Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
10903 New Hampshire Avenue
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CLINICAL REVIEW

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Reviewer Name	Arthur Simone, M.D., Ph.D.
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Established Name	Phentolamine Mesylate
Proposed Trade Name	OraVerse
Therapeutic Class	local anesthetic reversal agent
Applicant	Novalar Pharmaceuticals, Inc.
Priority Designation	S
Formulation	injection solution
Dosing Regimen	intraoral submucosal injection
Indication	reversal of local anesthesia for dental procedures
Intended Population	healthy dental patients over 12 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The evidence submitted in support of efficacy for OraVerse (NV-101) in adults indicated that a substantial reduction in the time required for return of normal sensation and function occurred with NV-101 compared to placebo (sham injection) following the administration of a local anesthetic and vasoconstrictor. The adverse reactions to treatment with NV-101 in this population did not substantially differ from that of placebo. Thus, there was a clearly favorable benefit-risk ratio in this population, and it is recommended that NV-101 be approved for the proposed indication in adults.

For pediatric subjects ages 12 to 17 years old, the Applicant provided adequate evidence that a substantial reduction in the time required for return of normal sensation in the lip (the primary endpoint) as well as in the tongue and to baseline perception of and ability to function (secondary endpoints) occurred with NV-101 compared to sham injection following the administration of a local anesthetic and vasoconstrictor. The magnitude of the reductions in time to normal sensation in these soft tissues, an hour or more, was sufficient to confer a clinical benefit and thereby diminish the concern raised regarding content validity of the metric used to assess subjects' perception of their recovery from the local anesthetic. That metric nonetheless provided some support that a clinical benefit was associated with the reduction in the duration of anesthesia in that it demonstrated subjects could appropriately perceive normalization of function and less need to worry about possible self-inflicted soft tissue injury. The magnitudes of the reductions in the times for return of normal sensation, perception of recovery and recovery of function for this age group were similar to those of the concomitantly studied adults. The safety profile of NV-101 in this segment of the pediatric population was similar to that of the adults. It was noted that the only nerve injury reported in the clinical program occurred in a 14 year old patient who received NV-101. However the nature of the injury did not substantially impact the overall safety profile. Thus, there was a favorable benefit-risk ratio in this population, and it is recommended that NV-101 be approved for the proposed indication in pediatric patients from age 12 to 17 years old.

For pediatric subjects ages 6 to 11 years old, the Applicant provided adequate data that a substantial reduction in the time required to return to normal sensation occurred with NV-101 compared to placebo following the administration of a local anesthetic and vasoconstrictor. The magnitude of the reduction in the time to return of normal sensation for this age group was similar to those of the older pediatric patients and the adults. Some of the subjects in this age group were unable to adequately perform the lip palpation test of sensation and were not included in the assessment of efficacy. There was no assessment of subjects' perception of their recovery from anesthesia and no assessment of their ability to speak, smile, drink, and not drool. The safety profile of NV-101 in this age group was similar to that of the adults. While no subjects sustained a soft tissue injury from biting their tongue, lip or cheek while anesthetized,

this age group may be more vulnerable to such injury than their elders. Based on the substantial reduction in time to return to normal sensation, a safety profile indicative of minimal risk, and the potential benefit of reduced injury, it is recommended that NV-101 be approved for the proposed indication in pediatric patients 6 to 11 years of age.

For pediatric subjects ages [redacted] years old, the Applicant neither collected nor provided any efficacy data. Safety and tolerability of NV-101 were assessed in this age group and were found to be similar to that of the adults and older pediatric patients. While no subjects in this age group sustained a soft tissue injury from biting their lip, tongue or cheek while anesthetized, this age group may be even more vulnerable to such injury than those ages 6-11 years old. [redacted]. The safety data and the potential for self-inflicted injury while anesthetized in this age group warrant further study by the Applicant as a Postmarketing Commitment.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity was required for NV-101 as it has no properties, e.g., mind-altering effects, which would make it likely to be abused, and its use is not associated with tolerance or addiction.

1.2.2 Required Phase 4 Commitments

The Applicant should assess the safety and efficacy of NV-101 when used in dental patients ages 3-5 years old. The evaluation of efficacy may be limited to characterizing the time to return of normal sensation in the lip and, where applicable, the tongue and the cheek. Efficacy should be evaluated over the range of dental procedures commonly performed in this age group, as well as for the range of local anesthetic-vasoconstrictor combinations routinely used and dental nerve blocks commonly employed. Safety evaluations should include actively assessing for nerve injury secondary to trauma of NV-101 injection and self-inflicted injury during the period of soft tissue anesthesia.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Novalar Pharmaceuticals, Incorporated, proposes that phentolamine mesylate (NV-101), a non-selective α-adrenergic antagonist, can reverse the effects of local anesthetics used for dental procedures. Specifically, the applicant claims that NV-101 reverses soft tissue anesthesia, i.e., anesthesia of the lip, tongue and cheek, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. To this end, the Applicant has conducted clinical trials involving patients aged 4 years and older. The development plan included nine clinical trials in which 497 subjects were treated with NV-101. Dosing ranged from 0.002 mg to 0.8 mg of submucosal phentolamine, which is substantially lower than the approved 5-mg (adult) and 1-mg (pediatric) intravenous or intramuscular doses of phentolamine for the prevention of hypertensive episodes related to pheochromocytoma. Phentolamine has not been approved either in the United States or abroad for the proposed dental indication, thus the clinical data source is limited to the studies conducted by the Applicant.

1.3.2 Efficacy

NV-101 is supplied in a dental cartridge containing 1.7 mL of solution with 0.4 mg of phentolamine mesylate, a competitive, nonselective, α-adrenergic blocking agent which acts in the peripheral vasculature system as a vasodilator. Phentolamine has been marketed in the United States since 1952 for use in the diagnosis and treatment of patients with pheochromocytoma and for the treatment and the prevention of dermal necrosis following intravenous administration or extravasation of norepinephrine. The Applicant proposes that NV-101, under the trade name OraVerse, is indicated for the reversal of soft tissue anesthesia (STA) for dental procedures resulting from administration of local anesthetics containing vasoconstrictors. The Applicant indicates that the appropriate dose of NV-101 is predicated on the dose of local anesthetic using a 1:1 volume ratio, such that 0.2 mg of NV-101 would be used to reverse half a dental cartridge of local anesthetic with vasoconstrictor, 0.4 mg of NV-101 would be used to reverse a full cartridge, and 0.8 mg of NV-101 would be used to reverse 2 cartridges worth of local anesthetic with vasoconstrictor. The Applicant further proposes that NV-101 is suitable for use in patients [redacted]. This use of phentolamine constitutes a new indication for the drug product, and, if it is approved, NV-101 would be the first product approved for the reversal of soft tissue anesthesia resulting from the administration of local anesthetic containing a vasoconstrictor.

The development plan for NV-101 included nine human studies. These included an adult and a pediatric pharmacokinetic study, two dose-ranging studies, a pediatric efficacy trial and three efficacy trials that evaluated safety and efficacy in adult and older pediatric patients, two of which were conducted under Special Protocol Assessments (SPA). In addition, the Applicant developed two metrics; one to assess patients' perceptions regarding their recovery from STA [the Soft Tissue Anesthesia Recovery (STAR) questionnaire] and the other to assess the return of

function with recovery from STA [the Functional Assessment Battery (FAB) tests]. The recommendations for the regulatory action rely most heavily on the two SPA trials, both of which included STAR and FAB assessments, and the two pediatric studies.

The two SPA trials evaluated the times to return of normal sensation of the lip and, where applicable, the tongue for patients undergoing various dental procedures following the performance of routine dental nerve block involving the administration of a commonly used dental anesthetic (a vasoconstrictor-containing local anesthetic drug product). Both trials also assessed the times to return of baseline values for the STAR and FAB scores for these subjects. One of the trials, NOVA 04-100, evaluated dental procedures involving the mandible; the other, NOVA 04-200, evaluated dental procedures involving the maxilla. The data from NOVA 04-100, demonstrated that use of NV-101 resulted in an 85-minute reduction in the median time to return of normal sensation of the lip; and a 60-minute reduction in the median time to return of baseline STAR and FAB scores. The data from this trial also demonstrated a 65-minute reduction in the median time to return of normal sensation of the tongue with the use of NV-101. The data from NOVA 04-200, demonstrated that use of NV-101 resulted in an 83-minute reduction in the median time to return of normal sensation of the lip; and a 60-minute and a 45-minute reduction in the median time to return of baseline STAR and FAB scores, respectively.

Studies NOVA 03-001 and NOVA 05-PEDS evaluated the times to return of normal sensation of the lip, and, where applicable, the tongue, chin and cheek for patients undergoing various dental procedures following the performance of routine dental nerve block involving the administration of a commonly used dental anesthetic. These two studies did not include an assessment of either STAR or FAB scores. The data from NOVA 03-001 demonstrated that use of NV-101 resulted in a 56-minute and a 78-minuted reduction in the median time to return of normal sensation of the lower and upper lips, respectively, and a 48-minute and a 34-minute reduction in the median time to return of normal sensation for the chin and tongue, respectively. NOVA 05-PEDS evaluated return of normal sensation only in the lip for pediatric patients ages 6-11 years old and found an overall 75-minute reduction in the median time to return of normal sensation.

The benefits of these substantial reductions in the times-to-return-of-normal sensation were placed into a clinically relevant context by the STAR and FAB scores. Although the FAB scores were not formally validated, the individual parameters assessed by FAB would have qualified as secondary endpoints in their own right and thereby mitigated the need for validation. The STAR questionnaire was formally validated for adults. In the adult subjects, these Applicant-developed metrics provided evidence that subjects perceived, and demonstrated, an early return to the pre-anesthetized state in terms of speaking, smiling, drinking, and not drooling. NV-101-treated subjects became less concerned about self-inflicted injury, i.e., biting their cheek, lip or tongue, sooner than those treated with sham injections.

For pediatric subjects ages 12-17 years old, both the STAR and FAB scores again provided evidence of the clinical relevance for the faster return to normal sensation associated with NV-101. Although neither of these metrics was formally validated in this subpopulation, there was no compelling argument to disregard their use as secondary endpoints or not consider them clinically relevant in performing the benefit-risk analysis for this group.

For pediatric subjects ages 6-11 years old, only the return of normal sensation in the lip was evaluated by the Applicant, and no attempt was made to provide a clinically relevant context for assessing the benefit to be gained from the faster return of normal sensation obtained with NV-101. However, the pediatric dental literature consistently raises the concern for self-induced soft tissue trauma in younger patients who do not understand the effects of local anesthetics. The American Academy of Pediatric Dentistry[1] recommends that "residual soft tissue anesthesia should be minimized in pediatric and special health care needs patients to decrease risk of self-inflicted injuries." Thus, the benefit of the effects of NV-101 was considered in the context of enhanced patient safety for this age group.

NV-101 was assessed only for safety and tolerability in pediatric subjects ages 4-5 years old. Its use was not assessed in any subjects less than 4 years old.

1.3.3 Safety

The assessments for safety included evaluations of the hemodynamic effects associated with phentolamine for which blood pressure and heart rate changes were monitored; the potential for phentolamine to produce arrhythmias, which was assessed in one study looking at 2-lead Holter monitor recordings; local tissue reactions that were assessed by frequent oral cavity examinations; pain associated with either the injections or early dissipation of anesthesia, which was monitored by pain-scale scores; and adverse event reporting by the patients, their caregivers and the Investigators.

The safety profile for NV-101 differed little from that of placebo, either placebo injections or sham injections. There was slightly more pain or discomfort associated with NV-101 treatment compared to placebo and slightly more incidents of abnormalities on oral cavity examinations with NV-101 treatment, e.g., edema or erythema. None of these adverse events occurred in sufficiently greater frequency or with more severity than placebo to warrant restrictive use of NV-101. Similarly, there were slightly more incidents of bradycardia and increased blood pressure observed with NV-101 compared to placebo, but neither the frequency nor magnitude for either of these adverse events posed a clinically relevant risk for the use of NV-101. Lastly, a single incident of nerve injury was observed in the entire clinical program. A 14-year old female patient experienced a lingual nerve injury following treatment with NV-101; however, the cause of the injury cannot be definitively assigned to NV-101 treatment, i.e., the drug or the injection. The subject was lost to follow up before complete resolution was recorded.

1.3.4 Dosing Regimen and Administration

The dosing regimen recommended by the Applicant following an injection of a local anesthetic containing a vasoconstrictor is:

- ½ cartridge (0.2 mg) of NV-101 to reverse ½ cartridge of local anesthetic
- 1 cartridge (0.4 mg) of NV-101 to reverse 1 cartridge of local anesthetic
- 2 cartridges (0.8 mg) of NV-101 to reverse 2 cartridges of local anesthetic

- If the patient's weight is 15-30 kg the maximum dose of NV-101 recommended is ½ cartridge (0.2 mg).

The Applicant is not requesting that NV-101 be approved for use in patients under the age of 6 years old; therefore, the last bullet should be modified to read:

[redacted]

1.3.5 Drug-Drug Interactions

Drug-drug interactions, in the classical sense, were not evaluated as the systemic levels of phentolamine following intraoral injection were relatively low and the product is intended for acute use. The effect of an intraoral NV-101 injection on the pharmacokinetics of a previously administered local anesthetic and vasoconstrictor were evaluated in an effort to understand the mechanism of action for the reversal of the soft tissue anesthesia.

In a Phase 1 pharmacokinetic crossover study, administration of NV-101 significantly delayed lidocaine T_{max} (mean T_{max} values were 43 and 28 minutes for local anesthetic with and without NV-101, respectively). [redacted] Lidocaine AUC and C_{max} values were not affected by administration of NV-101.

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

1.3.6 Special Populations

The Applicant has provided a substantial amount of safety data for the pediatric patient population ages three-years old and up. Efficacy has been evaluated to varying degrees in segments of this population as well; however, the type and quantity of efficacy data diminished with decreasing subject age hindering as thorough an assessment of efficacy as was conducted in the adult population. The following findings in pediatric patients were the basis for the approval recommendations made above. More detail related to these findings can be found in the body of this review.

- Overall, the safety findings in the pediatric patients for the nature and frequency of adverse events did not differ substantially by age groups for 3-11, 12-17, and 18-64 year olds. There were no deaths, serious adverse events or dropouts among the pediatric subjects, as was the case for the adult subjects. Unlike the adult subjects, there were no adverse events described as severe in the pediatric subjects.
- Efficacy was assessed for subjects ages 12-17 years old in the same manner as adult subjects, i.e., palpation techniques were used to assess return of sensation in the lip, tongue, cheek and nose, and the clinical relevance of the return of sensation was assessed

by patient-reported outcomes, which included the Soft Tissue Anesthesia Reversal (STAR) questionnaire and the Functional Assessment Battery (FAB) tests. In this pediatric age group it was observed that:

  - The times to return of normal sensation of each of the soft tissues were reduced by amounts similar to those observed for adult subjects for both mandibular and maxillary procedures.
  - The times to return to a STAR score of 0, i.e., the subject perceived sensation and function to have returned to normal and was not concerned about possible soft tissue injury from biting, were reduced by amounts similar to those observed for adult subjects for both mandibular and maxillary procedures.
  - The times to return to normal functioning, i.e., the subject was able to speak, smile, drink and not drool, were reduced by amounts similar to those observed for adult subjects for both mandibular and maxillary procedures.

- The assessment of efficacy for subjects ages 6-11 years old consisted only of identifying the reduction in time to return of normal sensation in the lip. NV-101 produced results in this group of subjects, at least those who could be successfully trained in the technique of lip palpation, that were similar to those of older subjects.
- Efficacy was not assessed in subjects less than six years of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

NV-101 (proposed trade name: OraVerse) contains the active ingredient phentolamine mesylate, an alpha-adrenergic blocking agent. OraVerse is a new dosage form of phentolamine, which is currently marketed for intravenous and intramuscular injection under the trade name Regitine and as generics. OraVerse will be marketed for oral submucosal injection and is packaged in a dental cartridge for injection.

The Applicant proposes that OraVerse be indicated for:

> "the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor."

The Applicant seeks to market OraVerse for use on dental patients ages [redacted] years old and older. The proposed dosing regimen is based on the amount of local anesthetic-vasoconstrictor injected as follows:

- ½ cartridge (0.2 mg) of OraVerse when ½ cartridge of local anesthetic has been administered.
- 1 cartridge (0.4 mg) of OraVerse when 1 cartridge of local anesthetic has been administered.
- 2 cartridges (0.8 mg) of OraVerse when 2 cartridges of local anesthetic have been administered.

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

The following dosing guidelines are to apply to specific subpopulations of pediatric dental patients:

- For pediatric patients weighing 15-30 kg, the recommended maximum dose of OraVerse is 1/2 cartridge (0.2 mg).
- Use in pediatric patients under [redacted] years of age or <15 kg is not recommended.

2.2 Currently Available Treatment for Indications

If approved, NV-101 (OraVerse) will be the first product indicated for the reversal of soft-tissue anesthesia for dental procedures.

2.3 Availability of Proposed Active Ingredient in the United States

Phentolamine mesylate, the active ingredient in NV-101, is readily available in the United States and is marketed for other indications under the trade name, Regitine, and as generic formulations.

2.4 Important Issues with Pharmacologically Related Products

No issues with pharmacologically related products have been identified that would be expected to have an impact on either the safety or efficacy of NV-101.

2.5 Presubmission Regulatory Activity

The following are highlights of the regulatory activity that occurred during the development program for NV-101.

IND 65,095 was opened on June 20, 2002, with the submission by Novalar Pharmaceuticals, Inc. that included the protocol for NOVA 02-01.

On June 26, 2002, the IND was transferred from the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products to Division of Anesthetic, Critical Care, and Addiction Drug Products, now the Division of Anesthetic, Analgesic and Rheumatology Products.

An **End-of-Phase 2** meeting was held on October 30, 2003. The key clinical issues that were discussed at that time are itemized below.

- Resolution of the effects of the local anesthetics at the lip is a reasonable efficacy endpoint.
- Sites selected for assessment of local anesthetic reversal should be those for which reversal provides some benefit.
- Secondary endpoints, e.g., total resolution, will be evaluated and considered in the benefit-risk analysis by FDA.
- Evidence of the clinical benefits for reversing local anesthetic effects following dental procedures should be provided, e.g., improved patient satisfaction, reduction in injury such as tongue or lip biting. The benefits should be in some way quantifiable, i.e., baseline patient satisfaction levels or injury rates need to be elucidated.
- The following would need to be addressed for FDA to consider a general indication for reversal of local anesthetics containing a vasoconstrictor:
  - The mechanism for reversal has not been fully elucidated such that demonstration of efficacy with a few members of a drug class can be extrapolated to the entire class.
  - A demonstration that phentolamine exerts its effect by reversing vasoconstriction caused by vasoconstrictors co-administered with local anesthetics.
  - The full range of concentrations of available vasoconstrictors, as well as the full range of local anesthetics need to be evaluated.

