed for the assignment of study treatment, as described below.

Randomization to local anesthetic was to have been performed prior to the start of the dental procedure. Subjects were to be randomized, in a 2:1 ratio, to either 2% lidocaine with 1:100,000 epinephrine or another anesthetic containing a vasoconstrictor. The 2:1 ratio was used as 2% lidocaine with 1:100,000 epinephrine is the most commonly used anesthetic in dental practice. The other anesthetic/vasoconstrictor combinations were to include:

1) 4% articaine with 1:100,000 epinephrine
2) 4% prilocaine with 1:200,000 epinephrine
3) 2% mepivacaine with 1:20,000 levonordefrin

These were to have been randomly assigned in a 1:1:1 allocation ratio, resulting in a 6:1:1:1 overall ratio. No stratification factors were used for randomization to anesthetic.

Following completion of the dental procedure, subjects who met all eligibility criteria were to have been randomized to receive NV-101 or sham (control) in a 1:1 allocation ratio using a dynamic (adaptive) randomization scheme. The Applicant indicated that this scheme was utilized to balance important stratification factors across treatment groups including study center, anesthetic, the number of cartridges of anesthetic administered (1 or 2), and subject age (12-17 years, 18-64 years, 65 years or older) using an algorithm designed to minimize numerical imbalance within each stratum. Subjects who received a single cartridge of anesthetic were to have received a single injection of NV-101 or a single sham injection; subjects who received two cartridges of anesthetic were to have received two injections of NV-101 or two sham injections. Sham injections were to mimic the time, preparation and application of NV-101, through the use of a syringe with a capped needle that did not allow tissue penetration.

The Investigator who administered the anesthetic was also to have administered the NV-101 or sham and was not to have been blinded. The subject was to have been blinded to the study treatment. A visual barrier was to have been **used to obstruct the subject's view of the** preparation and administration of study drug. A separate member of the investigative team, who was blinded to the treatment assignment, was to have performed subsequent assessments during the 5-hour observation period.

Study personnel who were to be involved in assessments following administration of study drug were not to have been present at the time of the preparation and administration of study drug, but

were to have been informed about the site(s) of anesthetic and study drug administration and the site of the procedure.

The efficacy assessments were to have comprised the following variables: observed soft tissue sensation in the upper lip, perception of function/sensation (STAR-7), observed functions of smiling, speaking, drinking and drooling (FAB), and pharmacodynamics. The following sequence was to have been used for efficacy assessments:

4. lip palpation
5. STAR questionnaire
6. functional assessment battery (FAB)

When a time point did not require the STAR assessment, the lip sensation rating was to be done first followed by the FAB.

Recovery from soft tissue anesthesia (STA) in the upper lip was to have been determined by palpation every 5 minutes for 5 hours after completion of study drug administration starting at 10 minutes after study drug administration. Palpation was to have consisted of soft tapping of the **upper lip with the subject's index or** middle finger. Subjects were to have rated the degree of lip **numbness as "numb," "tingling," or "normal." T**ingling was to have been defined as a sensation **of "pins and needles." Prior to the start of the d**ental procedure, subjects were to have received training on the required lip palpation technique according to standardized instructions.

The time to recovery of normal sensation for the lip was to have been calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation. The recovery of normal sensation was also to have been considered to occur if the sensation test was rated normal at **the subject's final evalua**tion and the rating from the preceding assessment was other than normal (i.e., not done, numb, or tingling). Subjects who did not meet these criteria before the end of the 5-hour observation period were to have been **right-censored at the time of the subject's last s**ensation rating. No imputation was to have been used for missing sensation data.

The STAR scoring was to have been based on the STAR-7 questionnaire, which was to have been self-administered every 30 minutes during the 5-hour observation period after the administration of study drug.

Smiling, speaking, drinking and drooling were to have been assessed by both the subject and the observer using the FAB tool. A subject was to **have been considered to have "abnormal function" if one or more functions were deem**ed abnormal. The tests were to have been conducted in the following sequence: (1) smiling, (2) speaking, (3) drinking, and (4) drooling. Initially, assessments of smiling, speaking, and drooling, but not drinking, were to have been done every 5 minutes starting at 10 minutes after study drug administration until the results were found to be normal by both the subject and the observer. The drinking assessment was then to have been started, and all four functions were then to be tested every 5 minutes until all four functions were normal on two consecutive assessments by both subject and observer ratings. Thereafter, the frequency of testing was to have been decreased to every 30 minutes for the remainder of the 5-hour observation period.

The onset (recovery from STA) and possible offset (re-emergence of numbness or tingling) of the NV-101 treatment effect were to have been determined during the 5-hour observation period using the standardized palpation procedure.

The safety and tolerability of NV-101 was to have been evaluated based on the following parameters:

- incidence, severity, and duration of intraoral pain as measured by the Heft-Parker Visual Analog Scale (H-P VAS)
- clinically significant findings from oral cavity assessments
- analgesic requirements for the treatment of intraoral pain
- changes in vital signs (blood pressure, pulse, respiration, and temperature)
- incidence, severity, and duration of adverse events

General and specific oral cavity assessments (OCA) were to have been performed to evaluate complications of the intraoral submucosal injection(s) used in the study. The general oral cavity assessment was to have consisted of a broad evaluation of the mouth. The specific oral cavity assessments were to have consisted of evaluations of oral tissues at the injection site(s) and procedural site(s). The general OCA was to have been done before anesthetic administration, before randomization, and prior to discharge. The specific OCA was to have been done immediately after anesthetic and study drug administration, every 15 minutes after administration of study drug for the first hour and hourly thereafter. Clinically significant abnormal OCA findings were to have been recorded as adverse events on the appropriate case report form (CRF).

The use of analgesics for intraoral pain was to have been evaluated following the dental procedure. Subjects who requested an analgesic for intraoral or mouth pain were to have been given ibuprofen. Subjects who were intolerant or allergic to ibuprofen were to be given acetaminophen.

Blood pressure and pulse were to have been assessed before and after administration of anesthetic and study drug, either in the supine or sitting position, or after standing for one minute, as follows. Blood pressure and pulse were to have been determined before administration of anesthetic, before randomization, every 15 minutes after study drug administration during the first hour, hourly thereafter, and prior to discharge. Standing (for one minute) blood pressure and pulse were to have been measured before administration of anesthetic, and within 5 minutes and between 10 and 20 minutes of study drug administration. Temperature and respiration were to have been determined immediately prior to local anesthetic administration, within 15 minutes after administration of study drug and prior to discharge.