  - A claim may need to be limited to those local anesthetics/ vasoconstrictors studied.
- The reductions in time to normal sensation in NOVA 03-001 appeared to be clinically significant. However, the clinical relevance, e.g., possible injury, patient satisfaction with anesthetic, needs to be demonstrated.
- Specific concerns identified regarding the use of NOVA 03-001, a Phase 2 study, as a pivotal trial included the following:
  - Limited types of blocks and procedures were studied.
  - Only healthy subjects 10 years of age and older were included.
  - Repeat dosing (to 0.8 mg) was not evaluated.
- The full range of blocks actually used in the clinical setting should be evaluated.
- Soft-tissue anesthesia for the tongue is important even if the lip may not be numb. Consideration should be given as to whether it is appropriate to exclude such patients.
- Ultimately, the efficacy database must demonstrate safety and efficacy in the target population for which the drug is intended. This would generally include, among other things, the following:
  - Reasonable representation of blocks/infiltrations to be reversed and procedures for which the blocks will be used, e.g., cleanings, scalings, restorations, extractions, fixed prosthodontics.
  - Patients in good and poor health.
  - A full range of ages for the patients including geriatric populations.
  - A significant number of patients exposed to the proposed highest-labeled dose.
- Thorough evaluation of about 300 patients given the doses proposed for marketing could provide a sufficient database assuming no safety issues are identified, and a broad range of patients (in terms of demographics, health status, injection sites, procedures and dose) are assessed.
- Information from the Description, Contraindications, Warnings, Precautions, and Adverse Reactions sections of the current label will likely carry over to the Novalar label. It may be necessary to provide additional information to these sections based on results of the current studies.
- Additional label information that should be provided in an NDA includes the following:
  - Dose ranging study information.
  - Effects of the drug on bleeding following the procedures.
  - Information concerning local tissue or nerve toxicity.
  - Use of the drug when local irritation/abscess is present.
  - Usefulness of the drug when other blocks, e.g., palatal infiltration or superior alveolar nerve block, are utilized.
- The Division stated consideration should be given to distinguishing the phentolamine carpules from those of local anesthetics as this could be the first non-anesthetic, dental drug product that would be available in a standard carpule.
- The potential risk of increased bleeding following local anesthetic reversal should also be evaluated.
- Children ages 10-17 were included in the phase 2 study, NOVA 03-001, [redacted]

[redacted]
The Division stated that the label will reflect the populations studied, but potential off-label use will be a consideration in the overall benefit/risk analysis for the drug.
- Approximately 100 children with an adequate age distribution should provide a sufficient safety database; although, adequacy of the database size would depend in part upon clinical findings, dosing, and demographic considerations.
- The Sponsor stated it would be hard to collect efficacy data in the younger population versus just safety data. 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 Sponsor questioned if a pediatric study could be a post marketing commitment. The Division stated that this should be addressed at the time of the NDA filing.

A teleconference took place on March 16, 2004, to discuss the proposed SPA-advice letter issued February 6, 2004. The key concerns of the Division are summarized below:

- The primary endpoint, duration of numbness, must be linked within the trials to other endpoint(s) that assess the clinical meaningfulness of the drug effect e.g., patient perceived reduction in the adverse consequences of numbness.
- The secondary endpoints themselves may not need to achieve statistically significant differences among treatment groups, but should clearly demonstrate changes in the desired direction among the groups.
- The secondary endpoints might not be a basis for a labeling claim without replication and clear validation of these endpoints.
- Specific domains that should also be addressed to perform the benefit/risk analysis include, among others, post-procedure pain, bleeding, pain on injection of test drug, disability and injury related to numbness.

On November 18, 2004, a meeting was held to discuss the advice letter issued on February 6, 2004, regarding the SPA for NOVA 04-100. The meeting addressed issues regarding the design of the proposed studies and endpoints to be evaluated. In particular, attention was centered on the development of the STAR questionnaire. The following are the key points made by the Division at that time.

- Evidence of an earlier return of function as well as an earlier return of the perception of return of ability to function with NV-101 would be sufficient to demonstrate clinical relevance of lip palpation assessment of numbness.
- The primary surrogate endpoint should be return to sensation. The other observed outcomes (i.e., eating, drinking, smiling, drooling, speaking, etc.) are secondary and would be supportive.
- Assessment of tongue numbness may have clinical relevance in terms of speech and swallowing capabilities; it also assesses STAR in another soft tissue; therefore, its assessment as a secondary endpoint should be performed on patients undergoing mandibular blocks.
- Testing for tongue numbness should be standardized to the degree done for lip testing.
- While a reduction in time to normal sensation of greater than one hour would be expected to be of clinical benefit, this would have to be demonstrated by a significant improvement

in the patients' attitudes toward STA and/or significant reduction in time to normal speech, swallowing, or cessation of drooling. If a metric such as the STAR questionnaire is to serve this purpose, a rationale for what constitutes a clinically meaningful change in STAR score is required.

- If only one control is to be used in the pivotal trials, it should be the sham injection.
- A basis for determining a clinically relevant change in STAR scores/return of sensation had to be provided.
- The items in the STAR questionnaire assessing patients' impressions of their ability to carry out certain functions should be compared to the patients' actual ability to execute those functions before and while recovering from the anesthetic. Evaluation of function by a treatment-blinded observer would provide an objective assessment of the effects of residual STA and demonstrate the validity of the questionnaire.
- A question regarding global assessment of a patient's attitude toward reversal of STA should be included.
- The STAR response options are anchored to phrases. Evidence is required to show that these represent equal intervals. Alternatively, only the two extremes could be provided, i.e., "not at all" and "very much," for use with the 0-4 scoring.
- Limiting anesthetics to 2% lidocaine with epinephrine 1:100,000 could result in labeling restrictions if sufficient evidence is not presented to indicate clinically meaningful reversal can be achieved for other local anesthetic and vasoconstrictor combinations.
- Safety concerns related to the use of NV-101 could lead to a requirement that it be evaluated with other dental anesthetics because of the reasonable expectation that NV-101 could be used to reverse STA produced with all currently marketed products.
- Evidence of validity of the STAR questionnaire in the pediatric population is required. The Division encouraged the Sponsor to test the questionnaire in the pediatric population rather than rely on extrapolated validation and stated that this may be a matter of review as to whether this data would be acceptable.
- The STAR questionnaire, as a secondary endpoint, generally, would not be considered for the purpose of a claim, but findings related to the questionnaire could be included in the labeling if the Agency determines that there is sufficient weight of evidence and clinical value to include those claims.
- The questionnaire cannot be broken down into components for the purpose of making claims as it was not developed or validated to be used in that way.
- Reversal of STA is a new indication; as such, this application may be brought before an Advisory Committee for input.

On March 17, 2005, a meeting was held to discuss the special protocol assessment letter issued on February 4, 2005. The following are the key points made by the Division at that time.

- It was important to characterize the pharmacodynamic profile of phentolamine-induced STAR including onset, duration, and offset of effect.
- Collecting data every 30 minutes would not provide clinically meaningful information, especially, regarding the onset of drug action.
- For the duration and offset of action, it will be required that sufficient data be collected to demonstrate that the effects of phentolamine-induced STAR do not diminish before the anesthetic block would be expected to resolve spontaneously, i.e., that patients do not become "reanesthetized" following reversal.

- Appropriate characterization of the onset of effect of the phentolamine was important for guiding clinicians in determining whether or not their attempt at reversing the anesthetic was successful, as well as if and when a repeat injection of phentolamine may be indicated. This characterization was to be established for each of the types of blocks and each of the anesthetics used.
- The development and testing of the FAB appeared to be adequate.

A preNDA meeting was held on December 8, 2006. The following items summarize the understandings reached between the Sponsor and the Division at that time.

- The Division had concerns for patient safety based on the potential for clinicians to confuse NV-101 with marketed dental anesthetics. It was important, therefore, that NV-101 be readily discernable from other products when the cartridges are inside the blister packs, separated from the blister packs, and mounted in syringes.
- The Division expressed concern that the blue ferrule on the cartridge is not visible when the cartridge is inserted into a dental syringe. The use a blue plunger to distinguish the product from dental anesthetics could be considered. If it was decided to add a hologram or to etch the carpule glass, the Sponsor could either ensure that the glass manufacturer's drug master file (DMF) was updated with this information, or could include this information in Module 3 of the NDA. The risks associated with confusion of NV-101 with local anesthetics are likely to be non-life-threatening and only mild to moderate in nature, and that the severity of the risk would determine the extent to which NV-101 would have to be made discernible from other injectable dental products.
- The Division agreed that the population studied, the local anesthetics and vasoconstrictors administered, the types of blocks used and the dental procedures performed, were adequate to support the indication of reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral injection of a local anesthetic containing a vasoconstrictor
- The pooling strategy for the integrated safety evaluation could be modified such that
  - Study NOVA 04-PK could be removed from the pool of the four studies (NOVA 02-01, NOVA 02-02, NOVA 02-03, and NOVA 04-PK) where dental procedures were not performed.
  - Safety data for study NOVA 04-PK would still be submitted with the NDA.
  - Ultimately, there will be three pools of safety data: one including the five studies involving dental procedures, one including the three studies of healthy subjects, and one including study NOVA 04-PK.
- Justification for granting a partial pediatric waiver request pursuant to the Pediatric Research Equity Act (PREA) for pediatrics 0-2 years of age should be included in the NDA.

2.6 Other Relevant Background Information

Some of the protocols have been modified to accommodate the requirements for European approval; however, there are no significant regulatory actions, reported by the Applicant, that have been instituted outside of the United States. There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review was complete at the time of this review. There were no pending CMC issues that would preclude an approval action. The microbiology reviewer on completion of his initial review noted a number of deficiencies that could block an approval action if not resolved in time for the action. The Applicant was provided with a listing of these deficiencies and responded with a major amendment to the NDA that extended the PDUFA deadline for the review. The review of this submission has been completed by the microbiology review team and was found to satisfactorily resolve all of the outstanding issues. Their conclusion was that there were no pending microbiology issues that would preclude an approval action.

3.2 Animal Pharmacology/Toxicology

The Applicant conducted 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 are not required for this 505(b)(2) application for the proposed indication.

Local toxicology: In the single-dose local toxicology study no test article-related changes were observed in any of the parameters examined with the exception of the histopathology of local tissues. Minimal to mild inflammation was seen at the injection site of all groups. The 1X clinical formulation group showed muscle degeneration and fibrosis which was not seen at the higher doses. Minimal to moderate hemorrhaging in lymph nodes and minimal inflammation in lymph nodes and salivary glands was observed in both vehicle and treated animals. Several vehicle and 10X clinical formulation dogs showed minimal inflammation and degeneration in the trigeminal ganglia. Nerve fiber degeneration was observed in the superior alveolar nerve of one 1X clinical formulation dog but nerve fiber degeneration was not observed at higher doses. In the absence of intact (un-injected) control dogs, it is not possible to determine whether the pathologies observed in nerves, muscle and surrounding tissues seen in the vehicle group are due to pre-existing lesions or to needle placement. This drug product will be administered via a commonly used dental needle. Any potential pathology resulting from needle placement would be no greater than an injection of the dental anesthetic and is, therefore, of no toxicologic concern. It was concluded that phentolamine mesylate, [redacted], at doses up to ten times the intended human dose, did not cause considerably greater levels of toxicity than the vehicle injection in this study.

Genetic toxicology: The genotoxic potential of phentolamine mesylate was evaluated in the *in-vitro* Bacterial Reverse Mutation Assay (Ames Test), the *in-vitro* Chromosome Aberration Assay

using CHO cells and the *in-vivo* Mouse Micronucleus Assay. The Applicant submitted two separate studies for each test. The first Ames Test submitted did not utilize a high enough concentration of the test article and was concluded to be invalid. Phentolamine mesylate was negative in the second Ames Test. Phentolamine mesylate was negative in the first *in-vitro* Chromosome Aberration Assay in both the presence and absence of metabolic activation and negative in the second assay in the presence of metabolic activation. In the second assay, in the absence of metabolic activation, the high concentration showed an equivocal result. In both *in-vivo* Micronucleus Assays, phentolamine mesylate was negative. The weight of evidence suggests that phentolamine mesylate is most likely not mutagenic or clastogenic.

The levels of [redacted] impurities, [redacted], exceed ICH guidelines. The Applicant conducted the Bacterial Reverse Mutation Assay (Ames Test) and the *in-vitro* Mammalian Chromosome Aberration Assay for [redacted] compounds. [redacted] was negative in both assays and [redacted] was negative in the Ames Test and positive in the i*n-vitro* Mammalian Chromosome Aberration Assay. To further assess the clastogenic potential of [redacted], it was evaluated in the *in-vivo* Micronucleus Test where it yielded a negative result. The weight of evidence suggests that [redacted] are most likely not mutagenic or clastogenic.

Male Fertility: The Applicant submitted a male fertility study with phentolamine mesylate. At concentrations up to 143 times the human therapeutic exposure levels, phentolamine mesylate was shown to have no adverse effects on male fertility in the rat.

The Pharmacology-Toxicology review team concluded that there are no nonclinical safety issues relevant to the clinical use of NV-101.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data used in this review were derived from trials conducted by the Applicant. Literature pertaining to the safety of intravenously or intramuscularly administered phentolamine was reviewed as well as data obtained from an AERS Database search in order to compare the safety profile of NV-101 with that of the approved phentolamine products for intravenous and intramuscular injection.

4.2 Tables of Clinical Studies

The table below lists all clinical trials conducted for or by the Applicant and provides cursory information on the study design, objectives, subject demographics, and doses studied.

Table 4-1: Summary of all clinical trials

Study ID	**No. of Study Centers Location Total Enroll-ment**	**Study Design**	**Study Objective**	**Study & Ctrl Drugs Dose - N Route**	**Subject Gender (M/F) Median Age (yrs.) (Age Range)**	**Inclusion Criteria**	**Primary Endpoints**
NOVA 04-100	18 U.S. 244	Phase 3 Blinded, randomized, controlled	Efficacy, safety	NV-101 0 (sham) - 122 0.4 mg - 89 0.8 mg – 33 Intraoral submucosal	120/124 32 (12-92)	Subjects undergoing standard mandibular dental procedures	Time to recovery of normal sensation of the lower lip
NOVA 04-200	16 U.S. 240	Phase 3 Blinded, randomized, controlled	Efficacy, safety	NV-101 0 (sham) - 120 0.4 mg - 113 0.8 mg – 7 Intraoral submucosal	111/129 34 (12-81)	Subjects undergoing standard maxillary dental procedures	Time to recovery of normal sensation of the upper lip

Study ID	No. of Study Centers Location Total Enroll-ment	Study Design	Study Objective	Study & Ctrl Drugs Dose - N Route	Subject Gender (M/F) Median Age (yrs.) (Age Range)	Inclusion Criteria	Primary Endpoints
NOVA 05-PEDS	11 U.S. 152	Phase 2 Blinded, randomized, controlled	Safety, efficacy	NV-101 0 (sham) - 56 0.2 mg - 74 0.4 mg – 22 Intraoral submucosal	75/77 8 (4-11)	Pediatric subjects aged 4 to 11 years undergoing standard dental procedures	Acceleration of the time to normal lip sensation in maxillary and mandibular procedures; for mandibular procedures, acceleration of time to normal tongue sensation
NOVA 03-001	7 U.S. 122	Double-blind, randomized, placebo-controlled	Efficacy, safety	NV-101 0 (placebo) - 61 0.4 mg - 50 0.8 mg – 11 Intraoral submucosal	54/68 23 (10-61)	Subjects under-going standard dental procedures	Time to return to normal sensation in lips, tongue, nose, and chin
NOVA 02-01	1 U.S. 20	Double-blind, randomized, placebo-controlled	Efficacy, safety	Phentolamine Mesylate 0 (placebo) - 10 0.2 mg - 10 Intraoral submucosal	9/11 43 (27-50)	Healthy subjects	Time to return to normal sensation in lips, tongue, teeth, and chin

Study ID	No. of Study Centers Location Total Enroll-ment	Study Design	Study Objective	Study & Ctrl Drugs Dose - N Route	Subject Gender (M/F) Median Age (yrs.) (Age Range)	Inclusion Criteria	Primary Endpoints
NOVA 02-02	1 U.S. 40	Dose-ranging, double-blind, randomized, placebo-controlled	Efficacy, safety	Phentolamine Mesylate 0 (placebo) - 10 0.02 mg - 10 0.06 mg - 10 0.4 mg – 10 Intraoral submucosal	20/20 36 (19-60)	Healthy subjects	Time to return to normal sensation in lips, tongue, teeth, and chin
NOVA 02-03	1 U.S. 32	Dose-ranging, double-blind, randomized, placebo-controlled	Efficacy, safety	Phentolamine Mesylate 0 (placebo) - 9 0.02 mg - 8 0.08 mg - 7 0.4 mg – 8 Intraoral submucosal	16/16 26 (18-48)	Healthy subjects	Time to return to normal sensation in upper lip, teeth, and nose
NOVA 04-PK	1 U.S. 16	Phase 1, Open-label, 4-treatment, 4-period, crossover	PK/PD, safety	NV-101 0.0 mg - 16 0.4 mg - 16 0.8 mg - 16 Intraoral Submucosal 0.4 mg 16 Intravenous	7/9 23 (18 – 65)	Healthy subjects	Time to normal sensation in the upper lip, lower lip and tongue in subjects who had numbness and/or tingling in these sites
NOVA 05-PEDS-PK	3 U.S. 19	Phase 1, open-label	PK, safety	NV-101 0.2 mg - 8 0.4 mg - 11	13/6 9 (3 – 16)	Pediatric patients under-going dental procedures under general anesthesia or conscious sedation	Not applicable

4.3 Review Strategy

All clinical trials were reviewed for safety. Those trials containing efficacy data related to the return of normal sensation were considered in the overall assessment of efficacy; however, the primary focus for the efficacy review was on the two pivotal trials, which contained secondary endpoints that provided a clinical context in which the relevance of the primary efficacy endpoint could be considered. Studies used to validate the STAR questionnaire did not involve the administration of NV-101 and were reviewed separately by the SEALDT team.

4.4 Data Quality and Integrity

Due to a large number of protocol deviations associated with the conduct of the Functional Assessment Battery (FAB), the Division of Scientific Investigations (DSI) was asked to conduct an audit of the applicant's data collected at four clinical sites. Data from these sites, all of which were dental offices, constituted over half the efficacy data from the pivotal trials; therefore, assurance of the private practitioners' adherence to the protocol was needed to assess the quality of the data collected. The inspection revealed no significant regulatory violations. In addition, the inspection encompassed an audit of all subjects' records and noted that primary endpoint efficacy data were verified for all subjects.

4.5 Compliance with Good Clinical Practices

The Applicant has attested to adherence with the ICH Guidelines for Good Clinical Practice and to the conduct of clinical trials in agreement with the Declaration of Helsinki as amended by the World Medical Association, 2000. The Applicant has also attested that no services of any person debarred under §306 of the Federal Food, Drug and Cosmetic Act were used in connection with this application.

4.6 Financial Disclosures

The Applicant has attested to the fact that they have not entered into any financial arrangements with their clinical Investigators whereby the value of compensation to the Investigator could be affected by the outcome of the study as defined in 21 CFR §54.2(a). The Applicant also certified that no Investigator had a proprietary interest in NV-101 or a significant equity in the Applicant as defined in 21 CFR §54.2(b), and that no Investigator was the recipient of significant payments of other sorts as defined in 21 CFR §54.2(f).

5 CLINICAL PHARMACOLOGY

Two pharmacokinetic studies were completed, using the to-be-marketed formulation. Since the drug is injected into soft tissues to obtain a local treatment effect, the critical clinical pharmacology focus was on systemic phentolamine exposure.

5.1 Pharmacokinetics

Pharmacokinetic parameters from two, single-dose studies were obtained. One was conducted with adults, the other with pediatric subjects.

The following table contains overall PK parameters. It appears that there is a clear difference in phentolamine C_{max}, due to subject body weight or age. Phentolamine C_{max} in subjects who weigh less than 30 kg (pediatric subjects 3–8 years of age, all of whom received 0.2 mg of NV-101) increased approximately 70% compared to those with > 30 kg body weight (pediatric subjects > 8-years old, all of whom received 0.4 mg of NV-101).

Table 5-1: Summary pharmacokinetic data (from the primary Clinical Pharmacology review)

Study	**Treatments (Dose, Dosage Form, Route)**	**Phentolamine - Mean Parameters (SE)**						
		C_{max} (ng/mL)	**AUC_{last}** (ng.hr/mL)	**AUC_{inf}** (ng.hr/mL)	**T_{max}** (min)	**$t_{1/2}$** (hr:min)	**Cl** (L/hr)	**V_d** (L)
NOVA 04-PK	NV-101, 0.4 mg intraoral submucosal	1.34	1.69	2.88	15 ± 2	3:08 ± 0:55	160.93 ± 24.02	470.61 ± 62.72
	NV-101, 0.8 mg intraoral submucosal	2.73	3.29	4.58	11 ± 1	02:14 ± 00:25	203.64 ± 36.21	499.68 ± 60.08
	NV-101, 0.4 mg IV	10.98	1.71	2.76	7 ± 3	2:24 ± 0:38	175.49 ± 30.36	441.99 ± 83.68
NOVA 05-PEDS-PK	NV-101, 0.2 mg intraoral submucosal	2.60	1.93	3.62	10 ± 1	2:32 ± 0:34	58.79 ± 8.06	190.56 ± 35.69
	NV-101, 0.4 mg intraoral submucosal	1.47	1.81	3.39	21 ± 4	2:59 ± 0:56	132.18 ± 17.59	396.50 ± 22.98

5.2 Pharmacodynamics

In NOVA 04-PK, the sensation rating for the upper lip was evaluated for Treatments A (maxillary injection), C (both mandibular and maxillary injections), and D (both mandibular and maxillary injections). Only subjects who experienced numbness or tingling in their upper lip were evaluable for return of normal sensation in the upper lip. For treatments A, B (intravenous injection), and C, the time to return of normal sensation was calculated relative to the time of NV-101 injection. For Treatment D, NV-101 was not administered; thus, for this treatment, the time to normal sensation ("adjusted time") was calculated relative to the injection time of the local anesthetic plus a constant equal to the mean time between the first injection of local anesthetic and first injection of NV-101 for Treatment C. The key pharmacodynamic findings included:

- By 60 minutes after injection of NV-101 for Treatments A and C or by the "adjusted time" for Treatment D, the percentage (%) of evaluable subjects with normal sensation in the upper lip was markedly greater with Treatments A and C than with Treatment D.
- By 90 minutes after injection of NV-101 for Treatment C, all evaluable subjects had normal sensation in the upper lip, with maintenance of normal upper lip sensation through the rest of the 5-hour follow-up period.
- After Treatment A, all evaluable subjects had normal upper lip sensation by 170 minutes after injection of NV-101.
- With Treatment D, not until 230 minutes "adjusted time" did all evaluable subjects regain normal upper lip sensation. Consistent with the NV-101 findings, the median time to normal sensation of the upper lip for Treatment D was approximately twice as long as the median times for Treatments A and C.

The sensation rating for the lower lip was evaluated for Treatments C and D (both mandibular and maxillary injections), but not for Treatment A (maxillary injection) and B (IV injection). Only subjects who experienced numbness and/or tingling in their lower lip were evaluable for return of normal sensation in the lower lip. The key pharmacodynamic findings in this group of subjects included:

- All evaluable subjects regained normal lower lip sensation after Treatment C by 170 minutes after dosing with NV-101.
- In contrast, with Treatment D, at the 170 minute "adjusted time" time point only approximately 10% of evaluable subjects had regained normal lower lip sensation, and by 250 minutes "adjusted time" to the end of the 300- minute "adjusted-time" follow-up period, only approximately 80% of evaluable subjects had regained normal lower lip sensation.
- Consistent with these findings, the median time to normal sensation of the lower lip for Treatment D was approximately twice as long as the median time for Treatment C.

The sensation rating for the tongue was evaluated for Treatments C and D (both mandibular and maxillary injections), but not for Treatments A (maxillary injection) and B (IV injection). Only subjects who experienced numbness and/or tingling in their tongue were evaluable for return of normal sensation in the tongue. The key pharmacodynamic finding for this parameter was that all evaluable subjects regained normal tongue sensation after Treatment C by 160 minutes after dosing with NV-101. In contrast, with Treatment D, at the 160 minute "adjusted-time" time

point only approximately 25% of evaluable subjects had regained normal tongue sensation, and from 260 minutes "adjusted time" to the end of the 300-minute "adjusted-time" follow-up period, approximately 95% of evaluable subjects had regained normal tongue sensation. Consistent with these findings, the median time to normal sensation of the tongue for Treatment D was approximately twice as long as the median time for Treatment C.

5.3 Exposure-Response Relationships

NV-101 is injected at the tissue site where the local anesthetic was injected to achieve the desired effect. The phentolamine concentrations at the local sites were not analyzed; therefore, no exposure-response relationship for this product is available. However, the Applicant explored other markers (return of sensation to lips, tongue, teeth, and chin) produced by an injection of lidocaine/epinephrine and found that NV-101-induced reductions in the time to return to normal sensation in affected tissues occurred in conjunction with an increase in lidocaine C_{max} and a decrease in lidocaine T_{max}. The PK changes observed for lidocaine suggest that NV-101 hastens recovery of normal sensation by reversing the effect of the vasoconstrictor, i.e., increasing local tissue circulation, and washing out the local anesthetic.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Applicant seeks an indication for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor in dental patients [redacted] years of age and older.

6.1.1 Methods

Four clinical trials were conducted in which subjects underwent dental procedures prior to receiving study drug. Data from these studies, NOVA 03-001, NOVA 05-PEDS, NOVA 04-100 and NOVA 04-200, were the bases for assessing the efficacy of NV-101

Clinical data from NOVA 04-100 and NOVA 04-200 provided efficacy information regarding the time required for the return to normal sensation of soft tissues, i.e., the lip and the tongue, and the time to return to baseline levels for the STAR and FAB scores. Both trials were done under SPA agreements with the Division and constituted the pivotal studies conducted for NV-101. These two trials provided efficacy data for subjects who were 12 years of age and older using the proposed dosing regimen. These trials also involved the use of the most commonly employed dental blocks with the most commonly used local anesthetic-vasoconstrictor combinations, and evaluated the use of NV-101 following an assortment of dental procedures for which local anesthetic blocks are generally used.

NOVA 03-001 assessed efficacy in dental patients whose ages ranged from 10-years old and older. Time to return of normal sensation in the lips, tongue, nose, and chin were the only efficacy endpoints evaluated in this study. Similar to the pivotal studies, these trials also involved the use of the most commonly employed dental blocks with the most commonly used local anesthetic-vasoconstrictor combinations, and evaluated the use of NV-101 following an assortment of dental procedures for which local anesthetic blocks are generally used. The doses of NV-101 used in this study were consistent with that of the proposed labeling.

NOVA 05-PEDS evaluated efficacy in pediatric patients who were 6-11 years old and able to properly perform the palpation tests used to assess sensation. Acceleration of the time to normal lip sensation in maxillary and mandibular procedures, and, for mandibular procedures, acceleration of time to normal tongue sensation were the only efficacy endpoints employed. The dosing of NV-101 in this study was consistent with that proposed in the label. Patients less than 6 years old and those who were older but unable to properly perform the palpation test were included only in the safety analysis.

6.1.2 General Discussion of Endpoints

The primary endpoint for the clinical trials was the return of normal sensation to the lip following anesthesia induced by the combination of a local anesthetic and vasoconstrictor. Secondary endpoints involving sensation included the return of normal sensation to the tongue, cheek, chin, nose and teeth. Assessment of the return to normal sensation was by patient palpation of the soft tissues, i.e., tongue, lip, cheek, and nose, and by grinding to assess sensation of the teeth. The manner in which palpation was to be performed was codified in the study protocols. Subjects were trained in the technique and were included in the efficacy assessment only if they were able to successfully perform the test.

The other secondary efficacy endpoints, Soft Tissue Anesthesia Recovery (STAR) questionnaire and Functional Assessment Battery (FAB) test scores, were employed only in the two SPA-designated protocols: NOVA 04-100 and NOVA 04-200. These were designed to assess the clinical relevance of the reversal of soft tissue anesthesia in terms of subjects' changes in perception of their abilities and their actual functioning relative to their pre-anesthesia baselines.

The STAR questionnaire consisted of 12 questions assessing the subjects' perception of their concerns for self-inflicted injury while their soft tissues were anesthetized and of their ability to function at baseline levels for speaking, drinking, smiling and not drooling. The metric was developed by the Applicant and validated for use in adults with input from the SEALD team. A shorter version of the metric, STAR-7, consisted of seven of the 12 questions and was also found to be valid in adults. The STAR-7 was used in the pivotal trials.

The validation study, NOVA-05-SQV, was conducted to evaluate the applicability of the STAR questionnaire to adolescent subjects who were 12-17 years of age. Although the SEALD team raised concern about the adequacy of the content validity from the study, its use as a secondary endpoint provides some insight as to the subjects' concerns regarding possible self-inflicted injury and ability to function.

The FAB tests scores were not formally validated; however, the assessments of subjects' ability to speak, smile, drink and not drool corresponded to concerns raised by patients while dental anesthesia was ongoing. The use of a composite score based on normal or abnormal findings for each function provided a simple and meaningful means of assessing subjects' changes from and return to baseline functioning following induction of and recovery from soft tissue anesthesia, respectively. The metric was used by both subjects and treatment-blinded observers to provide subjective and objective assessment of function. The use of this metric as a secondary endpoint for both pediatric and adult patients provided substantiation for the STAR questionnaire findings of complete recovery from the soft tissue anesthesia.

6.1.3 Study Design

The studies used to evaluate the efficacy of NV-101: NOVA 03-001, NOVA 05-PEDS, NOVA 04-100 and NOVA 04-200, were similar in design. Each was randomized, controlled, double-blinded and multi-centered. The two pivotal trials, NOVA 04-100 and NOVA 04-200, were

conducted under SPA agreements with the Division. Unlike some of the Phase 2 trials, each of these studies involved the administration of the study drug following a dental procedure. The incorporation of the dental procedure was an important component of these studies in that return of pain related to the dental procedure following reversal of local anesthesia with NV-101 could limit the usefulness of this product in the clinical setting. These trials also included a range of dental procedures, local anesthetic-vasoconstrictor drug products, dental nerve blocks and dental patients that would allow an assessment of safety and efficacy for the variety of clinical situations in which NV-101 would likely be used if marketed.

The doses of NV-101 chosen for use in these clinical trials were based on Phase 2 and PK studies conducted by the Applicant. These studies included both pediatric and adult subjects and adequately identified a dosing regimen that appeared to be efficacious without incurring significant risk.

The control for these trials included a placebo injection in NOVA 03-001 (consisting of the inactive ingredients in NV-101) and sham injections in the other three studies. The use of a sham injection was considered important by the Division as it allowed a safety comparison that accounted for the risks of the injection of NV-101 as well as risks associated with the drug product itself. The risks that were specifically associated with the additional needle stick(s) included nerve and soft tissue trauma, bleeding and infection. The sham injection consisted of the dentist placing a syringe in the subject mouth and pressing against the local anesthetic injection site(s) without penetrating the mucosal membrane. To maintain the double blind in these studies, another investigator, who was blinded to the study treatment administered, performed the post-treatment safety and efficacy assessments.

In summary, the studies of efficacy were adequately designed and appropriately controlled so as to allow a thorough assessment of efficacy and safety.

6.1.4 Efficacy Findings

Detailed reviews of the clinical trials conducted to assess efficacy can be found in Section 10.1 of this review.

The primary efficacy endpoint in all four studies assessing the efficacy of NV-101 when used following a dental procedure was time to recovery of normal sensation in the lip as measured by subjects using a standardized lip-palpation procedure. The time to recovery of normal lip sensation was calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation of the lip. According to the study protocol, lip-palpation procedures were to be performed at screening, before randomization to study drug, and every 5 minutes for 5 hours after completion of study drug administration starting 10 minutes after study drug administration. In NOVA 03-001, palpation testing started 5 minutes after study drug administration was performed every 5 minutes for at least 3 hours or until normal sensation returned in all designated soft tissues; in NOVA 05-PEDS , the testing was started 15 minutes following administration of the study drug and performed every 15 minutes for 4 hours.

For NOVA 03-001, NOVA 04-100 and NOVA 04-200, the ITT analysis set was used for the analysis of return to normal sensation in the lip. The ITT analysis set was defined as all subjects randomized, irrespective if study drug was administered or not. For NOVA 05-PEDS, a modified ITT (mITT) analysis set was used per the statistical analysis plan. The mITT lip-sensation analysis set was defined as all randomized subjects 6-11 years of age who were trainable in the standardized palpation procedure. Subjects who did not have lip numbness at the end of the dental procedure were excluded from the mITT.

The Kaplan-Meier method was used to determine the median and the associated 95% confidence interval for the time to recovery of normal sensation of the lip. The stratified log-rank test was used to test for treatment group differences in the primary endpoint.

As shown in the table below, there was a substantial and significant difference between treatment groups with respect to time of recovery of normal sensation of the lip for all four studies. The effect of NV-101 represented a median reduction of 85 minutes (55% reduction), 83 minutes (62% reduction), and 75 minutes (56% reduction) compared to sham in NOVA 04-100, NOVA 04-200, and NOVA 05-PEDS, respectively.

For NOVA 05-PEDS, the subgroup results delineating the location of the anesthetic administration, dental procedure (mandible or maxilla) and study drug administration were also compared to the pivotal efficacy studies. The results from the pediatric study are consistent with the mandible (NOVA 04-100: 55% reduction, NOVA 05-PEDS: 67% reduction) and maxilla (NOVA 04-200: 62% reduction, NOVA 05-PEDS: 47% reduction) pivotal study results with respect to the magnitude and direction of the treatment effect.

Table 6-1: Log-rank analysis of time to recovery of normal sensation

Study Number	***(number of subjects)*** **Median time to recovery of normal sensation (min.)[1] (95% CI)**					
	Lip			***Tongue***		
	NV-101	***Sham***	***p*-value**	***NV-101***	***Sham***	***p*-value**
NOVA 04-100	*(122)* 70 (65, 80)	*(121)* 155 (140, 165)	< 0.0001	*(93)* 60 (55, 70)	*(103)* 125 (110, 135)	< 0.001
NOVA 04-200	(120) 50 (45, 60)	*(119)* 133 (115, 145)	< 0.0001	*NA*	*NA*	*NA*
NOVA 03-001	*(61)* 70 (55, 101)	*(61)* 155 (135, 165)	< 0.0001	*(30)* 74 (60, 92)	*(31)* 105 (90, 125)	0.0011

Study Number	*(number of subjects)* **Median time to recovery of normal sensation (min.)[1] (95% CI)**					
	Lip			***Tongue***		
	NV-101	***Sham***	***p*-value**	***NV-101***	***Sham***	***p*-value**
NOVA 05-PEDS (overall)	*(72)* 60 (45, 75)	*(43)* 135 (105, 165)	< 0.0001	*NA*	*NA*	*NA*
NOVA 05-PEDS (mandible)	*(38)* 60 (45, 75)	*(19)* 180 (135, 180)	< 0.0001	*(32)* 45 (30, 45)	*(16)* 112.5 (45, 150)	< 0.0001
NOVA 05-PEDS (maxilla)	*(n=34)* 60 (45, 75)	*(n=24)* 113 (75, 150)	0.0002	*NA*	*NA*	*NA*

[1] Kaplan-Meier medians and stratified Log-Rank Test p-values

In the table below, the results of the subgroup analyses for the primary efficacy variable are shown for the two SPA protocols. The results indicate that a significant and fairly consistent treatment effect was observed across all categories.

Table 6-2: Subgroup analysis of time to recovery of normal lip sensation for NOVA 04-100 and NOVA 04-200 (based on Table 14 in the Statistical team review)

Variable	NV-101		Sham		% Reduction (Log-rank test p-value)
	N	Median Time (minutes)	N	Median Time (minutes)	
Overall	242	62.5	242	140	55% (p<0.0001)
Sex					
Male	122	65	109	145	55% (p<0.0001)
Female	120	60	133	140	57% (p<0.0001)
Age Group					
12 to 17 years	26	88	29	160	45% (p=0.01)
18 to 64 years	187	60	187	140	57% (p<0.0001)
≥ 65 years	29	55	26	113	51% (p<0.0001)
Race					
White	191	65	186	140	54% (p<0.0001)
Non-White	51	60	56	153	61% (p<0.0001)
Number of Cartridges					
1	204	58	207	140	59% (p<0.0001)
2	38	85	35	155	45% (p<0.0001)
Anesthetic					
Lidocaine	161	60	161	140	57% (p<0.0001)
Other	81	75	81	155	52% (p<0.0001)

Dental Procedure					
Cavity	166	68	167	145	5% (p<0.0001)
Crown	3	30	7	130	77% (p<0.001)
Periodontal maintenance	73	55	68	143	61% (p<0.0001)
Type of Injection					
Inf. alveolar nerve block	201	70	199	145	52% (p<0.0001)
Other	41	35	43	120	71% (p<0.0001)

The findings for the three secondary efficacy endpoints are described below in the order of their ranking: the STAR-7 score, the FAB score and the time to return of normal sensation for the tongue.

As per the statistical analysis plan for NOVA 04-100 and NOVA 04-200, the secondary efficacy endpoint ranking first in order of importance was the time to return of the STAR-7 score to zero. The STAR-7 questionnaire was not utilized in the NOVA 05-PEDS study. The STAR-7 score was calculated by adding the responses to items 2, 3, 4, 6, 7, 8, and 11 on the STAR questionnaire. The time to STAR-7 score of zero was calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive STAR-7 scores of zero. The STAR questionnaire indicates the subject's perceived recovery from the effects of soft-tissue anesthesia and increases (worsens) as subjects become numb and decreases (improves) as normal sensation returns. According to the study protocol, the STAR-7 questionnaire was to be self-administered at screening, before randomization to study drug, and every 30 minutes for 5 hours after study drug administration.