All AEs occurring after the study drug administration were to have been recorded on the CRF and reviewed by the Medical Monitor. All adverse events were to have been followed until resolution.

On completion of the study, a final quality audit was to have been performed before locking the database. All variables received for a random sample of 10% of all subjects were to have been

audited against the CRFs. The 10% of subjects were randomly selected. The acceptable error rate was deemed ≤ 0.05%, excluding text and dictionary fields. In the case of an error rate > 0.05%, data for an additional 10% of subjects were to have been audited. In the case that the error rate for the second group also was > 0.05%, all data for all subjects were to have been audited. Any error found was to have been corrected. Additionally, the database was to have been audited against the CRFs for the following semicritical variables using a separate random sample of 10% of subjects: inclusion/exclusion criteria, subject demographics, STAR questionnaire, FAB, adverse events, anesthetic and study drug administration, end of study record. The acceptable error rate was set at ≤ 0.01%. Additional audits were to have been performed as outlined above, using the error rate cutoff of ≤ 0.01%. Finally, lip palpation data were to have been audited for all subjects. Any error that was found was to have been corrected in the database.

10.1.2.6 Schedule

Table 10-8: Schedule of Study Assessments (Table 9-1 from Final Study Report)

Assessment	Period 1	Period 2	Period 3	Period 4	Period 5
	Screening Day -14 to Day 1	Dental Procedure Day 1	Study Drug Day 1	Observation Day 1	Follow-Up Day 2 to Day 3
Informed Consent/Assent & Assign Screening Number	X				
Medical/dental history/Concurrent Illness	X[A]				
Demographics (incl. ht. & wt.)	X				
Urine pregnancy test, if applicable	X				
Training: lip palpation, STAR, FAB, H-P VAS	X				
BP & pulse (after standing for 1 min.)		X[C]		X[J]	
BP & pulse (supine or sitting)		X[C]	X[E]	X[J]	
Temperature & respirations		X[C]		X[J]	
Confirm Baseline Criteria	X[B]				
Randomization to Anesthetic		X			
Apply Topical Anesthetic, if needed		X[C]			
Administer Local Anesthetic & record time		X			
Dental Procedure & record time		X			
Confirm Selection Criteria			X[F]		
Randomize to Study Drug - record time & assign Subject ID #			X		
Place Visual Barrier for Blinding			X[G]		
Administer Study Drug & record time			X		

Assessment	Period 1	Period 2	Period 3	Period 4	Period 5
	Screening Day -14 to Day 1	**Dental Procedure Day 1**	**Study Drug Day 1**	**Observation Day 1**	**Follow-Up Day 2 to Day 3**
Remove Visual Barrier				X	
Lip & tongue palpation	X		X[E]	X[J]	
STAR Questionnaire	X		X[E]	X[J]	
FAB	X		X[E]	X[J]	
H-P VAS – anesthetic injection(s)		X[D]			
H-P VAS - study drug injection(s)				X[H]	
H-P VAS - on side of dental procedure			X[E]	X[J]	
General Oral Cavity Assessment		X[C]	X[E]	X[J]	
Specific Oral Cavity Assessments (Injection/Procedure Sites)		X[D]		X[J]	
Concomitant Medications	X[I]	X	X	X[J]	X
Adverse Events				X[J]	X
Schedule/Telephone Follow-Up				X	X
Discharge subject (record time)				X	

[A] Update during Baseline Evaluation on Day 1 if different from day of Initial Screening of Selection Criteria

[B] Normal upper lip sensation, STAR-7 score is zero, FAB by subject and observer rating is normal, no opioids or opioid-like analgesics within 24 hours, pregnancy criteria/negative pregnancy test, if applicable

[C] Immediately prior to administration of local anesthetic

[D] Immediately after administration of local anesthetic

[E] Prior to randomization to NV-101 or sham

[F] Subject has numbness of the upper lip on the side of the dental procedure at completion of dental procedure, dental procedure was completed within 60 minutes of first administration of local anesthetic, not more than 2 cartridges of local anesthetic (excluding supplemental buccal or lingual infiltrations) were used, no nitrous oxide, sedatives, opioid or opioid-like analgesics were used to perform the dental procedure

[G] Prior to preparation and administration of study drug

[H] Immediately after administration of study drug

[I] Record concomitant medications taken within 24 hours of local anesthetic administration

[J] Post study drug:

Efficacy Assessments

Lip palpation every 5 minutes for 5 hours after completion of study drug administration starting at 10 minutes after study drug administration

STAR questionnaire every 30 minutes after administration of study drug for 5 hours

FAB smiling/speaking/drooling every 5 minutes until normal by both subject and observer ratings starting at 10 minutes after study drug administration; then add drinking and continue to test every 5 minutes until all 4 functions are normal on 2 consecutive assessments by both subject and observer ratings; thereafter, decrease the frequency of testing to every 30 minutes for the remainder of 5-hour observation period.

Safety Assessments

All were performed within a 15-minute window, unless specified otherwise.

H-P VAS for pain in the mouth on the side of the procedure every 30 minutes post study drug for the first 2 hours and hourly for the next 3 hours; and prior to analgesics, as needed

BP and pulse after standing for 1 minute within 5 minutes and between 10 and 20 minutes of study drug administration

BP and pulse in supine or sitting position every 15 minutes during the first hour, then hourly during the first quarter of the hour and prior to discharge

Temperature and respirations within 15 minutes post study drug and prior to discharge

Specific oral cavity assessments of the injection and procedure site(s) after study drug, every 15 minutes for the first hour, and hourly thereafter during the fourth quarter of the hour.
General oral cavity assessment prior to discharge
Adverse events during the 5-hour observation period; in addition, question the subject hourly for adverse events
Concomitant medications taken during the observation period, including any analgesics taken for intraoral pain, medications previously prescribed (subjects will supply their own medications), and medications required to treat an adverse event

10.1.2.7 Amendments to the Protocol

The protocol was amended once on November 9, 2005, which was prior to the randomization date of the first subject on February 10, 2006. The amendment included the transfer of certain Sponsor obligations for the conduct of the trial to [redacted]. These obligations included the following: b(4)

- Selecting monitors as defined under CFR 312.53 (d).
- Monitor the progress of all clinical investigations conducted under this IND as defined under 21 CFR §312.56 (a).
- Maintain complete and accurate records showing financial interest as defined under CFR §312.57 (b and c).
- Permit FDA inspection and access to, and copy, and to verify any records and reports relating to the clinical investigation as defined under CFR §312.58 (a).