The modified intent-to-treat (mITT) STAR-7 analysis set was used for this analysis. The mITT STAR-7 analysis set included all randomized subjects who had a STAR-7 score greater than zero for the STAR-7 questionnaire given immediately before the randomization to study drug. The Kaplan-Meier method was used to determine the median time and associated 95% CI for the time required for the STAR-7 score to return to zero. The stratified log-rank test was used to test for treatment group differences in this endpoint. As shown in the table below, there was a substantial and statistically significant difference between treatment groups with respect to time to STAR-7 score of zero in both studies. The effect of NV-101 represented a median reduction of 60 minutes (40% reduction) and 60 minutes (50% reduction) compared to sham in NOVA 04-100 and NOVA 04-200, respectively.

Table 6-3: Time to normal STAR-7 for the mITT population (from Table 40 in NDA ISE)

Study	**NV-101**		**Sham**		**Time Difference (% Reduction)**	**Stratified Log-Rank *p*-Value**
	N	**Median (95% CI)**	**N**	**Median (95% CI)**		
NOVA 04-100	118	90 (60, 90)	121	150 (120, 150)	60 (40%)	<0.0001
NOVA 04-200	109	60 (60, 90)	111	120 (120, 150)	60 (50%)	<0.0001

As per the statistical analysis plans for NOVA 04-100 and NOVA 04-200, the secondary efficacy endpoint ranking second in order of importance was the time to normal FAB score. The FAB was not performed in NOVA 05-PEDS. Smiling, speaking, drinking, and drooling were assessed by both the subject and observer using the FAB tool. A subject was considered to have "abnormal function" if one or more functions were deemed abnormal. Time to return to normal function was calculated by the number of minutes elapsed from the administration of study drug to the first of 2 consecutive assessments where both the subject and observer rated smiling, speaking, drinking, and drooling as normal or not present. The FAB, which initially included 3 of 4 functional tests (smiling, speaking and drooling), was to be conducted at screening, before randomization to study drug, and every 5 minutes starting at 10 minutes after study drug administration until they were found to be normal by both subject and observer. The drinking assessment was then to be started, and all 4 functions were then to be tested every 5 minutes until all 4 functions were normal on 2 consecutive assessments by both subject and observer ratings. Thereafter, the frequency of testing was to be decreased to every 30 minutes for the remainder of the 5-hour observation period. The mITT FAB analysis set was used for this analysis. Per the statistical analysis plan, the mITT FAB analysis set included all randomized subjects who were rated abnormal by both the subject and the observer for at least one of the individual functional tests (not necessarily the same test) given immediately before the randomization to study drug.

The Kaplan-Meier method was used to determine the median time and the 95% confidence interval for the return to normal FAB. The stratified log-rank test was used to test for treatment group differences in this endpoint. As shown in the table below, there was a substantial and statistically significant difference between treatment groups with respect to time to normal FAB for both studies. The effect of NV-101 represented a median reduction of 60 minutes (50% reduction) and 45 minutes (43% reduction) compared to sham in NOVA 04-100 and NOVA 04-200, respectively.

Table 6-4: Time to normal FAB for the mITT population (from Table 41 in NDA ISE)

Study	NV-101		Sham		Time Difference (% Reduction)	Stratified Log-Rank *p*-Value
	N	Median (95% CI)	N	Median (95% CI)		
NOVA 04-100	103	60 (50, 75)	103	120 (110, 130)	60 (50%)	<0.0001
NOVA 04-200	100	60 (50, 65)	89	105 (85, 125)	45 (43%)	<0.0001

In the final study reports, it was noted that more than 50% of patients were found to have protocol deviations; most were related to study procedures. Of the 422 procedural deviations, 220 (53%) involved use of the FAB tool. The Applicant attributed the study procedure deviations to the complexity of the FAB data collection schedule. A review of the FAB related deviations indicated that most resulted from assessments not performed at the scheduled time point. To confirm the Applicants claim that the deviations did not significantly impact on the overall findings for the FAB tests, the statistical review team was asked to reassess the data eliminating those data coming from subjects with FAB related protocol deviations. The results

of the additional analysis are shown in the table below and indicated that the data were quite robust as the outcomes differed little from the original analysis.

Table 6-5: Time to normal FAB for subjects with no FAB-related protocol deviations

Study	NV-101		Sham		Time Difference (% Reduction)	Stratified Log-Rank *p*-Value
	N	Median (95% CI)	N	Median (95% CI)		
NOVA 04-100	64	55 (45, 75)	71	120 (110, 130)	65 (54%)	<0.0001
NOVA 04-200	67	55 (45, 60)	64	98 (80, 125)	43 (44%)	<0.0001

As per the statistical analysis plan for NOVA 04-100, the secondary efficacy endpoint ranking as third in order of importance was the time to normal sensation of the tongue as measured by a standardized tongue-palpation procedure. These data were also collected in the NOVA 05-PEDS study for subjects who had procedures in the mandible. Time to normal sensation of the tongue data was not collected in the NOVA 04-200 study, which considered only dental procedures involving the maxilla; tongue anesthesia is only a concern in mandibular procedures.

The time to recovery of normal tongue sensation was calculated by the number of minutes elapsed from the administration of study drug to the first of 2 consecutive reports of normal sensation of the tongue. The mITT tongue analysis set was used for this analysis. This was defined as all randomized subjects who had numbness of the tongue based on the standardized palpation procedure performed immediately before randomization of study drug. For NOVA 05-PEDS, the mITT definition included only subjects 6-11 years of age who were trainable in the standardized palpation procedure.

The Kaplan-Meier survival method was used to determine the median time and 95% confidence interval for the return to normal sensation of the tongue. The stratified log-rank test was used to test for treatment group differences in this endpoint.

As shown in the table below, there was a substantial and significant difference between treatment groups with respect to time to normal tongue sensation for both studies. NOVA 04-100 demonstrated a 65 minute reduction (52%) in time and NOVA 05-PEDS showed a 68 minute reduction (60%) in time for subjects treated with NV-101 compared to sham.

Table 6-6: Time to recovery of tongue sensation (from Table 42 of NDA ISE)

Study	NV-101		Sham		Time Difference (% Reduction)	Stratified Log-Rank *p*-Value
	N	Median (95% CI)	N	Median (95% CI)		
NOVA 04-100	93	60 (55, 70)	103	125 (110, 135)	65 (52%)	< 0.0001
NOVA 05-PEDS	32	45 (30, 45)	16	113 (45, 150)	68 (60%)	0.0003

6.1.5 Clinical Microbiology

NV-101 is not an antimicrobial; therefore, this section is not applicable.

6.1.6 Efficacy Conclusions

The Applicant has provided sufficient data from adequate and well-controlled studies to conclude the following relative to placebo:

- When administered to adults and pediatric patients over the age of 12 years old, NV-101 substantially reduces the time to return to normal sensation in the lip and tongue following dental nerve blocks with local anesthetics containing a vasoconstrictor.
- In adults and pediatric patients over the age of 12 years old, NV-101 reduces the time required to return to baseline levels of both the perception of the ability to function normally and the concern over risk of self-inflicted injury to the tongue, the lip or the cheek.
- In pediatric patients from ages 6-11 years old, NV-101 substantially reduces the time to return to normal sensation in the lip
- No efficacy data was obtained in pediatric patients less than 6 years of age.

The STAR questionnaire was validated for adult subjects, as was the use of a subset of 7 questions from the questionnaire as a composite score to measure the impact of local dental anesthesia in adults. The latter metric, the STAR-7, was supported by the instrument development/validation plan submitted. Therefore, the 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 fully support the content validity of the STAR Questionnaire for use in patients 12-17 years of age. In the study, 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 SEALD team indicated that the questionnaire may need to be revised for use in this age group of patients.

The Applicant did not provide any information concerning the development of the Functional Assessment Battery (FAB) in order to ascertain its content validity. Therefore, the SEALD team could not determine the adequacy of this instrument in terms of measuring function as a result of dental anesthesia.

The STAR questionnaire and the FAB test were used as secondary endpoints in NOVA 04-100 and NOVA 04-200. They were to provide a measure of whether or not the reduction in the time to return to normal sensation had any clinical impact, and their use in these trials is valuable, despite restrictions in content validity or lack of any validation, for the reasons given below.

The components of the FAB test (speaking, smiling, drinking and drooling) were items which could have been utilized as secondary endpoints in their own right. Their combination in a single-score metric, based on normal or abnormal ratings, posed a more stringent means of assessing when baseline levels of functioning returned than would have occurred if each component had been evaluated independently. Therefore, the use of FAB testing in both the pediatric and adult subjects was considered an important component of the overall assessment of efficacy.

Although the STAR questionnaire was considered fully valid only for adult subjects, the results obtained in the older pediatric subjects corroborated the results for the sensation testing and the FAB testing. Thus, the questionnaire results were included in the overall assessment of efficacy.

Efficacy was not evaluated in pediatric patients less than 6 years of age. As pediatric patients between the ages of 3 and 6 years old may require dental procedures that necessitate the use of local anesthetics with vasoconstrictors, it is recommended that the Applicant develop a means to assess efficacy in this age group and conduct clinical trials to assess whether the reduction in the time to return to normal sensation is as substantial in these patients as in the older patients.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The data sources for the safety review included the study reports for all of the clinical trials involving NV-101. These included the preliminary dose-finding studies, initial studies assessing the return of sensation with NV-101 versus a comparator, and the pivotal trials, which assessed the return of sensation as well as the return of function and patient's perception of their recovery from the soft tissue anesthesia. In the controlled studies, one of two types of comparators was used. Placebo controls consisted of the injection of a volume of either normal saline or the inactive ingredients in NV-101 equal to that of the NV-101 under evaluation. Sham controls consisted of a sham injection in which the investigator placed a syringe with a needle attached into the subject's mouth and placed the needle against the gum without penetrating the tissue. The use of a sham injection was done at the Division's request to assess risks associated with an additional injection, particularly when the injection was made in anesthetized tissues in the vicinity of nerves.

Safety issues related to the use of intravenous and intramuscular phentolamine as reported in the Regitine label, the AERS database and the literature were also reviewed to provide some focus to the safety review and to determine whether there were rare but significant adverse reactions associated with the use of this drug substance that could impact the benefit-risk analysis for NV-101.

The key safety findings from the clinical trials include the following:

1. None of the NV-101-related adverse events appeared to be dose dependent.
2. Compared to controls, use of NV-101 was not associated with any clinically relevant changes in blood pressure or heart rate.
3. There was no evidence to suggest an increased risk related to a second injection or to the injection of NV-101.
4. A single incidence of "lingual nerve trauma" was reported to have occurred with "sensory and motor findings" in a subject who received 0.8 mg of NV-101. While it is not possible to assign causality to either the drug itself or the manner in which it was injected, the occurrence of this relatively uncommon event, constitutes the most notable, albeit relatively benign, adverse reaction in the clinical studies.

The review of the literature and the AERS database resulted in no findings of a safety concern that was not already listed in the Regitine label or that would have a negative impact on the benefit-risk analysis for NV-101.

7.1.1 Deaths

No deaths occurred in any of the treatment arms in any of the studies conducted with NV-101.

7.1.2 Other Serious Adverse Events

No serious adverse events occurred in any of the treatment arms in any of the studies conducted with NV-101.

7.1.3 Dropouts and Other Significant Adverse Events

No subject in any of the treatment arms in any of the studies conducted with NV-101 was discontinued because of an adverse event.

7.1.3.1 Overall profile of dropouts

This section is not applicable as there were no dropouts.

7.1.3.2 Adverse events associated with dropouts

This section is not applicable as there were no dropouts.

7.1.3.3 Other significant adverse events

There were no reported adverse events that would be classified as "significant" under ICH guide lines. Specifically, there were no marked laboratory abnormalities, which did not meet the definition of serious; no events that led to dropouts or required interventions such as protocol modifications, dose reductions or significant additional concomitant therapy; and no potentially important abnormalities otherwise identified.

A total of nine severe adverse events were reported in the development program for NV-101. Four of these events occurred in subjects undergoing dental procedures and five occurred in healthy volunteers involved in the pharmacokinetics study, NOVA 0-PK.

In study NOVA 04-PK, each subject was randomly assigned to one of four treatments sequences in which the subject would receive four treatments over the course of two clinic visits during which two treatments were administered separated by a period of 24 hours. The treatments included the following:

A. 1 cartridge of local anesthetic and 1 cartridge of NV-101
B. 1 cartridge of IV injection of phentolamine mesylate
C. 4 cartridges of local anesthetic and 2 cartridges of NV-101
D. 4 cartridges of local anesthetic

Subject PK-01-01/01 experienced general weakness and shakiness following treatment D, which was her second treatment. No therapeutic interventions were made and both adverse events resolved in under an hour. It is likely that the reaction was due to systemic absorption of the local anesthetic.

Subject PK-01-04 experienced left ear paresthesias and left-side body twitching following treatment C; these adverse events resolved over 2 hours and 1 hour, respectively. Both of these

adverse events resolved without therapeutic intervention. These reactions are also consistent with toxicity related to localized spread and systemic absorption of the local anesthetic, respectively.

Subject PK-01-09 experienced pain in his left upper cheek following treatment C. The pain spontaneously resolved over the next 14 hours. This reaction is likely due to local tissue trauma caused by the injection or possibly due to nerve injury from either the needle or injection of some of the local anesthetic or the NV-101 into the nerve sheath.

Subject PK-01-12 experienced pain above the IV site during treatment B. It resolved without therapy after 20 minutes. Such an event is likely due to a mechanical event such as the dislodging of a clot during the injection or the injection of cold or warm solution. If the subject were experiencing irritation related to the phentolamine, erythema would likely have occurred. The formula is not generally associated with irritation or pain on injection as occurs with non-water-soluble injectates.

7.1.4 Other Search Strategies

Review of the safety data revealed no indication for the use of non-routine search strategies; therefore, none were performed.

7.1.5 Common Adverse Events

The primary foci for the safety profile of NV-101 were the following:

- risks associated with injections in the oral cavity in the vicinity of nerves, i.e., nerve injury and infection
- known effects of phentolamine when administered intravenously and intramuscularly as per the labeled use of Regitine
- risks associated with the release of local anesthetics and vasoconstrictor into the systemic circulation

The risk of infection is associated with any breach of skin or mucosal tissues. The concern for NV-101 was that its use necessitated a single or possibly multiple breaches that in conjunction with the injection(s) of local anesthetics and the normal bacterial flora of the oral mucosa might increase the risk of infection over that associated with injection of local anesthetics alone. The concern for nerve damage was, in part, due to the need to inject NV-101 in the vicinity of the local anesthetic injection, i.e., near the nerves, and due to the inability for the patient to discern whether the injection is traumatizing a nerve secondary to the residual effects of the local anesthetic.

The dose of phentolamine used for reversal of soft tissue anesthesia is substantially smaller than that used for the prevention or control of hypertensive episodes related to pheochromocytomas (5 mg for adults and 1 mg for pediatric patients), and for the prevention or treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine

(5-10 mg). Thus, the expectation was that only minimal changes in hemodynamic parameters would occur with exposure to the proposed dose; however, the effects of an inadvertent intravascular injection of a small dose of phentolamine in a patient without pheochromocytoma or unexposed to exogenous norepinephrine have not been heretofore fully elucidated.

Lastly, the release of local anesthetic and vasoconstrictive agents following the injection of NV-101 poses the theoretical risk of toxicity related to either agent; although such risk was expected to be minimal, inadvertent intravascular injections of such agents have been associated with adverse reactions.

7.1.5.1 Eliciting adverse events data in the development program

The safety evaluations included protocol-specified timing of vital sign assessments, oral cavity examinations, and solicitation of adverse events from subjects. The timing of assessments varied from study to study, but was sufficiently frequent and closely enough associated with key pharmacokinetic and pharmacodynamic time points so as to be likely to capture significant derangements from baseline values. Post-treatment follow-up evaluations were also appropriately timed.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Preferred terms for adverse events were derived from MedDRA. Review of the applicant's categorization of the terms used by subjects and investigators in the cases of severe adverse events and in the adverse events from the pivotal trials indicated appropriate classification was performed.

7.1.5.3 Incidence of common adverse events

The applicant divided the adverse events summaries according to whether the study involved a dental procedure or not, and provided separate safety data for one of the PK studies, NOVA 04-PK, consistent with discussion that took place during the preNDA meeting. Those studies not involving a dental procedure, labeled as "healthy subject" studies included dose exploration and pharmacokinetics studies. The three sets will be considered independently and then combined in this review.

The tables below are taken from the NDA Integrated Summary of Safety (ISS) and summarize all the treatment emergent adverse events. It should be noted that the control treatments are different for the two tables. Sham injections were used in the dental studies; placebo injections were used in the healthy subject studies.

Table 7-1: Summary of All Treatment Emergent AEs in Healthy Subjects (NDA ISS Table 27, p. 91)

SOC/PT	Phentolamine Mesylate[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 (%)
Number of AEs	***6***	***3***	***8***	***6***	***3***	***26***	***7***
Subjects with AEs	***4(22)***	***3 (30)***	***6 (86)***	***5 (50)***	***2 (11)***	***20 (32)***	***7 (24)***
Cardiac disorders	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	1 (3.4)
Abdominal pain	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Aphthous stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
General disorders and administration site conditions	1 (5.6)	0 (0.0)	3 (42.9)	1 (10.0)	2 (11.1)	7 (11.1)	0 (0.0)
Injection site edema	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Injection site pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (3.2)	0 (0.0)
Injection site reaction	0 (0.0)	0 (0.0)	1 (14.3)	1 (10.0)	0 (0.0)	2 (3.2)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Tenderness	1 (5.6)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Musculoskeletal and connective tissue disorders	1 (5.6)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	2 (3.2)	0 (0.0)
Pain in jaw	1 (5.6)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	2 (3.2)	0 (0.0)
Nervous system disorders	1 (5.6)	2 (20.0)	1 (14.3)	3 (30.0)	1 (5.6)	8 (12.7)	1 (3.4)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (1.6)	0 (0.0)
Headache	1 (5.6)	1 (10.0)	0 (0.0)	1 (10.0)	1 (5.6)	4 (6.3)	0 (0.0)
Lethargy	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Migraine without aura	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (1.6)	1 (3.4)
Respiratory, thoracic and mediastinal disorders	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Nasopharyngeal disorder	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular disorders	2 (11.1)	0 (0.0)	1 (14.3)	1 (10.0)	0 (0.0)	4 (6.3)	3 (10.3)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (1.6)	0 (0.0)
Hematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Hypertension	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Hypotension	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	2 (6.9)

[A] All subjects 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] All subjects received placebo injection.

Table 7-2: Summary of All Treatment Emergent AEs in Dental Subjects (NDA ISS Table 20, p. 72)

SOC/PT	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 (%)
Number of AEs	***17***	***116***	***28***	***161***	***120***
Subjects with AEs	***15 (18)***	***82 (29)***	***20 (39)***	***117 (28)***	***96 (27)***
Cardiac disorders	0 (0.0)	25 (8.8)	3 (5.9)	28 (6.7)	30 (8.4)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bradycardia	0 (0.0)	5 (1.8)	2 (3.9)	7 (1.7)	1 (0.3)
Extrasystoles	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Sinus bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Sinus tachycardia	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.7)	7 (1.9)
Supraventricular extrasystoles	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Tachycardia	0 (0.0)	17 (6.0)	2 (3.9)	19 (4.5)	20 (5.6)
Ventricular extrasystoles	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Eye disorders	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Lacrimation increased	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Ocular hyperemia	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal disorders	1 (1.2)	5 (1.8)	2 (3.9)	8 (1.9)	5 (1.4)
Abdominal pain	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Abdominal pain upper	1 (1.2)	0 (0.0)	1 (2.0)	2 (0.5)	0 (0.0)
Aphthous stomatitis	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Diarrhea	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)	1 (0.3)
Gingival disorder	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)
Glossodynia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nausea	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.6)
Sensitivity of teeth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Toothache	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Vomiting	0 (0.0	1 (0.4)	1 (2.0)	2 (0.5)	0 (0.0)
General disorders and administration site conditions	6 (7.2)	19 (6.7)	5 (9.8)	30 (7.2)	21 (5.8)
Facial pain	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Feeling cold	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Injection site discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Injection site hemorrhage	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)	2 (0.6)
Injection site pain	5 (6.0)	15 (5.3)	2 (3.9)	22 (5.3)	14 (3.9)
Injection site reaction	1 (1.2)	1 (0.4)	0 (0.0)	2 (0.5)	1 (0.3)
Edema peripheral	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	1 (0.3)
Pyrexia	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)
Tenderness	0 (0.0)	1 (0.4)	1 (2.0)	2 (0.5)	1 (0.3)
Infections and infestations	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)
Injury, poisoning and procedural complications	5 (6.0)	25 (8.8)	7 (13.7)	37 (8.9)	29 (8.1)
Contusion	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Nerve injury	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)
Open wound[C]	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.7)	2 (0.6)
Oral pain	2 (2.4)	1 (0.4)	1 (2.0)	4 (1.0)	1 (0.3)
Pain in jaw	0 (0.0)	1 (0.4)	1 (2.0)	2 (0.5)	0 (0.0)
Post procedural complication	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)

SOC/PT	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 (%)
Post procedural discomfort	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)	2 (0.6)
Post procedural pain	3 (3.6)	17 (6.0)	5 (9.8)	25 (6.0)	23 (6.4)
Investigations	3 (3.6)	1 (0.4)	0 (0.0)	4 (1.0)	3 (0.8)
Blood pressure diastolic increased	2 (2.4)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)
Blood pressure increased	1 (1.2)	1 (0.4)	0 (0.0)	2 (0.5)	1 (0.3)
Heart rate increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Pain in jaw	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Nervous system disorders	0 (0.0)	13 (4.6)	4 (7.8)	17 (4.1)	19 (5.3)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Headache	0 (0.0)	10 (3.5)	3 (5.9)	13 (3.1)	14 (3.9)
Hypoesthesia	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	2 (0.6)
Migraine	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Paraesthesia[D]	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.5)	0 (0.0)
Paresthesia oral[D]	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Sinus headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tension headache	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Tremor	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	5 (1.8)	1 (2.0)	6 (1.4)	1 (0.3)
Cough	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Dry throat	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Nasal congestion	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Paranasal sinus hypersecretion	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Pharyngeal erythema	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	5 (1.8)	2 (3.9)	7 (1.7)	2 (0.6)
Cold sweat	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Petechiae	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Pruritus	0 (0.0)	1 (0.4)	1 (2.0)	2 (0.5)	1 (0.3)
Rash macular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Swelling face	0 (0.0)	2 (0.7)	1 (2.0)	3 (0.7)	1 (0.3)
Vascular disorders	0 (0.0)	6 (2.1)	0 (0.0)	6 (1.4)	5 (1.4)
Hemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Hypertension	0 (0.0)	4 (1.4)	0 (0.0)	4 (1.0)	3 (0.8)
Pallor	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)

[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.

[C] Open wound: intraoral, soft tissue injuries due to lip, tongue and cheek biting; all resolved during the study.

[D] Reports of paresthesia were mild and resolved during the study.

7.1.5.4 Common adverse event tables

Based on the information from the tables above, individual preferred-term data for all doses of NV-101 were combined as were the data for the control groups. Based on this combination, the table below was created by including those adverse events which occurred at a rate of greater than or equal to 1% for the NV-101-treated subjects and differed by more than 1.5% from the control-treated subjects. Also included in the table are the cardiac and dental adverse events for which a difference between treatment groups might have been anticipated. To discern whether a second injection alone may have contributed to administration site adverse events, adverse events reported from the studies involving only a sham injection are also listed.

Table 7-3: Table of adverse events occurring at rates ≥ 1% and differing from control by > 1.5%

Adverse Event	NV-101 (N=481)	Control (N=388)	Sham Control Alone (N=359)
Cardiac disorders			
Bradycardia	7 (1)	1 (0)	
Elevated blood pressure[A]	9 (2)	5 (1)	
Gastrointestinal disorders			
Abdominal pain	4 (1)	1 (0)	
General disorders and administration site conditions			
Injection site reaction	4 (1)	1 (0)	
Injection site pain	24 (5)	14 (4)	14 (4)
Jaw pain	4 (1)	0 (0)	
Oral pain	4 (1)	1 (0)	1 (0)
Tenderness	4 (1)	1 (0)	

[A] Includes incidents classified by the preferred terms: hypertension, blood pressure increased, and blood pressure diastolic increased.

The table demonstrates that the injection of NV-101 is not associated with any clinically relevant changes in the occurrence of adverse events than either placebo injection or sham injection. The frequency of the adverse events that were reported is remarkable for the relatively low levels in both treatment groups.

In the table below, the occurrence of the most frequent adverse events across age groups are listed. Overall, there were no substantial differences in occurrences of adverse events between NV-101- and sham-treatment groups with the possible exception of tachycardia in the 12-17 year old subjects. However, the numbers of subjects are too low to allow a definitive conclusion to be drawn.

Table 7-4: The most frequent treatment-emergent adverse events across age groups in dental subjects (Table 44 from NDA ISS)

Adverse Event by **System Organ Class** Preferred Term	Age 3 to 11 years (N = 165)		Age 12 to 17 years (N = 85)		Age 18 to 64 years (N = 472)		Age ≥ 65 years (N = 55)	
	NV-101[A]	Control[B]	NV-101	Control	NV-101	Control	NV-101	Control
	(N=109)	(N=56)	(N=45)	(N=40)	(N=235)	(N=237)	(N=29)	(N=26)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of AEs[C]	27	15	22	16	105	85	7	4
Number of subjects with AEs[C]	23 (21)	15 (27)	18 (40)	15 (38)	70 (30)	63 (27)	6 (21)	3 (12)
Cardiac Disorders								
Bradycardia	0 (0)	0 (0)	3 (7)	0 (0)	4 (2))	1 (0)	0 (0)	0 (0)
Sinus tachycardia	1 (1)	0 (0)	0 (0)	0 (0)	2 (1)	7 (3)	0 (0)	0 (0)
Tachycardia	0 (0)	0 (0)	8 (18)	5 (13)	11 (5)	14 (6)	0 (0)	1 (4)
Injury, Poisoning, and Procedural Complications								
Post procedural pain	6 (6)	7 (13)	3 (7)	3 (8)	15 (6)	12 (5)	1 (3)	1 (4)
General disorders and administration site conditions								
Injection site pain	6 (6)	3 (5)	1 (2)	3 (8)	13 (6)	8 (3)	2 (7)	0 (0)
Nervous system disorders								
Headache/tension headache	0 (0)	1 (2)	3 (7)	3 (8)	10 (4)	10 (4)	1 (3)	0 (0)
Investigations								
Blood pressure increased	4 (4)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders								
Hypertension	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	1 (0)	1 (3)	2 (8)

Notes: Individual types of AEs by PT are shown if they were reported in ≥ 3% of subjects in any age/treatment subset. Data are based on the following clinical studies: NOVA 04-100, NOVA 04-200, NOVA 03-001, NOVA 05-PEDS, and NOVA 05-PEDS-PK. Abbreviations: SOC, system organ class (MedDRA); PT, preferred term (MedDRA); AE, adverse event.

[A] Data represent total number of AEs for all doses of NV-101 in each age 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.

[C] Total number of AEs and total number of subjects with AEs in each age category

7.1.5.5 Identifying common and drug-related adverse events

As there were no differences in adverse-event occurrences between NV-101 and the controls in the clinical trials and no evidence of a dose response to adverse-event occurrences within or between trials, no adverse events were identified that could be reasonably be considered to be drug related.

7.1.5.6 Additional analyses and explorations

As there were no adverse events that appeared to be clearly drug related or even possibly drug related, no additional analyses or explorations were indicated and none were performed.

7.1.6 Less Common Adverse Events

There was only one adverse event of significant concern that appears to be relatively rare and may be unrelated to either NV-101 or the injection required to administer it. The event consisted of a single incidence of "lingual nerve trauma" that was reported to have occurred with "sensory and motor findings" in a 14 year old female subject (subject 301-03-325) in study 03-001. The subject presented for a filling in a tooth in the right lower quadrant. She received two injections of prilocaine with epinephrine as her local anesthetic (1.8 mL followed by 1.0 mL), and later received two injections of study drug, in this instance, two 1.8 mL injections of 0.8 mg of NV-101. According to the case report form (CRF), the two sets of injections were made over the right mandible with the second injection located 4 mm inferior to the first. The local anesthetic injections were made 20 minutes apart and the study-drug injections were made 43 and 45 minutes following the second local anesthetic injection. At 6, 7 and 8 hours following the study drug injections, the subject reported mandibular jaw soreness scores of 7/100, 17/100 and 17/100, respectively. Her oral cavity exams were normal up to 3 hours after study drug administration, after which no more were performed. Normal sensation in the lip, chin and tongue were reported by the patient prior to discharge. The patient reported that half an hour after discharge (3 hours and 45 minutes after study drug administration) she noted a tingling sensation on the right anterior portion of the tongue, which diminished over the next three days. At a follow-up visit, three days after the injections, it was noted that her tongue deviated approximately 1 cm to the right when extended, there was normal movement of the tongue, and no fasiculations were observed; the remainder of the oral cavity exam was unremarkable. The patient was lost to follow-up, but the CFR noted that she had been seen by her dentist ten times following her participation in the study and that she never reported her symptoms to him.

While the changes in lingual sensation experienced by this subject are consistent with lingual nerve injury, causality cannot be ascertained with certainty. The deviation of the tongue to the right is suggestive of a hypoglossal nerve pathology; not a lingual nerve condition. As for the lingual nerve injury, any one of the four injections or a combination of them could be responsible either through mechanical injury from the needle, a compression injury secondary to injection inside the neuronal sheath, or chemical injury from any of the drugs, or a combination of mechanisms could be responsible. Such injuries are relatively rare and for the most part resolve with time. The additional injections required for administration of the NV-101 as well as the volume of the drug product and perhaps a component of the drug product may increase the incidence of lingual nerve injury. A study powered to detect such phenomenon would require thousands of patients and would not likely provide information that would significantly alter the benefit-risk profile unless the nature of the injury was found to be significantly more symptomatic or of significantly longer duration. [redacted]

7.1.7 Laboratory Findings

Due to the acute use of NV-101 and limited systemic exposure at even the highest doses, as well as the safety profile for Regitine, no post-baseline laboratory evaluations were required of the applicant and non were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

For studies NOVA-02-01, NOVA-02-02, NOVA-02-03, and NOVA-03-001, vital signs [sitting blood pressure (BP) and pulse rate only] were measured within 5 minutes prior to the injection of study drug and at 5-minute intervals from 5 to 30 minutes after the injection of study drug. Patients were to have been in the sitting position for at least 3 minutes prior to measurement of vital signs.

In the pivotal dental trials, vital signs were assessed after study drug administration as follows:

- 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

Vital sign results were summarized descriptively by treatment group. In addition, the number and proportion of subjects in each treatment group who met one or more of the following criteria were determined:

- Decrease in systolic blood pressure (supine or sitting) of > 20 mm Hg in two consecutive measurements after the administration of study drug relative to the baseline systolic blood pressure
- Decrease in diastolic blood pressure (supine or sitting) of > 20 mm Hg in two consecutive measurements after the administration of study drug relative to the baseline diastolic blood pressure
- Increase in pulse (supine or sitting) of > 20 bpm in two consecutive measurements after the administration of study drug relative to the baseline pulse

For purposes of this analysis, two reference values were to be used for baselines: the result measured just before the administration of local anesthetic and the result measured just before the administration of study drug. Separate tabulations were provided for each reference baseline value.

In addition, changes in blood pressures and pulse were evaluated by comparing the result measured while the subject was sitting or supine to that measured after standing for 1 minute at selected time points. The number and proportion of subjects in each treatment group who met one or more of the following criteria were determined:

- Decrease in systolic blood pressure after standing for 1 minute of > 30 mm Hg relative to the systolic blood pressure taken immediately prior to this measurement while the subject was supine or sitting
- Decrease in diastolic blood pressure after standing for 1 minute of > 30 mm Hg relative to the diastolic blood pressure taken immediately prior to this measurement while the subject was supine or sitting
- Increase in pulse after standing for 1 minute of > 30 bpm relative to the pulse taken immediately prior to this measurement while the subject was supine or sitting

In the pediatric trial, NOVA-05-PEDS, blood pressure and pulse were assessed before and after administration of anesthetic and study drug, either in the supine or sitting position and were determined before administration of anesthetic, before randomization, every 15 minutes after study drug administration during the first hour, hourly thereafter during the first quarter of the hour, and prior to discharge. Temperature and respirations were determined within 15 minutes after administration of study drug and prior to discharge.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The Applicant combined vital sign data, i.e., blood pressure and heart rate data, for the dental trials to assess the use of NV-101 on these parameters as would occur in the clinical setting. A separate comparison was made by similarly combining data for subjects participating in studies not involving dental procedures. Both sets of studies included control groups for comparison.

7.1.8.3 Standard analyses and explorations of vital signs data

Vital sign data was evaluated in three ways:

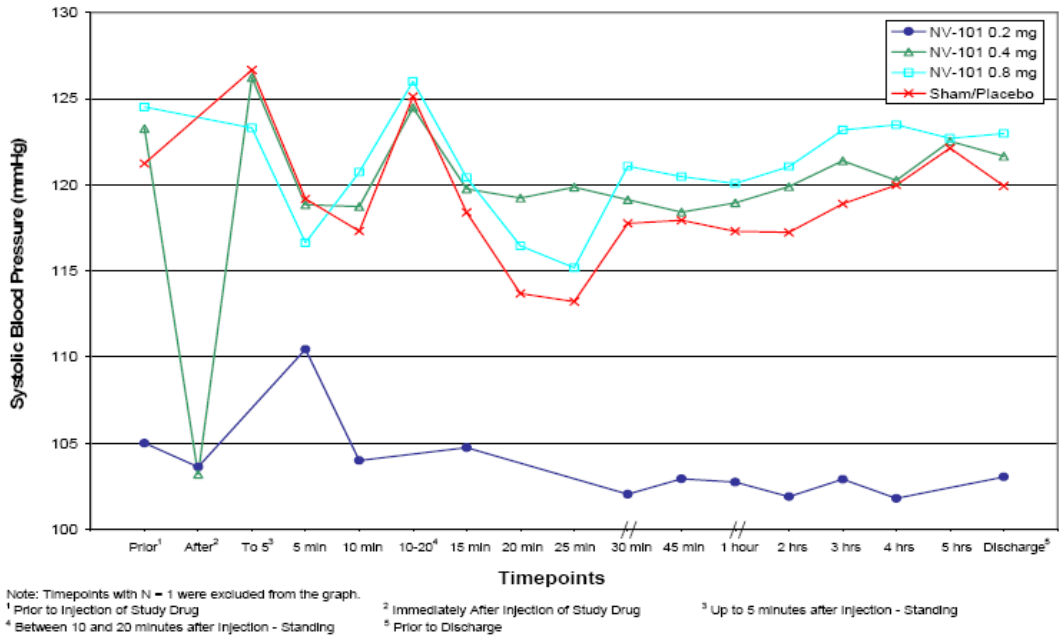
1. comparisons of changes from the baselines in the mean blood pressures and heart rates following study drug administration, which were assessed separately for subjects undergoing and not undergoing dental procedures
2. comparisons of proportions of subjects whose changes from baseline values for blood pressure and heart rate fell outside of normal boundaries
3. evaluation of the subjects whose changes from baseline values for blood pressure or heart rate constituted marked outliers which posed potential risk to the subject's well being

7.1.8.3.1 Analyses focused on measures of central tendency

The mean values for systolic blood pressure in the dental subjects are shown in Figure 1 below, which is taken from the NDA. The mean values for systolic blood pressure were determined before and after administration of study drug and showed modest fluctuations from baseline over all treatment periods and were at or near established normal ranges for adults according to criteria of the National Heart, Lung, and Blood Institute (NHLBI), and within normal ranges for children and adolescents. The results were nearly identical for both the subjects treated with NV-101 and those who were treated with the control. The 0.2 mg dose group had overall lower systolic blood pressures because, with a single exception - the adult subject who received ½ cartridge of NV-101, all subjects in this group were children 3 to 11 years of age, i.e., they were from NOVA 05-PEDS and NOVA 05-PEDS-PK. This lower systolic blood pressure was within normal limits for this age group, and the small increase in the mean value at the 5-minute time point was attributed by the Applicant to anxiety from the injection of study drug.

A lower mean value for the 0.4 mg group at the "immediately after study drug" timepoint was observed. This finding was attributed by the Applicant to the fact that all blood pressure measurements at this time point, in this dose group, were taken in children or adolescents 3 to 17 years of age from NOVA 05-PEDS-PK, whereas the values shown at the remaining timepoints were taken primarily in adult subjects. This drop could also be associated with the fact that all blood pressure measurements in NOVA 05-PEDS-PK were taken while subjects were under general anesthesia or conscious sedation, in the supine position. Consistent with this theory, drops in systolic pressure, albeit less marked, were also observed at the 5- and 10-minute timepoints. Measurements at these time points were taken with subjects in the supine position. By comparison, increases in mean systolic and diastolic blood pressure were observed at the timepoints 10 to 20 minutes after study drug when measurements were performed after subjects stood for 1 minute.