In addition, the Investigator's Brochure was revised to include information from previous studies.

10.1.2.8 Post Hoc Changes

The following addition was made to the analysis plan:

Correlation Among Time-to-Event Efficacy Endpoints
The timing and correlation of STAR-7 with other time-to-event efficacy endpoints was investigated to determine whether **subjects' perception of recover**y (STAR-7) occurred before actual recovery (as determined by assessing lip sensation and FAB scores). This analysis used the Weibull AFT data for each time-to-event endpoint (recovery of normal upper lip sensation, normal FAB, and STAR-7 score of zero). Correlations between all possible pairs of time-to-event endpoints were also examined for the randomized treatment groups.

10.1.2.9 Results as Reported by the Sponsor

Patient Demographics
The subject population was balanced with respect to sex, race, age, height, and weight. Slightly more females (54%) than males (46%) were enrolled. The majority (76%) of all subjects was

white, 13% were black, and the rest were of other races. The mean (± SD) age for the overall group was 38 ± 18 years, with similar means for each treatment group; overall, ages ranged from 13 to 81 years. While the majority (78%) of subjects were between the ages of 18 and 64 years, the study also enrolled 24 adolescents between the ages of 12 and 17 years (10% of all subjects), and 28 adults ≥ 65 years of age (12% of all subjects). Because of the stratification used for randomization, the treatment groups were comparable with respect to the numbers of subjects in each age group.

Patient Exposures and Treatment Arm Characteristics

The numbers of subjects included in each analysis data set are shown in the table below. The primary endpoint analysis used the ITT analysis data set and comprised all 240 randomized subjects, as specified in the protocol. The modified ITT (mITT) analysis data sets for STAR-7 and FAB comprised 220 and 189 subjects, respectively. Twenty subjects (11 randomized to NV-101; 9 randomized to sham) could not be evaluated for STAR-7 because each reported a STAR-7 score of zero at the end of the procedure, immediately prior to study drug administration, i.e., they did not feel they were experiencing untoward effects of the local anesthesia. Fifty-one subjects (20 randomized to NV-101; 31 randomized to sham) could not be evaluated for recovery of function by FAB because all assessed functions were rated normal at the end of the procedure, immediately before administration of study drug. The safety analysis data set comprised all 240 treated subjects. Each analysis data set was balanced between the two randomized treatment groups.

Table 10-9: Division of Randomized Subjects by Analysis Data Set (Table 11-1 in final report)

Data Set	NV-101			Sham		
	Number of Cartridges[A]			Number of Cartridges[A]		
	1	2	Total	1	2	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ITT[A]	113 (100)	7 (100)	120 (100)	116 (100)	4 (100)	120 (100)
mITT						
STAR-7	102 (90)	7 (100)	109 (91)	107 (92)	4 (100)	111 (93)
FAB	93 (82)	7 (100)	100 (83)	86 (74)	3 (75)	89 (74)
Safety[B]	113 (100)	7 (100)	120 (100)	116 (100)	4 (100)	120 (100)

[A] Based on the number of cartridges of anesthetic injected
[B] Based on the number of cartridges of study drug injected

Baseline characteristics related to the dental procedure and the anesthetic used for the ITT population are shown in the table below. The majority of subjects (69%) underwent cavity preparation, restoration, and/or filling, while 28% underwent periodontal maintenance procedures. Seven subjects had crown procedures. The type of procedure was balanced between the treatment groups. Slightly more than half of all subjects (N = 130; 54%) underwent

procedures involving the left maxilla, while the remainder (N = 110; 46%) underwent procedures involving the right maxilla.

In addition to being stratified by subject age group, study drug randomization also was stratified by the previously assigned anesthetic/vasoconstrictor combination and by the number of cartridges of anesthetic used. Thus, the NV-101 and sham groups were comparable with respect to these stratification factors. As described above, because of the 6:1:1:1 randomization ratio, lidocaine was used for 66% of subjects, articaine, prilocaine and mepivacaine were each used for 11% of subjects. The majority (N=229; 95%) of subjects required injection of a single cartridge of anesthetic, and the remaining subjects (N=11; 5%) required injection of two cartridges of anesthetic. Nearly all subjects received the primary injection of anesthetic and the study drug injection by either supraperiosteal injection (86%), or superior anterior nerve block (11%). The eleven subjects (5 randomized to NV-101; 6 randomized to sham) who required supplemental injections of anesthetic received one-half cartridge (0.9 mL) given as buccal or palatal infiltrations. The table below summarizes the exposures to the two treatment arms.

Table 10-10: Dental procedures and anesthesia (Table 11-3 from the final study report)

Variable	NV-101	Sham	Total
	N=120	N=120	N=240
	N (%)of Subjects	N (%) of Subjects	N (%) of Subjects
Dental Procedure			
Cavity[A]	78 (65)	88 (73)	166 (69)
Crown	3 (3)	4 (3)	7 (3)
Periodontal maintenance[B]	39 (33)	28 (23)	67 (28)
Mouth Quadrant[C]			
Right Upper	63 (53)	67 (56)	130 (54)
Left Upper	57 (48)	53 (44)	110 (46)
Type of Anesthetic[D,E]			
Lidocaine	79 (66)	80 (67)	159 (66)
Other	41 (34)	40 (33)	81 (34)
Articaine	17 (4)	10 (8)	27 (11)
Prilocaine	14 (127)	13 (11)	27 (11)
Mepivacaine	10 (8)	17 (14)	27 (11)
Number of Cartridges of Anesthetic[D,F]			
1	113 (94)	116 (97)	229 (95)
2	7 (6)	4 (3)	5 (5)
Primary Injection Type			
Supraperiosteal injection	105 (88)	101 (84)	206 (86)
Superior anterior alveolar nerve block	9 (8)	17 (14)	26 (11)
Infraorbital nerve block	6 (5)	2 (2)	8 (3)
Secondary Injection Type			
Supraperiosteal injection	7 (6)	5 (4)	12 (5)
Supplemental Injections			
Half Cartridge (0.9 mL)	6 (5)	5 (4)	11 (5)
Buccal Infiltrations	2 (2)	4 (3)[G]	6 (3)
Palatal infiltrations	4 (3)	2 (2)[H]	6 (3)