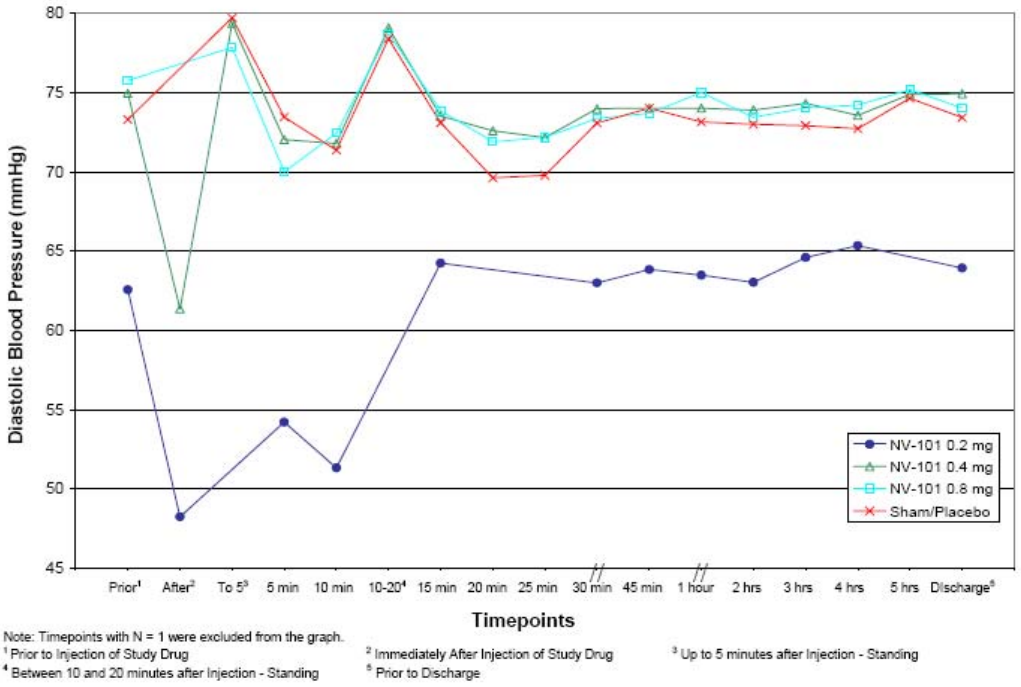
Figure 1: Mean systolic blood pressures over time for dental subjects (Figure 1 from NDA ISS, p.105)



Changes in diastolic blood pressure are shown in the Figure 2 below, which is taken from the NDA. As was observed for systolic blood pressure, mean values for diastolic blood pressure showed modest fluctuations from baseline over all treatment periods and were at or near established normal ranges for adults according to criteria of the NHLBI, and within normal ranges for pediatric subjects. Results were nearly identical for the subjects in both treatment groups. Overall, lower mean diastolic blood pressures were observed for the 0.2-mg dose group compared to the other dose groups. This was attributed, as with the systolic data, to the fact that, with one exception, all subjects in this dose group were children 3 to 11 years of age from either NOVA 05-PEDS or NOVA 05-PEDS-PK. All of the mean diastolic blood pressure values observed were within normal limits for this age group. In the 0.2-mg dose group, a decrease in the mean diastolic value was observed immediately after study drug. This drop was also observed immediately after study drug in the 0.4-mg dose group. This drop may be attributable to the fact that the measurements immediately after injection of study drug were

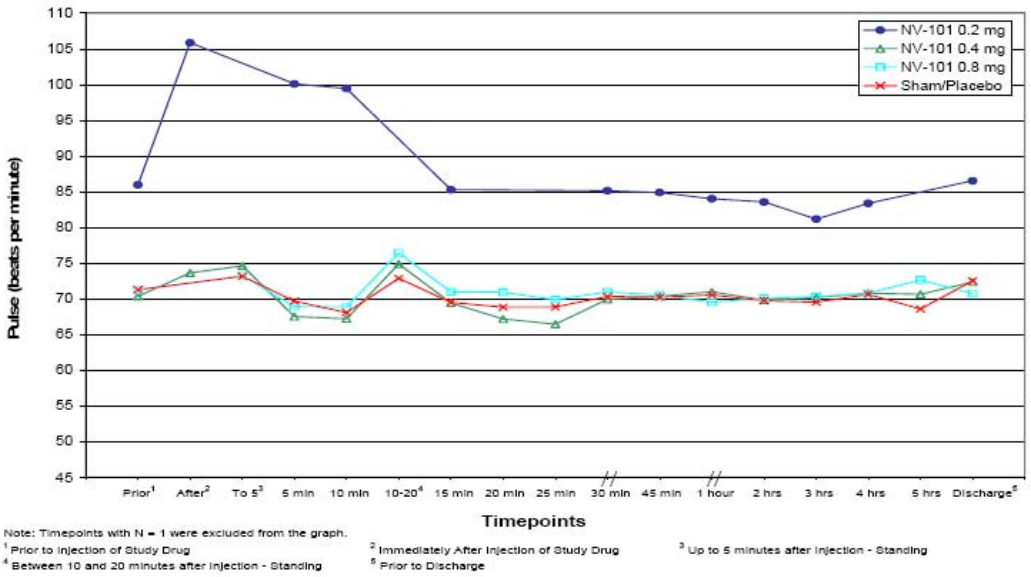
taken only in the NOVA 05-PEDS-PK study with subjects in supine position and under general anesthesia or conscious sedation. These findings suggest no untoward effects of NV-101 on either systolic or diastolic blood pressure in the overall cohort of dental subjects.

Figure 2: Mean diastolic blood pressures over time for dental subjects (Figure 2.1 from NDA ISS amendment of 08-June-2007)



Changes in pulse rate over time are shown in Figure 3 below. Published normal range values for resting heart rates in different age groups are as follows: children 1 to 10 years of age, 70 to 120 bpm; children ≥ 10 years of age and adults, 60 to 100 bpm; well-trained athletes, 40 to 60 beats per minute. Pulse rates in all clinical studies of NV-101 were analyzed using a selected threshold of ± 30 bpm. Most subjects had values within this range. For the 0.4-mg and 0.8-mg dose groups, only minor fluctuations in mean pulse were observed over time, and results were nearly identical for the control group. The higher overall mean values in the 0.2-mg dose group compared with the other dose groups are consistent with the younger age of subjects who received 0.2 mg NV-101. With a single exception, these subjects were children or adolescents 3 to 17 years of age participating in either NOVA 05-PEDS or NOVA 05-PEDS-PK. The upward shift in pulse rate immediately after and after 5 and 10 min post study drug administration are largely due to one subject in the NOVA 05-PEDS-PK study (400-02-002) with readings of 133, 128, and 136 bpm. This subject's pulse had returned to normal at discharge. No trends were otherwise observed. These findings suggested no untoward effects of NV-101 on pulse in the cohort of dental subjects treated in these clinical studies.

Figure 3: Mean pulse rates over time in dental subjects (Figure 3 from NDA ISS, p. 108)



7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

To further assess the clinical significance of changes in blood pressure and pulse, the integrated data from the five clinical studies were also examined by the Applicant using the protocol-specified thresholds listed below:

- Post-study drug decrease in systolic blood pressure (supine or sitting) of > 20 mm Hg relative to the baseline systolic blood pressure taken before the administration of study drug at two consecutive assessment time points.
- Post-study drug decrease in diastolic blood pressure (supine or sitting) of > 20 mm Hg relative to the baseline systolic blood pressure taken before the administration of study drug at two consecutive assessment time points.
- Post-study drug increase in pulse (supine or sitting) of > 20 bpm relative to the baseline pulse taken before administration of study drug at two consecutive assessment time points.

In addition, clinically significant orthostatic changes in blood pressures and pulse were evaluated by comparing the result measured while the subject was sitting or supine to that measured after standing for one minute at selected time points. The number and proportion of subjects in each dose group who met one or more of the following criteria were reported:

- Decrease in systolic blood pressure after standing for 1 minute of > 30 mm Hg relative to the systolic blood pressure taken immediately prior to this measurement while the subject was supine or sitting.
- Decrease in diastolic blood pressure after standing for 1 minute of > 30 mm Hg relative to the diastolic blood pressure taken immediately prior to this measurement while the subject was supine or sitting.

- Increase in pulse after standing for one minute of > 30 bpm relative to the pulse taken immediately prior to this measurement while the subject was supine or sitting.

Results of this analysis, shown in the table below, indicate that few subjects treated with NV-101 experienced clinically significant changes in supine/sitting vital signs, defined as > 20 mm Hg decreases in systolic diastolic blood pressure, or > 20 bpm increases in pulse rate relative to the baseline measurement prior to study drug administration. Overall, 13% of subjects in the NV-101 group and 12% of subjects in the control group experienced 1 or more of these changes; most of these subjects (9% of subjects in the NV-101 group and 9% of subjects in the sham group) experienced a clinically significant decrease in systolic blood pressure. Fewer subjects experienced clinically significant decreases in diastolic blood pressure or pulse rate. There were no apparent differences among the different NV-101 dose groups.

Table 7-5: Frequencies of changes in vital signs at any time point relative to baseline taken prior to study drug administration in dental subjects (Table 31 from NDA ISS)

Change in Vital Signs at Any Time Point	**NV-101[A]**				**Control[B]**
	0.2 mg (N = 83)	**0.4 mg (N = 284)**	**0.8 mg (N = 51)**	**Total (N = 418)**	**(N = 359)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Systolic blood pressure					
> 20 mm Hg decrease[C]	6 (7)	28 (10)	4 (8)	38 (9)	30 (8)
≤ 20 mm Hg decrease	51 (61)	209 (74)	37 (73)	297 (71)	258 (72)
Diastolic blood pressure					
> 20 mm Hg decrease[C]	2 (2)	9 (3)	2 (4)	13 (3)	10 (3)
≤ 20 mm Hg decrease	45 (54)	193 (68)	36 (71)	274 (66)	230 (64)
Pulse					
> 20 bpm increase[C]	4 (5)	6 (2)	0 (0)	10 (2)	7 (2)
≤ 20 bpm increase	42 (51)	167 (59)	30 (59)	239 (57)	199 (55)
Met one or more criteria for clinical significance	11 (13)	36 (13)	6 (12)	53 (13)	43 (12)
Did not meet any criteria for clinical significance	72 (87)	248 (87)	45 (88)	365 (87)	316 (88)

Notes: Data are based on the following clinical studies: NOVA 03-001, NOVA 04-100, NOVA 04-200, NOVA 05-PEDS, NOVA 05-PEDS-PK. Baseline and post-baseline vital signs were measured in either sitting or supine position; unchanged and increased blood pressure and unchanged and decreased pulse are not included.

[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.

[C] Considered clinically significant.

As shown in the table below, fewer subjects experienced clinically significant orthostatic changes in vital signs, defined as > 30 mm Hg decreases in systolic or diastolic blood pressure or > 30 bpm increase in pulse at any time after study drug administration. Results were nearly equally distributed between the treatment groups. Overall, only 4% of subjects in the NV-101 group and 5% of subjects in the control group experienced one or more of these orthostatic vital sign changes. In the NV-101 group, 5 subjects experienced > 30 mm Hg orthostatic decreases in systolic blood pressure, 2 subjects experienced > 30 mm Hg orthostatic decreases in diastolic blood pressure, and 3 subjects experienced > 30 bpm orthostatic increases in pulse rate. Results for each vital sign were similar for controls. No differences were apparent for the different NV-101 dose groups. These results revealed no clinically significant effects of NV-101 on vital signs in these studies.

Table 7-6: Frequencies of orthostatic changes in vital signs at any time point relative to baseline taken prior to study drug administration in dental subjects (Table 31 from NDA ISS)

Orthostatic Change in Vital Signs at Any Time Point[C]	**NV-101[A]**				**Control[B]**
	0.2 mg (N = 0)	**0.4 mg (N = 202)**	**0.8 mg (N = 40)**	**Total (N = 242)**	**Control (N = 242)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Any time point					
Systolic blood pressure	NA				
> 30 mm Hg decrease[D]		5 (2)	0 (0)	5 (2)	6 (2)
≤ 30 mm Hg decrease		131 (65)	26 (65)	157 (65)	151 (62)
Diastolic blood pressure	NA				
> 30 mm Hg decrease[D]		1 (1)	1 (3)	2 (1)	2 (1)
≤ 30 mm Hg decrease		107 (53)	19 (48)	126 (52)	109 (45)
Pulse	NA				
> 30 bpm increase[D]		3 (2)	0 (0)	3 (1)	4 (2)
≤ 30 bpm increase		159 (79)	26 (65)	185 (76)	181 (75)
Met one or more criteria for clinical significance	NA	8 (4)	1 (3)	9 (4)	11 (5)
Did not meet any criteria for clinical significance		194 (96)	39 (98)	233 (96)	231 (96)

Notes: Data are based on the following clinical studies: NOVA 04-100, and NOVA 04-200. Orthostatic vital signs were not assessed in NOVA 03-001 or NOVA 05-PEDS. Baseline and post-baseline vital signs were measured in either sitting or supine position; unchanged and increased blood pressure and unchanged and decreased pulse are not included.

[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) or placebo (NOVA 03-001).

[C] Vital signs were measured after subjects had been standing for 1 minute at 2 time points: up to 5 minutes after administration of study drug administration and between 10 and 20 minutes after study drug administration.

[D] Considered clinically significant.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no dropouts in any of the clinical studies; therefore, the following criteria were used to assess whether there was a treatment related trend in abnormal hemodynamic parameters. As the analysis in section 7.1.8.3.2 above evaluated shift in vital signs, this analysis evaluated recorded vital signs that were outside the normal range for adults. The criteria are indicated in the table below, which shows the breakdown, by treatment groups, of the number of subjects who had at least one post-study-drug assessment that met the stated criteria. The table indicates that there were some differences in the percentages of subjects with abnormal readings. Specifically, there were slightly more subjects in the NV-101 group that had abnormally low systolic and diastolic blood pressures. Slight differences were also noted between the treatment groups for heart rate assessments. In all cases, the differences did not rise to the level of clinical significance. Similarly, the ranges of the abnormal values were similar between the NV-101 and control groups. Thus the magnitude and frequency of blood pressure and heart rate changes following treatment with study drug did not differ substantially between treatment groups and raised no concerns for safety from this perspective.

Table 7-7: Post-study-drug outliers for hemodynamic vital signs (subjects > 11 years old)

Parameter	**Treatment**						
	NV-101 (dose in mg)						**Control**
	0.02 N=18	**0.06** N=10	**0.08** N=7	**0.2** N=11	**0.4** N=275	**0.8** N=51	N=332
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Systolic BP							
≥ 180 mmHg	0	0	0	0	5 (2)	0	6 (2)
≤ 90 mm Hg	1 (6)	1 (10)	1 (14)	0	19 (7)	2 (4)	13 (4)
Diastolic BP							
≥ 90 mmHg	2 (11)	2 (20)	1 (14)	2 (18)	85 (31)	17 (33)	99 (30)
≤ 60 mm Hg	12 (67)	5 (50)	5 (71)	1 (9)	85 (31)	15 (29)	98 (30)
Heart Rate							
≥ 100 bpm	0	1 (10)	1 (14)	0	5 (1)	0	2 (1)
≤ 50 bpm	0	0	0	0	5 (1)	0	10 (3)

7.1.8.4 Additional analyses and explorations

No additional analyses were indicated and none were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Based on the relatively low doses of phentolamine used in the clinical studies, compared to the labeled doses for Regitine, it was not anticipated that NV-101 would have significant impact on

electrocardiac activity. NOVA 03-001 assessed ECGs following administration of study drug in an effort to assess any effect of NV-101 on the ECG, and the need for a more formal study in this regard.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

NOVA 03-001 required Holter monitoring of the ECG and evaluation of the 2-lead tracings recorded at Screening, 5 min before injection of the local anesthetic, and, then, every 5 minutes until 30 min after study drug administration. The electronic record was analyzed for the occurrence of arrhythmias and other abnormalities by machine and by a cardiologist at [redacted]. No clinically significant arrhythmias were reported for any of the abnormal ECG tracings observed in this study. The table below lists the observed abnormalities. The datasets and the final study report for this study provide no insight into the specifics of the abnormalities reported, e.g., durations, extent of QTc changes or ST depression. The timing of the abnormalities relative to study drug was also not specified in the final study report. Therefore, the lack of clinical presentations suggesting a cardiac problem must be relied upon for determining whether the abnormalities were of clinical relevance. Comparing the descriptions of the abnormalities between the two treatment groups provides no basis for concern that NV-101 is more arrhythmogenic than placebo.

Table 7-8: ECG abnormalities (modified Table 16.3.8 from NOVA03-001 final report)

Study Drug	Anesthetic / Vasoconstrictor	Procedure Location	Description
Placebo	lidocaine/epinephrine	Mandible	sinus arrhythmia, okay for study per p.i.
Placebo	lidocaine/epinephrine	Maxilla	sinus arrhythmia
Placebo	lidocaine/epinephrine	Maxilla	long qtc interval; st junctional depression is nonspecific.
Placebo	mepivacaine/levonordefrin	Mandible	sinus bradycardia - ok for the study per md.
Placebo	mepivacaine/levonordefrin	Mandible	normal sinus rhythm with j point repolarization changes
Placebo	mepivacaine/levonordefrin	Maxilla	early repolarization changes
Placebo	mepivacaine/levonordefrin	Maxilla	sinus bradycardia, non specific tw decrease v3. not significant ok for study
Placebo	prilocaine/epinephrine	Mandible	sinus bradycardia
Placebo	prilocaine/epinephrine	Mandible	early repolarization changes
Placebo	prilocaine/epinephrine	Mandible	early repolarization change normal signs rhythm - ok for study
Placebo	prilocaine/epinephrine	Maxilla	occasional premature atrial contractions.
Active	lidocaine/epinephrine	Mandible	sinus bradycardia, early repolarization changes
Active	lidocaine/epinephrine	Mandible	st elevation represents early repolarization changes

Study Drug	Anesthetic / Vasoconstrictor	Procedure Location	Description
Active	lidocaine/epinephrine	Mandible	non specific t-wave decrease in the third lead. normal sinus rhythm-ok for study
Active	lidocaine/epinephrine	Maxilla	sinus arrhythmia
Active	Lidocaine/epinephrine	Maxilla	sinus arrhythmia
Active	lidocaine/epinephrine	Maxilla	early repolarization changes
Active	mepivacaine/levonordefrin	Mandible	sinus arrhythmia, ok for study
Active	mepivacaine/levonordefrin	Mandible	sinus bradycardia
Active	mepivacaine/levonordefrin	Mandible	repolarization changes
Active	mepivacaine/levonordefrin	Mandible	mild repolarization changes
Active	mepivacaine/levonordefrin	Maxilla	sinus arrhythmia

The table below shows the relationship, or lack thereof, between ECG abnormalities and various parameters of the study. There was no difference by study drug overall, and a lower incidence of abnormal ECGs with two doses of NV-101 (0.8 mg) compared to two doses of placebo (1.8 mL of inactive ingredients in NV-101). However, substantial differences existed between the local anesthetic-vasoconstrictor combinations used;

Table 7-9: Occurrences of ECG abnormalities by key study parameters

Parameter	No ECG abnormality	ECG abnormality noted
	N (%)	N (%)
Local anesthetic used:		
Lidocaine/epinephrine	9 (30)	21 (70)
Articaine/epinephrine	30 (100)	0 (0)
Prilocaine/epinephrine	22 (85)	4 (15)
Mepivacaine/levonordefrin	26 (72)	10 (72)
Treatment arm:		
Active	50 (82)	11 (18)
Placebo	50 (82)	11 (18)
Use of two doses of study drug:		
Active	8 (73)	3 (27)
Placebo	4 (50)	4 (50)

7.1.9.3 Standard analyses and explorations of ECG data

The ECG data submitted were too limited to perform any analyses or explorations.