[A] Preparation, restoration, and/or filling
[B] E.g., teeth cleaning (non-surgical scaling and/or root planing)
[C] Quadrant for anesthetic injection, study drug injection, and dental procedure
[D] Randomization to treatment was stratified by this variable
[E] Anesthetic/vasoconstrictor combinations used were 2% lidocaine with 1:100,000 epinephrine; 4% articaine with 1:100,000 epinephrine; 4% prilocaine with 1:200,000 epinephrine; and 2% mepivacaine with 1:20,000 levonordefrin.
[F] Determined by the number (1 or 2) of cartridges anesthetic injected; the number of cartridges of study drug was equal to the number of cartridges of anesthetic
[G] One of the 4 subjects received 2 buccal infiltrations and 1 received both a buccal infiltration and a palatal infiltration
[H] One subject received both a buccal infiltration and a palatal infiltration

Treatment Compliance and Protocol Deviations

Treatment compliance with respect to administration of NV-101 was consistent with the requirements of the protocol. Subject 200-24-001 (randomized to sham), received ½ cartridge of anesthetic each in the primary and secondary injection sites, and study drug (sham) was administered in the same manner. Because the total dose of anesthetic was equivalent to 1 cartridge, the subject was analyzed as having received 1 cartridge of anesthetic and 1 sham injection.

As shown in the table below, a total of 136 of the 240 randomized subjects were found to have protocol deviations, with a similar distribution in each randomized treatment group (67/120 subjects randomized to NV-101; 69/120 subjects randomized to sham). In nearly all subjects with deviations (134/136 subjects), the deviations were related to study procedures.

Table 10-11: Summary of Subjects with Protocol Deviations (Table 10-3 in final study report)

Category	**NV-101** N (%)	**Sham** N (%)	**Total** N (%)
Number of Subjects Randomized	120 (100)	120 (100)	240 (100)
Number of Subjects With a Protocol Deviation	67 (56)	69 (58)	136 (57)
Inclusion/Exclusion criteria	0 (0)	1 (1)	1 (0)
Study drug	0 (0)	1 (1)	1 (0)
Randomization	0 (0)	0 (0)	0 (0)
Study procedure	66 (55)	68 (57)	134 (56)
Blinding	1 (1)	3 (3)	4 (2)

Note: Subjects could have more than 1 type of deviation; subjects with more than 1 deviation in a category were counted once in that category.

Examination by type and number of deviations revealed a total of 214 deviations, of which 208 (97%) involved study procedures as noted in the table below. Of the 208 procedural deviations, 111 (54%) involved use of the FAB tool, attributed to the complexity of the FAB data collection schedule. These study procedure deviations were, **in the Applicant's opi**nion, considered minor

in scope and would not have affected the overall conduct of the study or integrity of the data. In particular, it was noted that the deviations that occurred in the collection of FAB data did not change the overall interpretation of the FAB results, as the type and effect of the deviations were balanced between the 2 treatment groups. Also, a Kaplan-Meier analysis conducted using imputed FAB time to correct for protocol deviations did not alter the primary result for the comparison of the FAB endpoint between the treatment groups. Finally, it was noted that the FAB deviations represented approximately 0.1% of the maximal potential FAB data points. The Applicant, therefore, stated that these findings indicated that the FAB results are robust, with no effect of the reported FAB deviations on the data analysis, results, and interpretations.

Table 10-12: Summary of Protocol Deviations (Table 10-4 of final study report)

Category	NV-101		Sham		Total	
	Number (%) of All Deviations	Number (%) of Study Procedure Deviations	Number (%) of All Deviations	Number (%) of Study Procedure Deviations	Number (%) of All Deviations	Number (%) of Study Procedure Deviations
All	105 (100)		109 (100)		214 (100)	
Inclusion/ Exclusion criteria	0 (0)		1 (1)		1 (1)	
Study drug	0 (0)		1 (1)		1 (1)	
Randomization	0 (0)		0 (0)		0 (0)	
Study procedure	104 (99)		104 (95)		208 (97)	
Sensation rating		11 (11)		14 (13)		25 (12)
STAR-7		10 (10)		5 (5)		15 (7)
FAB		54 (52)		56 (54)		110 (53)
OCA		1 (1)		5 (5)		6 (3)
Vitals		6 (6)		8 (8)		14 (7)
H-P VAS		4 (4)		3 (3)		7 (3)
Telephone follow-up		13 (13)		10 (10)		23 (11)
Informed Consent		5 (5)		3 (3)		8 (4)
Blinding	1 (1)		3 (3)		4 (2)	

Efficacy Results

The median time to recovery of normal sensation in the lip was reduced by 83 minutes (62%) by NV-101: median times were 50 minutes for subjects randomized to NV-101 and 133 minutes for subjects randomized to sham. Results of the Cox proportional hazards model predicted a hazard ratio of 3.1 for NV-101 versus sham, indicating that subjects treated with NV-101 were 3.1 times more likely than subjects treated with sham to achieve normal upper lip sensation during the 5-hour observation period ($p < 0.0001$). Results of the Weibull AFT model predicted an event time ratio of 0.53 for NV-101 versus sham, indicating that NV-101 accelerated the time to recovery of normal sensation in the upper lip by 47%. The Cox model also showed no treatment group interaction effect of anesthetic or number of cartridges on the primary endpoint comparison.

Consistent differences between the treatment groups were observed for subsets of subjects treated with lidocaine, articaine, prilocaine or mepivacaine, for subjects treated with either 1 or 2 cartridges/sham injections, for subjects in the 3 age groups (12 to 17 years of age, 18 to 64 years of age and ≥ 65 years of age), for subjects treated with either inferior alveolar block or mental-incisive block, for subjects undergoing cavity preparation/restoration/filling or periodontal maintenance, and for both males and females. Reduction factors ranged from 37% to 68%.

Statistically significant differences between subjects randomized to NV-101 and subjects randomized to sham also were observed for all 3 secondary endpoints: perceived recovery from anesthesia according to STAR-7; normalization of function according to the FAB; and recovery of normal tongue sensation. STAR-7 recovery occurred after recovery of other endpoints for the majority of subjects in both treatment groups. These results indicate that perceived recovery of normal sensation in the lip and tongue did not occur earlier than actual recovery. The table below summarizes both the primary and the secondary endpoint findings.