7.1.9.4 Additional analyses and explorations

No additional analyses were indicated and none were performed.

7.1.10 Oral Cavity Assessments

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

Among all 777 dental subjects, 15 (2%) had clinically significant abnormalities in the OCAs as indicated in the table below. Most of the subjects with OCA abnormalities were enrolled in NOVA 03-001 in which oral cavity examinations revealed 5 NV-101 patients and 2 placebo patients with an aphthous ulcer, swelling, blanching, or bruising after study drug administration. There were also findings of mild cheilitis with mucosal fissures and minimal erythema in the follow-up physical examination of a subject who was treated with placebo. These findings were not recorded at the screening examination and not reported as an adverse event.

Table 7-10: Number of dental subjects with clinically significant abnormal oral cavity assessment findings (from Table 38 from NDA ISS)

Study ($N_{NV-101}/N_{Control}$)	**NV-101**	**Control[A]**	**Total**
	N (%)	**N (%)**	**N (%)**
NOVA 04-100 (122/122)	3 (2)	1 (1)	4 (2)
NOVA 04-200 (120/120)	1 (1)	0 (0)	1 (0)
NOVA 03-001 (61/61)	6 (10)	3 (5)	9 (7)
NOVA 05-PEDS (96/56)	1 (1)	0 (0)	1 (1)
NOVA 05-PEDS-PK (19/0)	0 (0)	NA	0 (0)
All (418/359)	11 (3)	4 (1)	15 (2)

[A] 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 specific abnormalities are listed in the table below. In most cases (11 of 15 subjects), the OCA abnormality was judged as related to study drug (NV-101 or control) by the Investigator. In three subjects, the oral cavity abnormalities were reported as adverse events not related to study drug, and in one subject, the oral cavity abnormality (hyperemic injection site between 30 minutes and 2 hours after study drug administration) was not reported as an adverse event. However, mild injection site reaction was reported as a possibly related adverse event in the same subject. Only 1 event (edema and slight appearance of swelling and redness at the

procedure site in an NV-101-treated subject) was treated with analgesics. In 14 subjects, the abnormality resolved; in 1 subject (NV-101 treatment arm), the abnormality was diminished; and in 1 subject (NV-101 treatment arm), the abnormality was noted to have resolved, but a related abnormal finding was observed at follow-up or discharge. In addition, three of the subjects had abnormalities in the oral cavity (2 NV-101-treated and 1 control-treated) that were reported as an adverse event, but were not reported as clinically significant OCA findings. These adverse events included a case of mild, possibly related, injection site edema (NV-101), mild aphthous stomatitis (control) and mild, possibly related, injection site reaction (NV-101).

The only severe adverse event was reported in the placebo group. A single subject reported a severe injection site reaction (upper lip blanching) and a moderate injection site edema (increased swelling of the upper lip) 19 minutes after study drug administration. Both adverse events resolved after 75 minutes. At the follow-up visit, a moderate injection site reaction (upper lip bruising) was reported as an adverse event in the same subject, which resolved after 9 days. In addition, three subjects in the NV-101 group and one subject in the control group in study NOVA 03-001 reported an adverse event with a visible abnormality in the oral cavity, but no abnormality was reported in the oral cavity assessment. The adverse events in the NV-101 group were a single incident of mild unrelated mouth ulceration (lower lip bite), a single case of mild, possibly related injection site reaction (gingival erythema), and a single incident of mild, possibly related injection site edema (left side facial swelling). These events did not require any treatments. It was noted by the Applicant that one moderate, possibly related injection-site reaction (hematoma at injection site) was reported as an adverse event, although the corresponding OCA findings indicated that the hematoma was present prior to study drug administration and did not increase in size (OCA description: 2 mm slight hematoma at injection site from before study drug administration to 1 hour after study drug). This event was treated with analgesics. In the control group, a single incident of an unrelated, mild, injection site reaction (bruise at angle of right oral fissure) requiring no treatment was reported.

Table 7-11: Summary of clinically significant abnormal oral cavity findings in dental subjects (Table 39 from NDA ISS)

Description of Abnormality[B]	**NV-101 N**	**Control[A] N**	**Total N**
Edema/swelling	4	1	5
(Procedure site)	(1)	(0)	(1)
(Injection site)	(3)	(1)	(4)
Bleeding	2	1	3
(Procedure site)	(1)	(1)	(2)
(Injection site)	(1)	(0)	(1)
Paleness/blanching at injection site	1	2	3
Petechia at injection site	1	0	1
Redness at procedure site	1	0	1
Abnormal mucosa at procedure site	1	0	1
Aphthous ulcer	1	1	***2***

Description of Abnormality[B]	NV-101 N	Control[A] N	Total N
Decreased sensation in lip and tongue	1	0	1
Bruising at injection site	1	1	***2***
Dysesthetic feeling	0	1	1
Hyperemia at injection site	1	0	1

[A] 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.

[B] Subjects may have experienced more than 1 symptom or abnormality; however, a symptom is counted only once per subject.

7.1.11 Intraoral Pain Assessments and Analgesic Use

Intraoral pain experienced by subjects treated with NV-101 or control was assessed using either the Heft-Parker Visual Analogue Scale (H-P VAS) [see Section 11.1.3] in studies NOVA 0-100, NOVA 0-200, and NOVA 03-001 or the Wong-Baker Pain Rating Scale (W-B PRS) [see Section 11.1.4] in study NOVA 05-PEDS. Each H-P VAS score was classified into 1 of 4 mutually exclusive severity categories such that the number and proportion of subjects reporting no pain, mild pain, moderate pain, or severe pain could be evaluated clinically. "No pain" corresponded to 0 mm on the 170-mm scale. "Mild pain" was defined as greater than 0 mm and less than or equal to 54 mm, and included the descriptors "faint", "weak", and "mild pain." "Moderate pain" was defined as greater than 54 mm and less than 144 mm. "Severe pain" was defined as ≥144 mm, and included the descriptors "strong", "intense", and "maximum possible." Scores greater than mild (> 54 mm) were considered to indicate clinically relevant pain.

More than half of the subjects in each treatment group did not experience pain during the first hour after administration of study drug: 57% reported no pain immediately after administration of NV-101, 53% reported no pain 30 minutes after NV-101, and 60% reported no pain 1 hour after administration of NV-101. Similar percentages of controls reported no pain at these time points. Mild pain was reported by 36% of subjects in the NV-101 group and 37% in the control group after administration of local anesthetic; this proportion did not change appreciably after administration of study drug: 36% reported mild pain immediately after administration of NV-101, 28% reported mild pain at 30 minutes, and 32% reported mild pain 1 hour after NV-101 administration. Similar results were observed for mild pain in the control group. Fewer than 10% of subjects in each treatment group reported moderate pain during the first hour, although the percentage did increase somewhat in the NV-101 group (3% before study drug to 8% 1 hour after study drug), and was higher than the control group at the 1-hour time point (8% vs. 3%).

Severe pain was reported by only 2 subjects treated with NV-101 (1 in the 0.4-mg dose group and 1 in the 0.2-mg dose group) during the first hour after study drug administration. The subject with severe pain from the 0.4-mg dose group (Subject 484 from NOVA 03-001) had severe pain immediately after administration of NV-101 and at the 1-hour time point (pain was not assessed at 30 minutes in NOVA 03-001). This subject continued to experience severe pain at the 2-hour and 3-hour timepoints and then had moderate pain through the remainder of the observation period; the pain resolved the following day. The subject from the 0.2-mg dose group

(Subject 300-12-017 from NOVA 05-PEDS) experienced severe pain 30 minutes after administration of NV-101. This subject also reported severe pain after administration of local anesthetic, but no pain immediately after administration of study drug, and moderate pain 1 hour after study drug administration. The pain resolved by the 90-minute time point. In the control group, only one subject (Subject 300-08-004 from NOVA 05-PEDS) experienced severe pain immediately after study drug (sham injection) administration. This subject also experienced severe pain immediately after administration of local anesthetic and prior to sham injection. The pain was rated moderate at 30 minutes, mild 1 hour, and resolved by 90 minutes after study drug administration. By comparison, 9 subjects (1%) [NV-101, N = 6; control, N = 3] in the overall cohort reported severe pain after the administration of local anesthetic and 5 (1%) [NV-101, N = 3; control, N = 2] reported severe pain before study drug administration. Thus, the proportion of subjects reporting severe pain after administration of NV-101 was less than 0.5% (2/399) of the active treatment group, which was lower than the small proportion of subjects who reported severe pain after local anesthetic. There was no apparent relationship between dose and either the level of pain reported, or the frequency with which pain was reported.

More than 30% of subjects in each treatment group (NV-101, 38%; control, 37%) did not experience oral pain at any time after study drug administration. The most severe level of pain was mild in 47% of subjects treated with NV-101 and 49% of controls, moderate in 15% of subjects treated with NV-101 and 13% of controls, and severe in only 2 subjects in each treatment group.

Thus, the majority of subjects experienced either no pain or mild pain after treatment with NV-101, and NV-101 did not appear to have been associated with increased risk of oral pain compared with administration of control (sham or placebo) or local anesthetic. The maximal pain experienced was similar for subjects treated with either NV-101 or control. The data suggest that subjects' perception of having an injection (sham), or the injection itself (placebo) rather than NV-101 specifically, may have contributed to their sense of experiencing of oral pain.

Table 7-12: Summary of intraoral pain levels during the observation period after study drug treatment in dental subjects (Table 35 of the NDA ISS)

	NV-101[A]				Control[B]
Pain Category[C]	0.2 mg (N = 75)	0.4 mg (N = 273)	0.8 mg (N = 51)	Total (N = 399)	Total (N = 359)
	N (%)	N (%)	N (%)	N (%)	N (%)
No Pain	50 (66.7)	93 (34.1)	10 (19.6)	153 (38.3)	132 (36.8)
Mild	16 (21.3)	141 (51.6)	29 (56.9)	186 (46.6)	177 (49.3)
Moderate	8 (10.7)	38 (13.9)	12 (23.5)	58 (14.5)	48 (13.4)
Severe	1 (1.3)	1 (0.4)	0 (0.0)	2 (0.5)	2 (0.6)

Notes: Data are based on the following clinical studies: NOVA 03-001, NOVA 04-100, and NOVA 04-200, and NOVA PEDS. NOVA PEDS used the Wong-Baker FACES Pain Rating Scale (W-B PRS); all other studies used the Heft-Parker Visual Analog Scale (H-P VAS). Pain was not rated on NOVA 05-PEDS-PK, thus a total of 399 subjects treated with NV-101 were included in the pain analysis.

[A] 0.2 mg dose was used in NOVA 05-PEDS; 0.4 mg dose was used in NOVA 04-100, NOVA 04-200, NOVA 03-001, and NOVA 05-PEDS ; 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).
[C] Pain categories were defined as follows:

- No pain was defined as 0 mm on the H-P VAS and Face 0 on W-B PRS.
- Mild pain was defined as > 0 mm and ≤ 54 mm on the H-P VAS and Face 1 on W-B PRS.
- Moderate pain was defined as > 54 mm and < 144 mm on the H-P VAS and Face 2 or Face 3 on the W-B PRS.
- Severe pain was defined as ≥ 144 mm on the H-P VAS and Face 4 or Face 5 on the W-B PRS.

The use of analgesics to treat intraoral pain within the observation period and within 24 hours of discharge was considered, in conjunction with intraoral pain, and is summarized in the table below. The majority of dental subjects did not use analgesics for intraoral pain, and the overall percentages were similar between treatment groups (NV-101, 96%; control, 98%). Of those treated with NV-101 who did use analgesics for oral pain, one subject not included in the table reported use prior to study drug administration. That subject took 12.5 mg of Orudis KT as needed for a toothache starting one week prior to the day of the dental procedure and discontinued the medication prior to study drug administration (0.4 mg NV-101). Of those treated with control, none reported using analgesics for oral pain prior to study drug.

Analgesic Usage for Intraoral Pain in Dental Subjects (Table 13 of NDA ISS)

Time and Usage Category	NV-101[A]			Control[B]	
	0.2 mg	0.4 mg	0.8 mg	Total	Total
	(N = 83)	(N = 284)	(N = 51)	(N = 418)	(N = 359)
	N (%)	N (%)	N (%)	N (%)	N (%)
Within observation period					
Yes	3 (4)	10 (4)	5 (10)	18 (4)	9 (3)
No	80 (96)	274 (96)	46 (90)	400 (96)	350 (97)
Within 24 hours after discharge					
Yes	3 (4)	5 (2)	0 (0)	8 (2)	8 (2)
No	80 (96)	279 (98)	51 (100)	410 (98)	351 (98)

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.
[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.

Of the subjects who did not undergo dental procedures, only one subject, treated with 0.02 mg of NV-101 used an analgesic for intra oral pain within the observation period. No other subjects

used an analgesic for this purpose during either time period indicating that the pain was likely associated with the dental procedure. The increased use of analgesics for intraoral pain during the observation period for subjects who received 0.08 mg of NV-101 (10% versus < 4% for all other NV-101-treated subjects and < 3% for the controls) suggests that the additional injection may have contributed to post-procedural pain. This finding is consistent with the intraoral pain findings discussed above.

7.1.12 Immunogenicity

NV-101 is intended for acute use with minimal exposure over the course of a patient's lifetime. Additionally, it contains no proteins or protein derivatives; therefore, it is not expected to elicit an immunogenic response, and an evaluation of immunogenicity has not been performed.

7.1.13 Human Carcinogenicity

Human carcinogenicity studies are not required due to the acute exposure to NV-101 for the indicated use.

7.1.14 Special Safety Studies

No special safety studies were requested, required or conducted for this NDA.

7.1.15 Withdrawal Phenomena and/or Abuse Potential

Phentolamine has been marketed for many years as an unscheduled drug product. There have been no reports of abuse or withdrawal phenomenal associated with its use. The abuse potential for NV-101 is, therefore, expected to be minimal.

7.1.16 Human Reproduction and Pregnancy Data

No formal studies in humans of the effects of NV-101 on reproduction or pregnancy were performed and none were required. No pregnant women were inadvertently exposed to NV-101 during the course of its development.

7.1.17 Assessment of Effect on Growth

No assessment on the effect on growth was performed. Due to the acute use of NV-101 and the limited exposure that would be experienced by younger pediatric patients, no impact on growth was considered likely, and no requirement for this assessment was made.

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 search 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 procedures (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 Applicant'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 subjects 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.

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 although the incidence is low, 2%, and the extent of hypotension was similar to that seen with placebo injections.
- Abdominal pain – possibly related although Regitine 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, and tenderness – possibly related; 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; however, 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 regard, 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.

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 included 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?"

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

> "The label will reflect the populations 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.

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.

[redacted]

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:

[redacted]

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 NOVA 04-100

"A Phase 3, Multicenter, Randomized, Blinded, 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 ≤ 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 ≤ 0.01%. Additional audits were to have been performed as described above using the error rate cutoff of ≤ 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:

- 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 whether 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" analysis 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." 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 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 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.

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:

- 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 recovery (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 opinion, 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.

10.1.7 NOVA 03-001

"A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of NV-101 in Dental Patients"

10.1.7.1 Study Design

This was a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy of NV-101 to reduce the duration of local anesthesia in the lip, chin, nose, and tongue produced by any one of four local anesthetic agents formulated with a vasoconstrictor and used in patients undergoing a dental procedure. In addition, the study was to evaluate the safety of NV-101 in dental patients and the ability of NV-101 to reduce post-operative pain at the injection site, jaw muscle soreness, and to assess the effect on post-operative pulpal pain in patients receiving an inferior alveolar nerve block or on post-operative pain at the injection site/pulpal pain in patients receiving a maxillary procedure. Placebo consisted of the inactive ingredients in NV-101.

One hundred twenty-two patients were enrolled who required treatment with one of four routine dental procedures that included and were limited to teeth cleaning, scaling and planing, cavity filling, and crowns. Each patient received one or more conventional injections of either articaine with epinephrine, lidocaine with epinephrine, prilocaine with epinephrine, or mepivacaine with levonordefrin. Local anesthetics were injected into no more than two sites. Injections of local anesthetic placed within 4 mm of each other constituted the same site. Subsequently, patients received an injection of study drug (1.8 mL) in each site at which local anesthetic had been injected (i.e., no more than 2 sites). The injection(s) of study drug were made at or near the completion of the dental procedure. Patients receiving maxillary dental procedures self-evaluated the return of normal sensation in the upper lip and nose by palpations at 5-minute intervals beginning 1 minute before study drug injection and continuing for a minimum of 3 hours or until the return of normal sensation in both the lip and nose. Mandibular patients self-evaluated the return of sensation in an identical manner except that the lower lip, chin, and tongue were evaluated and not the upper lip or nose.

Sensation was assessed in the lip by pinching with two fingers (or thumb and forefinger), in tongue by pinching the lateral edge of the tongue while it was extruded outside the mouth, and in the chin and nose by pressing with the forefinger. Responses were recorded separately for each tissue and categorized as numb (no feeling), feeling of pins and needles (tingling), or normal sensation.

Safety was assessed by the use of a Holter monitor, vital signs, pain ratings, and physical examinations including oral cavity examinations.

10.1.7.2 Results

One patient did not develop adequate pulpal numbness with a mepivacaine anesthetic and was discontinued prior to the administration of study drug. One patient (Subject No. 455) received approximately half of the volume of NV-101 due to a leaking syringe. The numbers of patients tested with each anesthetic were:

- lidocaine/epinephrine - 30
- articaine/epinephrine - 30
- prilocaine/epinephrine - 26
- mepivacaine/levonordefrin - 36

Treatment with NV-101was given to half of the patients in each anesthetic group; the other half was treated with placebo.

NV-101 significantly increased the rate of recovery to normal sensation in the upper and lower lip. The time to return to normal sensation in patients treated with NV-101 was reduced by an average of 56 minutes (35%) in the mandible and 78 minutes (53%) in the maxilla compared to placebo ($p < 0.001$), with an average reduction of 67 minutes (44%) for the combination of upper and lower lips. The drug-by-anesthetic interaction term had a p value greater than 0.15 indicating that NV-101 increased the rate of recovery with each of the four anesthetic products in a comparable manner. The drug-by-location interaction term indicated that the effect of NV-101 in the mandible was not different than its effect in the maxilla ($p = 0.098$). The mean times to return to normal sensation in the lip are presented in table below by anesthetic product used and location of the dental procedure performed (maxilla vs. mandible).