Table 10-13: Summary of Efficacy Findings as Reported by the Sponsor (NOVA 04-200)

Time-to-Event Endpoint	NV-101		Sham		P value	Time Difference (min.)	Reduction Factor With NV-101 (%)
	N	Time (min.) [median (95% CI)]	N	Time (min.) [median (95% CI)]			
Normal Lip Sensation	120	50 (45-60)	120	133 (115-145)	< 0.0001	83	62
STAR-7 = 0	109	60 (60-90)	111	120 (120-150)	< 0.0001	60	50
Normal FAB	100	60 (50-65)	89	105 (85-125)	< 0.0001	45	43

The time to return to normal sensation in the lip was further evaluated by clinically relevant subgroups as shown in the table below. The reduction factor for each subgroup was > 50% with two exceptions, both of which were related to local anesthetic used. Subjects who received mepivacaine with levonordefrin experienced a 46% reduction in median recovery time, which corresponded to a 65 minute difference for subjects treated with NV-101; however, there was no difference between treatment groups for subjects anesthetized with prilocaine and epinephrine. The prilocaine-anesthetized subjects had median recovery times of 60 minutes for both treatment groups. The lack of difference is attributable to the short duration of the anesthesia associated with prilocaine and epinephrine, at least, as it was observed in this trial. The other local anesthetic drugs had durations of 2 hours or more, based on sham-treatment observations.

Lastly, re-emergence of tingling was observed for one patient in each treatment arm. For the NV-101-treated subject, tingling recurred 20 minutes after onset of normal sensation and lasted for 10 minutes. He had been anesthetized with a single cartridge of mepivacaine and levonordefrin. For the sham-treated subject, tingling recurred 15 minutes after normal sensation

initially returned and resolved 30 minutes later. She had received a single cartridge of lidocaine with epinephrine for her anesthetic.

Table 10-14: Subset analysis of time to recovery of normal sensation in the lip (Table 11-8 from final study report)

Subgroup	NV-101		Sham		Reduction Factor (%)
	N	Median Time (minutes)	N	Median Time (minutes)	
Overall	120	50	120	132.5	62.3
Number of Cartridges					
1	113	50	116	130	61.5
2	7	55	4	150	63.3
Anesthetic					
Lidocaine	79	50	80	135	63.0
Other	41	60	40	120	50.0
Articaine	17	55	10	175	68.6
Mepivacaine	14	75	13	140	46.4
Prilocaine	10	60	17	60	0
Age Group					
12 to 17 years	10	120	14	155	22.6
18 to 64 years	94	50	94	130	61.5
≥ 65 years	16	37.5	12	97.5	61.5
Type of Primary Injection					
Supraperiosteal injection	105	55	101	130	57.7
Superior anterior alveolar nerve block	9	40	17	140	71.4
Infraorbital nerve block	6	32.5	2	100	67.5
Type of Procedure					
Cavity[A]	78	52.5	88	122.5	57.1
Periodontal maintenance[B]	39	55	28	152.5	63.9
Crown	3	30	4	80	62.5
Sex					
Male	56	50	55	115	56.5
Female	64	55	65	135	59.3

[A] Preparation, restoration, and/or filling
[B] E.g., teeth cleaning (non-surgical scaling and/or root planing)

Summary of Applicant-Reported Safety Results

A total of 38 subjects reported 50 adverse events (AEs), with similar frequencies in both randomized treatment groups. There were no deaths, or other serious or severe AEs, and no subject was discontinued because of an AE. All events were mild or moderate in severity. The majority of AEs were deemed related to study drug, with equal distribution between the two treatment groups. The most frequently reported study drug-related AEs were mild or moderate injection site pain, moderate post-procedural pain, and mild headaches. No relationship was apparent between the types of AEs and age group.

Over the course of the study, mean vital signs were relatively stable and nearly identical between the treatment groups. Results of the OCA, which involved both a broad evaluation of the mouth (general OCA) and effects of drug administration at the injection site and procedural site (specific OCA), showed minor abnormalities, some of which were present prior to study drug administration. In nearly all subjects, these findings were not clinically significant. Only 1 subject (200-23-008), who was randomized to NV-101, had clinically significant OCA abnormalities (redness and swelling in the cheek mucosa on the side of the procedure), which were reported as AEs that were unrelated to study drug. The subject was treated with oral analgesics, and the event resolved the next day.

Overall use of analgesics was minimal, with only 5 subjects (2 randomized to NV-101 and 3 randomized to sham) reporting use of such medications for the management of oral pain during the 5-hour observation period or during the 24-hour period following discharge.

No safety concerns (AEs, vital signs, H-P VAS, OCA) were evident for subjects treated with 2 versus 1 cartridge of NV-101, although the number of subjects treated with 2 cartridges was small.

10.1.2.10 Discussion of the Results

The protocol as submitted on September 13, 2005, and clarified in an e-mail on October 13, 2005 and further clarified in an e-mail on October 20, 2005, was reviewed by the Division as a Special Protocol Assessment. In a letter issued by the Division on October 26, 2005, the Sponsor was notified of the Division's agreement that the design and planned analysis of the study adequately addressed all issues raised by the Division and the study could proceed as proposed. Administrative changes were made in the single amendment to the protocol which also included a revised Investigator's brochure and an additional analysis as part of the Statistical Analysis Plan as described above. The amendments were made before the first patient was enrolled in the trial and would not be expected to alter either the conduct of the study or the results.

Of the 240 subjects randomized, all completed the study. One hundred thirty six of the randomized subjects were found to have a total of 214 protocol deviations; the distribution between treatment groups was similar treatment groups: 67 (56%) who received NV-101 and 69 (58%) who received sham treatment. All but six of the deviations involved study procedures; four of which were related to blinding. Just over half of the 208 deviations involving study procedures involved administration of the FAB tool (110 deviations; 53%). The deviations are summarized in the table below.

Table 10-15: Summary of Protocol Deviations (Table 10-4 from final study report)

Category	NV-101		Sham		Total	
	N (%) of all deviations	N (%) of study procedure deviations	N (%) of all deviations	N (%) of study procedure deviations	N (%) of all deviations	N (%) of study procedure deviations
All	105 (100)		109 (100)		214 (100)	
Inclusion/Exclusion Criteria	0 (0)		1 (1)		1 (0.5)	
Study Drug	0 (0)		1 (1)		1 (0.5)	
Randomization	0 (0)		0 (0)		0 (0)	
Study Procedure	104 (99)		104 (95)		208 (97)	
Sensation Rating		11 (11)		14 (13)		25 (12)
STAR-7		10 (10)		5 (5)		15 (7)
FAB		54 (52)		56 (54)		110 (53)
OCA		1 (1)		5 (5)		6 (3)
Vital Signs		6 (6)		8 (8)		14 (7)
H-P VAS		4 (4)		3 (3)		7 (3)
Telephone Follow-up		13 (13)		10 (10)		23 (11)
Informed Consent		5 (5)		3 (3)		8 (4)
Blinding	1 (1)		3 (3)		4 (2)	

The Applicant noted that the study drug deviation occurred in Subject 200-24-001 (randomized to sham), who received ½ cartridge of anesthetic in the primary location (tooth #12) and the remaining ½ cartridge of anesthetic in the secondary injection site (tooth #13). Because the total dose of anesthetic was equivalent to 1 cartridge, the subject was randomized as having received 1 cartridge of anesthetic. The Investigator administered the study drug (sham) in the same manner as the anesthetic was administered. Thus, the subject received ½ cartridge as sham injection at each anesthetic injection site; however, because the sites were adjacent and the syringe was not reloaded with a new cartridge, the study drug administration was considered to be 1 sham injection. Therefore, this subject was analyzed as having received 1 cartridge of anesthetic and 1 sham injection.

A review of the comments on the protocol deviations as extracted from the CRFs and included in section 16.2.2, listing 5, of the final study report revealed that most deviations related to inappropriate timing of FAB assessments or inappropriate timing for adding drinking to the FAB assessment based on previous FAB assessments. It appeared that the investigators did not fully comprehend the protocol regarding the use of this tool and when it was appropriate to allow patients to attempt to drink water. Based on the listing, it appears that 108 subjects had deviations related to timing **of FAB – missed, too frequent**, too infrequent, and extra assessments, and 66 subjects had deviations related **to adding drinking to the FAB assessment** – both too soon and too delayed. The sites with the most study procedure deviations were #1 (15/22 subjects), #13 (23/26 subjects), #20 (13/23 subjects) and #22 (25/26 subjects). Sites 13 and 22 were among the four chosen for routine inspection by the Division of Scientific

Investigations due to the relatively large numbers of patients enrolled at them. Due to the importance of the FAB assessment results for determining the clinical relevance dental soft tissue anesthesia reversal, the statistics review team reanalyzed the FAB data excluding patients for whom there were FAB-related protocol deviations. The results of this analysis are shown in the table below and indicate that the data were quite robust as the two treatment arms still differed at a level of $p < 0.0001$.

Table 10-16: Reanalysis of FAB assessment results based on protocol deviations

Parameter	All Subjects		Subjects without FAB-related protocol deviations	
	Sham (N=89)	NV-101 (N=100)	Sham (N=64)	NV-101 (N=67)
Time to recovery of normal FAB				
Median (minutes)	105	60	98	55
95% confidence limits (minutes)	85-125	50-65	80-125	45-60
Log-rank p value	< 0.0001		< 0.0001	

10.1.2.11 Conclusions

The study was conducted in accordance with the protocol approved by the Division under the Special Protocol Assessment. The study demonstrated a marked reduction in the time for soft tissue recovery from anesthesia following the injection of NV-101. The reduction in this time to recovery was accompanied by similar reductions in both the times at which patients perceived their recovery to be complete and the times at which their recoveries were demonstrated to be complete as assessed by the STAR questionnaire and the FAB assessments, respectively. Thus, the study satisfied the requirements of the SPA agreement and successfully demonstrated efficacy in the populations and clinical scenarios studied.

10.1.3 NOVA 04-PK

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

10.1.3.1 Study Design

NOVA 04-PK was a phase 1, single-center, open-label, 4-treatment, 4-period, crossover clinical study. The drug product used in this study was the to-be-marketed formulation of NV-101. Sixteen healthy subjects received treatments A, B, C, and D in 1 of 4 sequences. A blocked randomization scheme was used to randomly assign the subjects to 1 of the 4 treatment sequences in a 1:1:1:1 allocation. An interval of at least 24 hours separated each treatment. The four treatments were as follow:

- Treatment A: Subjects received 1 cartridge of 2% lidocaine HCl with 1:100,000 epinephrine (1.8 mL), given as a supra-periosteal infiltration over the first molar in the maxilla. Subjects received 1 cartridge of NV-101 (0.4 mg phentolamine in 1.7 mL) in the same location as the anesthetic/vasoconstrictor 30 minutes later.
- Treatment B: Subjects received 1 cartridge of NV-101 (0.4 mg in 1.7 mL) injected IV over 1 minute. A local anesthetic/vasoconstrictor was not administered as part of this treatment.
- Treatment C: Subjects received 4 cartridges of lidocaine/epinephrine: 3.6 mL administered as an inferior alveolar nerve block and 3.6 mL administered as a supraperiosteal infiltration over the first molar in the maxilla. These injections were administered in the same side of the face. Thirty minutes after the first injection of anesthetic/vasoconstrictor, 1 cartridge of NV-101 (1.7 mL) was injected at each site where anesthetic/vasoconstrictor was given, using the same injection technique. The total dose of phentolamine mesylate in this treatment was 0.8 mg (3.4 mL).
- Treatment D: This treatment served as a control for treatment C. Subjects received 4 cartridges of lidocaine /epinephrine: 3.6 mL administered as an inferior alveolar nerve block and 3.6 mL administered as a supra-periosteal infiltration over the first molar in the maxilla. These 2 injections were administered in the same side of the face. NV-101 was not administered to subjects in this treatment.

Serial blood samples were drawn after each treatment, 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) or injection of NV-101. Plasma was separated and assayed for concentrations of phentolamine using a validated LC/MS/MS method. PK parameters were estimated for phentolamine using non-compartmental methods.

All 16 subjects were included in the PK analysis for phentolamine treatments A (0.4 mg intraoral submucosal) and B (0.4 mg IV). The absolute bioavailability of the intraoral submucosal delivery was compared with the IV delivery of the to-be-marketed formulation.

10.1.3.2 Results

After intraoral submucosal injection of a single cartridge of NV-101, the key PK properties for phentolamine were the following:

- T_{max} was 15 minutes after injection.
- C_{max} was 1.34 ng/mL.
- $t_{1/2}$ was approximately 3 hours.

After IV injection of a single cartridge of NV-101, the PK properties for phentolamine were the following:

- T_{max} was 7 minutes after IV injection
- C_{max} was approximately 8 times that after intraoral submucosal injection
- Phentolamine was completely bioavailable after intraoral submucosal injection (104% of AUC) compared to its bioavailability after IV injection.

This was the only study to analyze the biopharmaceutic properties of the to-be-marketed formulation of NV-101.

10.1.4 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"**

10.1.4.1 Study Design

This was a randomized, double-blind, placebo-controlled study to evaluate 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 and epinephrine. The study also served to evaluate the safety of an injection of phentolamine mesylate in healthy subjects.

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). This injection was placed in a standardized location to achieve a right- or left-sided IANB. Subjects were randomly assigned to receive a single injection of placebo (1.8 mL of normal saline) 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.

All subjects self-evaluated the return of normal sensation in the lip, tongue, teeth, and chin by palpation at 5- minute intervals beginning 5 minutes before the phentolamine mesylate or placebo injection and continuing until all subjects present for testing had achieved the return of normal sensation in lip, tongue, teeth, and chin. Safety was assessed by the use of two-lead electrocardiogram (ECG), vital signs, pain ratings, and physical examinations including oral cavity examinations. No subjects were permitted to leave the clinic until all subjects had achieved the return of normal sensation.

A total of 20 subjects received study drug, and all of these subjects completed the study. The groups were similar in terms of age, gender, height, and weight. The study population averaged 40 years of age, was predominantly black, and approximately half of the subjects in each group were male and half were female.

10.1.4.2 Results

Phentolamine reduced the duration of soft-tissue anesthesia with no apparent risks to safety. Recovery in the lip, chin, and tongue was nearly twice as fast in subjects in the phentolamine-treated group than in the placebo-treated group. The mean durations of soft-tissue anesthesia were reduced by 38% to 51% in these tissues. There were few adverse events and cardiovascular measures such as heart rate, blood pressure, and ECG rhythm were not significantly affected by phentolamine. The table below summarizes the efficacy findings. The number of subjects in each category is not 10 because one placebo-treated subject did not experience tingling in any soft-tissue and one phentolamine-treated subject did not experience tingling in the lip or chin.

Table 10-17: Duration of numbness in minutes (Table 11.3 from final study report, p.31)

Treatment	Statistical Parameter	Lip	Chin	Tongue
Placebo	N	9	9	9
	Mean	72.2	75.6	52.2
	Median	80.0	80.0	50.0
	SD	27.2	29.5	31.9
	Range	35-100	30-115	20-100
NV-101 (0.4 mg)	N	9	9	10
	Mean	25.0	30.6	21.0
	Median	25.0	20.0	15.0
	SD	13.5	30.9	16.5
	Range	5-55	5-105	5-55
	p-value	<0.001	0.006	0.014*

* The Mann-Whitney Rank Sum test was used to analyze differences in the tongue rather than the *t*-test because of unequal variances in the two groups.

10.1.4.3 Discussion and Conclusions

This preliminary study demonstrated a significant and likely clinically relevant hastening of the return to normal sensation in subjects undergoing a common dental nerve block, IANB, using a typical dose of a commonly used local anesthetic, 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 µg).

10.1.5 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"**

10.1.5.1 Study Design

This was a dose-ranging, randomized, double-blind, placebo-controlled study. Forty 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). This injection was placed in a standardized location to achieve right- or left-side IANB. Subjects were randomly assigned to receive a single injection of placebo (1.8 mL of normal saline), 0.02 mg of phentolamine mesylate (1.8 mL of a 0.011 mg/mL solution), 0.06 mg of phentolamine mesylate (1.8 mL of a 0.033 mg/mL solution), or 0.4 mg of phentolamine mesylate (1.8 mL of a 0.2267 mg/mL solution) at 60 minutes after administration of the IANB, in the same site where the anesthetic was injected. Randomization was 1:1:1:1. The subjects did not undergo a dental procedure as part of this study.

All subjects self-evaluated the return of normal sensation in the lip, tongue, teeth, and chin by palpation at 5-minute intervals beginning 5 minutes before the phentolamine mesylate or placebo injection and continuing until all subjects present for testing had achieved the return of normal sensation in lip, tongue, teeth, and chin. No subjects (except drop-outs) were permitted to leave the clinic until all subjects had achieved the return of normal sensation.

Sensation was assessed in the lip by pinching with 2 fingers (or thumb and forefinger), in tongue by pinching the lateral edge of the tongue while extruding the tongue outside the mouth, in the teeth by biting (bringing the teeth together) and moving the teeth from side to side while the teeth were brought together, and in the chin by pressing with the forefinger. Responses for the lip, tongue, and chin were categorized as 1) numb (no feeling), 2) feeling of pins and needles (tingling), or 3) normal sensation. Responses for the teeth were categorized as 1) numb (no feeling) or 2) normal sensation.

Safety was assessed by the use of two-lead electrocardiogram (ECG), vital signs, pain ratings, and physical examinations including oral cavity examinations.

10.1.5.2 Results

The rate of recovery to the return of normal sensation in the group treated with phentolamine at the dose of 0.4 mg was approximately twice as fast as that for the placebo group in each tissue measured. The reductions were approximately one hour in length and were statistically significant. This effect was weakly dose-related, and recovery times in even the lowest dose group were significantly shorter than those in the placebo group. Recovery times in the highest dose group were only 17% to 40% shorter than the lowest treatment group times, although there was a 20-fold difference in the dose levels between the low dose and high dose.

The majority of the effect of reduced recovery times in the lip and chin occurred during the numbness phase. Subjects treated with 0.4 mg phentolamine mesylate passed through the numbness phase three times faster than placebo-treated controls, i.e., in under 40 minutes. Reduced recovery times in the tongue occurred mainly during the tingling phase with little change in the duration of numbness.

Table 10-18: Duration of Numbness in minutes (Table 11.3 from final study report, p.34)

Treatment	Statistical Parameter	Lip	Chin	Tongue
placebo	N	10	10	10
	Mean	100.1	107.6	46.6
	Median	115.0	115.0	40.5
	SD	47.9	49.1	28.0
	Range	36-190	26-200	10-95
NV-101 0.02 mg	N	10	10	10
	Mean	67.5	64.5	46.0
	Median	65.0	63.0	50.0
	SD	32.4	28.1	24.6
	Range	25-125	30-120	6-87
NV-101 0.06 mg	N	10	10	8
	Mean	66.5	67.6	53.1
	Median	52.5	55.0	32.5
	SD	48.2	45.2	49.3
	Range	10-165	10-165	10-155
NV-101 0.4 mg	N	10	10	10
	Mean	33.6	37.1	34.9
	Median	26.0	35.0	32.5
	SD	22.2	22.3	18.3
	Range	5-75	14-75	5-60
	ANOVA overall p-value	0.007	0.002	0.651
	Dunnett's p-values (one-sided)			
	0.02 mg vs. placebo	0.086	0.020	0.500
	0.06 mg vs. placebo	0.077	0.031	0.473
	0.4 mg vs. placebo	<0.001	<0.001	0.369

There were no dose-related trends in the number or type of adverse events. The severity of each adverse event was rated as mild. The nature of the adverse events of injection site pain and injection site reaction were described as typical of those encountered in standard dental practice. There were no serious adverse events and no withdrawals from the study due to adverse events. Treatments of ibuprofen were administered to two subjects for headache and to one subject for bone pain (pre-existing jaw soreness). These analgesic treatments were in violation of the protocol. No other treatments were offered to subjects for adverse events.

10.1.5.3 Discussion and Conclusions

As with study NOVA 02-01, this study demonstrated a significant and likely clinically relevant hastening of the return to normal sensation in subjects undergoing a common dental nerve block, IANB, using a typical dose of a commonly used local anesthetic, 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 μg). This study also demonstrated an advantage to the use of the higher dose of NV-101, i.e., 0.4 mg, in terms of efficacy for reversing soft tissue anesthesia in the lip chin and tongue. The 0.4mg dose of NV-101 was the only dose to achieve a significant difference from placebo in both lip and chin return to normal sensation. The importance of a rapid return to normal sensation in the tongue, both in terms of safety and a clinically relevant efficacy measure, remains to be elucidated. The safety data indicated no dose-related trends in adverse events indicating that the highest dose was suitable for further evaluation.

10.1.6 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"**

10.1.6.1 Study Design

Similar to NOVA 02-02, this was a dose-ranging, randomized, double-blind, placebo-controlled study. 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). This injection was placed in a standardized location. Subjects were randomly assigned to receive a single injection of placebo (1.8 mL of normal saline), 0.02 mg of phentolamine mesylate (1.8 mL of a 0.011 mg/mL solution), 0.08 mg of phentolamine mesylate (1.8 mL of a 0.044 mg/mL solution), or 0.4 mg of phentolamine mesylate (1.8 mL of a 0.2267 mg/mL solution) at 40 minutes after administration of local anesthetic, in the same site where the anesthetic was injected. Randomization was 1:1:1:1. The subjects did not undergo a dental procedure as part of this study.

All subjects self-evaluated the return of normal sensation in the upper lip, nose, and teeth by palpation at 5-minute intervals beginning 5 minutes before the phentolamine mesylate or placebo injection and continuing until all subjects present for testing had achieved the return of normal sensation in upper lip, nose, and teeth. No subjects (except drop-outs) were permitted to leave the clinic until all subjects had achieved the return of normal sensation.

Sensation was assessed in the upper lip by pinching with two fingers (or thumb and forefinger), in the teeth by biting (bringing the teeth together) and moving them from side to side, and in the nose by pressing the side of the nose with the forefinger. Responses for the upper lip and nose were categorized as 1) numb (no feeling), 2) feeling of pins and needles (tingling), or 3) normal sensation. Responses for the teeth were categorized as 1) numb (no feeling) or 2) normal sensation.

Safety was assessed by the use of two-lead electrocardiogram (ECG), vital signs, pain ratings, and physical examinations including oral cavity examinations.

10.1.6.2 Results

Eleven patients receiving maxillary procedures were not numb in the nose at the time of study drug injection, and therefore could not be included from the analysis of the time to return to normal sensation. Among the 21 patients analyzed, the mean time to return to normal sensation in the nose in patients treated with NV-101 was 25 minutes (59%) less than those in the placebo group, but the difference was not statistically significant for any of the NV-101 treatment groups.

The rate of recovery to the return of normal sensation in the group treated with phentolamine at the dose of 0.4 mg was nearly twice as fast as that for the placebo group in each tissue measured. The reductions were approximately one-half hour in length and were statistically significant in the lip and the teeth.

The majority of the effect of increased recovery rate in the lip occurred during the numbness phase, compared to the tingling phase. Subjects treated with 0.4 mg phentolamine mesylate passed through the numbness phase nearly three times faster than placebo-treated controls, in under 40 minutes. The table below summarizes the results for the evaluation of numbness.

Table 10-19: Duration of Numbness in minutes (Table 11.3 from final study report, p. 33)

Treatment	Statistical Parameter	Lip	Nose
Placebo	N	9	7
	Mean	83.6	60.7
	Median	95.0	68.0
	SD	45.9	53.5
	Range	10-160	8-140
NV-101 0.02 mg	N	8	5
	Mean	58.1	35.0
	Median	42.5	30.0
	SD	47.7	20.0
	Range	15-155	10-65
NV-101 0.08 mg	N	7	5
	Mean	49.9	39.8
	Median	50.0	50.0
	SD	22.3	22.5
	Range	20-80	5-60
NV-101 0.4 mg	N	8	4
	Mean	32.6	31.3
	Median	25.0	25.0
	SD	14.0	19.7
	Range	17-59	15-60
	ANOVA overall p-value	0.054	0.511
	Dunnett's p-values (one-sided)		
	0.02 mg vs. placebo	0.182	0.255
	0.08 mg vs. placebo	0.094	0.329
	0.4 mg vs. placebo	0.010	0.228

There were few adverse events in the study, suggesting that phentolamine was well tolerated. One or more adverse events were reported by 11 subjects (34% of the total study population). There were no dose-related trends in the number or type of adverse events. The severity of all adverse events was rated as mild.

The nature of the adverse events of injection site edema and injection site reaction was reported to be typical of those encountered in standard dental practice. There were no serious adverse events and no withdrawals from the study due to adverse events. No treatments were offered to subjects for adverse events.

10.1.6.3 Discussion and Conclusions

As with study NOVA 02-02, this study demonstrated a significant and likely clinically relevant hastening of the return to normal sensation in subjects undergoing a common dental nerve block, in this study, maxillary lateral incisor infiltration, using a typical dose of a commonly used local anesthetic, 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 μg). This study also demonstrated an advantage to the use of the higher dose of NV-101, i.e., 0.4 mg, in terms of efficacy for reversing soft tissue anesthesia in the lip but not the nose. The 0.4mg dose of NV-101 was the only dose to achieve a significant difference from placebo in return to normal sensation of the lip. The importance of a rapid return to normal sensation of the nose, both in terms of safety and a clinically relevant efficacy measure, remains to be elucidated but is not likely to be as clinically relevant as the return to normal sensation of the lip or the tongue, which is not an issue with this block. The safety data indicated no dose-related trends in adverse events indicating that the highest dose was suitable for further evaluation.