In an alternative approach to presenting the efficacy results, it was noted that 43% of NV-101 patients had returned to normal sensation in the lip within the first hour after study drug injection whereas only 3% of placebo patients reported a return to normal sensation in that time period. In contrast, 3% of NV-101 treated patients and 31% of placebo patients required more than 3 hours to return to normal sensation.

The effects of the covariates age, sex, time interval between anesthetic and study drug injections, number of injections of study drug (one or two), and type of dental procedure on the time to return to normal sensation in the lip were not statistically significant.

The effect of anesthetic type differed significantly when the times to normal recovery in the lip were pooled between active and placebo subjects. The duration of prilocaine-induced anesthesia was up to one hour shorter than the other anesthetics and this difference may be the chief cause for a significant effect in the anesthetic factor, although no paired comparisons were conducted to confirm this.

Secondary endpoints included times to return to normal sensation in the chin, tongue, and nose. Treatment with NV-101 significantly reduced the time to return to normal sensation by an average of 48 minutes (35%) in the chin and 37 minutes (32%) in the tongue compared to placebo ($p \leq 0.001$ for each tissue). The drug-by-anesthetic interaction term for both tissues had

a *p* value greater than 0.15 indicating that NV-101 reduced recovery time with all four anesthetic products in a comparable manner.

Table 10-20: Time to return of normal sensation in the lip (Table 11.5 of final study report)

Location	Anesthetic		Placebo	NV-101 (0.4 mg)	Difference Between Placebo & NV-101	Percent Reduction
Mandible	lidocaine/ epinephrine	N	7	8		
		Mean (min)	155.7	84.6	71.1	46%
		SD (min)	65.0	45.6		
		Range (min)	95-270	30-155		
	articaine/ epinephrine	N	8	7		
		Mean (min)	169.6	133.9	35.7	21%
		SD (min)	45.0	46.1		
		Range (min)	109-231	70-200		
	prilocaine/ epinephrine	N	7	6		
		Mean (min)	131.4	71.0	60.4	46%
		SD (min)	40.7	42.9		
		Range (min)	85-189	29-150		
	mepivacaine/ levonordefrin	N	9	9		
		Mean (min)	176.4	120.0	56.4	32%
		SD (min)	56.4	42.9		
		Range (min)	72-241	60-205		
	Total	Mean (min)	158.3	102.4	55.9	35%
Maxilla	lidocaine/ epinephrine	N	8	7		
		Mean (min)	150.8	49.6	101.2	67%
		SD (min)	33.7	47.7		
		Range (min)	106-200	11-150		
	articaine/ epinephrine	N	7	8		
		Mean (min)	173.0	87.8	85.2	49%
		SD (min)	29.7	43.7		
		Range (min)	110-195	35-166		
	prilocaine/ epinephrine	N	6	7		
		Mean (min)	111.2	64.6	46.6	42%
		SD (min)	50.8	65.6		
		Range (min)	30-170	20-165		
	mepivacaine/ levonordefrin	N	9	8		
		Mean (min)	157.1	79.0	78.1	50%
		SD (min)	67.2	60.0		
		Range (min)	50-261	20-180		
	Total	Mean (min)	148.0	70.2	77.8	53%
Total		Mean (min)	153.2	86.3	66.9	44%

As for the safety evaluation, the profile of adverse events in the NV-101 group was similar to the profile in the placebo group. All adverse events were mild or moderate in severity, with the exception of one adverse event (injection site reaction) that was reported as severe in a placebo-treated patient (1 injection). Adverse events were similar regardless if there were 1 or 2 injections. There were no withdrawals from the study due to adverse events, and there were no serious adverse events.

Tachycardia was the most frequently reported adverse event in patients in both treatment groups and was not considered by the investigators as related to treatment with NV-101. The incidences of tachycardia were mild, brief, and typically occurred within 10 minutes after study drug injection. Tachycardia was defined in the program analyzing Holter monitor data as a pulse rate of 100 or greater. Sixty-one of the 122 patients in the study were required to walk from the dentist's chair to a recovery room on the floor below a few minutes after study drug injection. All of these patients were tested by either Dr. [redacted] The majority of the incidences of tachycardia occurred in these patients. The remaining patients walked to a recovery room adjacent to the examining room.

Pain ratings at the mandibular injection site, mandibular jaw, and maxillary procedure/injection sites were increased at 1 hour after study drug administration in NV-101 patients relative to placebo patients. This increased pain reported by NV-101 patients may have been related to pain caused by injections of anesthetic and study drug that were unmasked by early reversal of the anesthetic.

The mandibular pulpal pain ratings were very low throughout the 8-hour reporting period following study drug administration and were not affected by NV-101, suggesting that the dental procedures conducted in this study did not result in residual pain after the procedure and recovery from anesthesia had been completed.

10.1.7.3 Discussion and Conclusions

Evaluating the efficacy of NV-101 at reversing soft tissue anesthesia following the use of one of four of the most commonly used dental anesthetic-vasoconstrictor combinations for either a mandibular or maxillary dental procedure, it was found that NV-101 significantly decreased the time to recovery of normal sensation in the lip, chin, and tongue, but not the nose. The average time to the return of normal sensation in the lip was reduced by 44% (67 minutes). Relative to placebo, treatment with 0.4 mg NV-101 increased the number of patients that returned to normal sensation in the lip within 1 hour after study drug administration and reduced the number of patients requiring more than 3 hours to recover to normal sensation. Recovery times in the chin and tongue were reduced by approximately one-third with 0.4 mg NV-101 treatment. The clinical relevance of these changes has not been evaluated; however, the magnitudes of the differences in recovery times are substantial and are likely to confer a benefit that could outweigh the relatively small risks observed.

Statistically significant differences were not found in comparisons of the effects of patient age or gender, the duration of the interval between the anesthetic and study drug injections, the type of

dental procedure performed, and the amount of study drug administered (one or two injections) on recovery time in the lip in analyses of covariance on these factors. These results demonstrated that a second injection of NV-101 in a location within 4 mm from the first injection was not additive in its effect on reversal.

The profiles of adverse events in the NV-101 and placebo groups were similar. Cardiovascular measures such as heart rate, blood pressure, and ECG rhythm were not affected by NV-101. A statistically significant increase in oral/jaw pain was found in patients one hour after receiving NV-101. The average pain rating in NV-101 patients at this time point was rated as "weak" compared to average ratings of "none" to "faint" in placebo treated patients. This effect was not considered clinically significant by the investigators.

10.1.8 NOVA 05-PEDS

"A Phase 2, Multicenter, Randomized, Blinded, Controlled Study of NV-101 for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedures

10.1.8.1 Study Design

This Phase 2 study was designed as a multicenter, randomized, blinded, controlled study to evaluate the safety and efficacy of NV-101 administered as a submucosal injection following completion of a restorative or periodontal maintenance procedure requiring local anesthesia with 2% lidocaine with 1:100,000 epinephrine in dental patients 4 to 11 years of age.

Eligible subjects were randomized to NV-101 or control (sham injection) in a 2:1 allocation ratio, respectively, and stratified according to the location of the dental procedure (mandible or maxilla) and study site. Study drug (NV-101 or sham) was administered by submucosal injection at the same site(s) as the local anesthetic by the same Investigator who administered local anesthetic. The Investigator who administered injections of anesthetics and study drug may or may not have conducted the dental procedure. Subjects were observed for up to 4 hours after administration of study drug by a member of the investigative team other than the Investigator who administered the anesthetic and study drug. Subjects were discharged after their observation period, and contacted by study staff for a 24-hour telephone follow-up.

The doses of local anesthetic and study drug (NV-101 or sham) depended upon the weight of the subject. For subjects in both weight groups, the volume of the dose of local anesthetic was equal to the volume of NV-101 as follows:

- Subjects weighing ≥ 15 kg and < 30 kg received a half cartridge of 2% lidocaine with 1:100,000 epinephrine and a half cartridge (0.2 mg phentolamine mesylate) of NV-101 or a sham injection.
- Subjects weighing ≥ 30 kg received a half or a whole cartridge of 2% lidocaine with 1:100,000 epinephrine and a whole cartridge (0.4 mg phentolamine mesylate) of NV-101 or a sham injection.

The observation period for safety assessments was 2 hours in subjects 4 to 5 years of age who were trainable in the Wong-Baker FACES Pain Rating Scale (W-B PRS) and subjects 6 to 11 years of age who were trainable in the W-B PRS, but not trainable in a standardized palpation procedure. The observation period for safety and efficacy assessments was 4 hours for subjects 6 to 11 years of age who were trainable in the W-B PRS and a standardized palpation procedure. During this observation period, study procedures were performed by study staff members who were blinded to treatment group assignment.

Subjects who were discharged less than 4 hours after study drug administration were contacted by telephone on the same day (Day 1) to evaluate adverse events, analgesics required for oral

pain, and other concomitant medications. All subjects were contacted by telephone on Day 2 or Day 3 for follow-up of adverse events and concomitant medications.

A safety review using blinded data was performed by the Medical Monitor for the study after 30 subjects had completed the study. As a primary objective, the study evaluated the safety and tolerability of NV-101 as measured by the incidence and severity of adverse events, incidence, severity and duration of oral pain as measured by the W-B PRS, clinically significant changes in vital signs and oral cavity assessments (OCAs), and analgesics required for oral pain.

As secondary objectives for subjects 6 to 11 years of age who were trainable in standardized palpation procedures, the study determined if NV-101 accelerates the time to normal lip sensation as measured by a standardized palpation procedure. In addition, the study determined if NV-101 accelerates the time to normal tongue sensation in mandibular procedures as measured by a standardized palpation procedure.

The study was to have been considered complete when approximately 150 subjects had been randomized to study drug (NV-101 or sham) and had completed the procedures of the protocol.

10.1.8.2 Results

This clinical study investigated the ability of NV-101 to accelerate recovery from soft tissue anesthesia (STA) in 152 pediatric subjects, ages 4 to 11 years undergoing restorative dental procedures in a single quadrant of the mouth and requiring local anesthesia with 2% lidocaine with 1:100,000 epinephrine administered by submucosal injection. Of the 152, a total of 37 subjects (24 in the NV-101 group and 13 in the sham group) were not trainable in the standardized palpation procedure. These 37 subjects were excluded from the modified ITT (mITT) efficacy analysis set and were to be evaluated for safety only.

NV-101 significantly reduced the median time required for recovery from STA in the lip by 75 minutes (56%) compared with sham. Median times to recovery of normal lip sensation were 60 minutes for subjects randomized to NV-101 and 135 minutes for subjects randomized to sham (stratified log rank $p < 0.0001$). Sixty-one percent of all subjects randomized to NV-101 achieved normal sensation in the lip within the first 60 minutes after administration of study drug, whereas only 21% of subjects randomized to sham achieved normal sensation within the same time period. Results of the Cox proportional hazards model predicted a hazard ratio of 4.2 for NV-101 versus sham, indicating that subjects treated with NV-101 were 4.2 times as likely to achieve normal sensation during the 4-hour observation period as subjects treated with sham ($p < 0.0001$). Additionally, the Weibull AFT model predicted an event time ratio of 0.49 for NV-101 versus sham, indicating that NV-101 accelerated the time to normal sensation in the lip by 51%.

The ability of NV-101 to reduce the time to recovery of normal lip sensation was also evaluated in lower and upper lip subsets of the overall cohort. For the lower lip, NV-101 significantly reduced the median time required for recovery from STA in the lip by 120 minutes (67%) compared with sham. Median times to recovery of normal lower lip sensation were 60 minutes for subjects randomized to NV-101 and 180 minutes for subjects randomized to sham (stratified

log rank $p < 0.0001$). For the upper lip, NV-101 significantly reduced the median time required for recovery from STA in the lip by 52.5 minutes (47%) compared with sham. Median times to recovery of normal upper lip sensation were 60 minutes for subjects randomized to NV-101 and 112.5 minutes for subjects randomized to sham (stratified log rank $p = 0.0002$).

A summary of the treatment group differences in the recovery of normal sensation of the lip was examined in various subgroups. The table below summarizes this subgroup analysis on the primary endpoint by displaying the median values for the various subgroup categories.

Table 10-21: Time to recovery of normal lip sensation – subgroup analysis (Table 11-12 from final study report)

Subgroup Category	NV-101		Sham		% Reduction
	N	Median (minutes)	N	Median (minutes)	
Number of Cartridges					
Half (subject < 30kg)	28	67.5	20	142.5	53
Half (subject ≥ 30 kg)	22	52.5	11	120	56
Full (subject ≥ 30 kg)	22	60	12	127.5	53
Dental Procedure					
Cavity prep, restoration, filling	70	60	42	135	56
Periodontal maintenance procedure	1	45	1	75	40
Crown	1	45	0	NA	NA
Nerve Block					
Inferior alveolar	23	75	13	180	58
Gow-Gates	7	45	4	135	67
Mental-incisive	4	45	2	187.5	76
Supraperiosteal injection	38	60	25	120	50
Sex					
Male	33	45	22	142.5	68
Female	39	60	21	135	56

Time to recovery of normal sensation of the tongue was also analyzed as a secondary efficacy objective. NV-101 significantly reduced the median time required for recovery from STA in the tongue by 67.5 minutes (60%) compared with sham. Median times to recovery of normal tongue sensation were 45 minutes for subjects randomized to NV-101 and 112.5 minutes for subjects randomized to sham (stratified log rank $p = 0.0003$). Ninety-one percent of all subjects randomized to NV-101 achieved normal sensation in the tongue within the first 60 minutes after administration of study drug, whereas only 44% of subjects randomized to sham achieved normal sensation within the same time period. Results of the Cox proportional hazards model predicted a hazard ratio of 3.5 for NV-101 versus sham, indicating that subjects treated with NV-101 were 3.5 times as likely to achieve normal tongue sensation during the 4-hour observation period as subjects treated with sham ($p = 0.0034$). Additionally, the Weibull AFT model predicted an event time ratio of 0.40 for NV-101 versus sham, indicating that NV-101 accelerated the time to normal sensation in the tongue by 60%.

The ability of NV-101 to reduce the time to recovery of normal lip sensation was also observed in subsets of the overall cohort based on number of cartridges, type of dental procedure, type of nerve block, and sex, with reduction factors ranging from 40% to 76%. These data indicated that doses of 0.2 mg and 0.4 mg of phentolamine mesylate are efficacious for inducing recovery of normal sensation in pediatric subjects.

This study also identified three subjects who experienced an offset of the treatment effect i.e., re-emergence of numbness or tingling of the lip. In the one subject treated with NV-101, normal sensation returned in 30 minutes. The two subjects treated with sham experienced a longer period of recurrent numbness in the lower lip (45 and 60 minutes). The Applicant surmised that these data indicated that offset of the treatment effect is not a unique risk for subjects treated with NV-101.

The safety evaluation revealed that a total of 35 of the 152 subjects (23%) reported 37 AEs, with similar frequencies in both treatment groups. There were no deaths or other serious AEs, and no subject was discontinued because of an AE. All but three adverse events were rated as mild or moderate. There was a single severe AE (post-procedural pain) in subjects randomized to NV-101 and two severe AEs (injection site pain and post-procedural pain) in subjects randomized to sham. The most frequently reported treatment-related AEs were injection site pain (5/96 [5%] subjects randomized to NV-101 and 3/56 [5%] subjects randomized to sham), post-procedural pain (2/96 [2%] subjects randomized to NV-101 and 1/56 [2%] subjects randomized to sham), increased diastolic blood pressure (2/96 [2%] subjects randomized to NV-101 and 1/56 [2%] subjects randomized to sham), and increased blood pressure (2/96 [2%] subjects randomized to NV-101 and 1/56 [2%] subjects randomized to sham).

Overall, no clinically-significant changes in vital signs were observed in association with administration of NV-101. The mean values over time for supine/sitting systolic and diastolic blood pressure and pulse were similar for the two randomized treatment groups, with only small deviations from the baseline values. Summaries were performed of the frequency of subjects with decreases in supine or sitting systolic and diastolic blood pressure of >20mm Hg and increases in pulse >20 bpm relative to baseline. For baseline taken just prior to local anesthetic administration, the number of subjects meeting any 1 of these 3 criteria was similar in the two treatment groups: 15% of subjects randomized to NV-101 and 14% of subjects randomized to sham. Also, for baseline taken prior to study drug administration, the number of subjects meeting any 1 of these 3 criteria was similar in the two treatment groups: 15% of subjects randomized to NV-101 and 16% of subjects randomized to sham. Thus, there was no evidence in this study for an effect of NV-101 treatment on vital signs.

The incidence of subjects with no intraoral pain (measured by the W-B PRS) was similar in both groups and ranged from approximately 50% to more than 90% at the time points over the 4-hour observation period. The highest mean W-B PRS values were obtained just after administration of local anesthetic and declined steadily over time. The mean values at all time points were less than 1 (“hurts just a little bit”) and similar in subjects randomized to NV-101 and subjects randomized to sham. The distribution of most severe intraoral pain scores was similar in subjects randomized to NV-101 and subjects randomized to sham; although the frequency of subjects in the moderate and severe categories was slightly higher in subjects randomized to

sham (11/56, 20%) than in subjects randomized to NV-101 (10/96, 10%). These data suggest that NV-101 was not associated with more severe oral pain than sham.

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, which, in nearly all subjects, were not considered clinically significant by the investigators. Only one subject had a clinically significant oral cavity assessment at any time point. A subject treated with NV-101 experienced hyperemia at the primary injection site. This abnormal finding resolved by 3 hours after study drug administration. The subject did not report using analgesics to treat this abnormal OCA finding. Overall, the frequency of subjects with analgesic use for intraoral pain was similar both within the 4-hour observation period (2/96 subjects [2%] randomized to NV-101 and 1/56 subjects [2%] randomized to sham) and within 24 hours after discharge (3/96 subjects [3%] randomized to NV-101 and 1/56 subjects [2%] randomized to sham).

10.1.8.3 Discussion and Conclusions

This study was adequately designed to assess safety and efficacy related to the use of NV-101 to hasten return to normal sensation of tissues affected by local anesthetics used prior to routine dental procedures in pediatric patients. However, the study was not designed to assess a clinical benefit related to the reversal of STA in this population. The data indicated that NV-101 does indeed provide a substantial and significant reduction in the duration of STA in patients ages 4-11 years old following a number of commonly used dental nerve blocks with 2% lidocaine with 1:100,000 epinephrine. The results obtained in this study were similar in magnitude to those obtained in adult clinical trials. Whether or not benefits for such reversal as seen in adult patients, e.g., earlier return to normal speech and ability to eat and drink, are relevant to pediatric patients, or whether such functions have actually returned sooner with NV-101 treatment, was not evaluated.

The safety profile for NV-101 in this patient population was comparable to that of the sham injection and not much different from that observed in the adult trials. None of the adverse events reported were of such severity, compared to sham injection, or posed such a significant risk to patients as to preclude further evaluation of NV-101 in this population in an effort to demonstrate a clear clinical benefit that outweighs the low level of risk observed to date.

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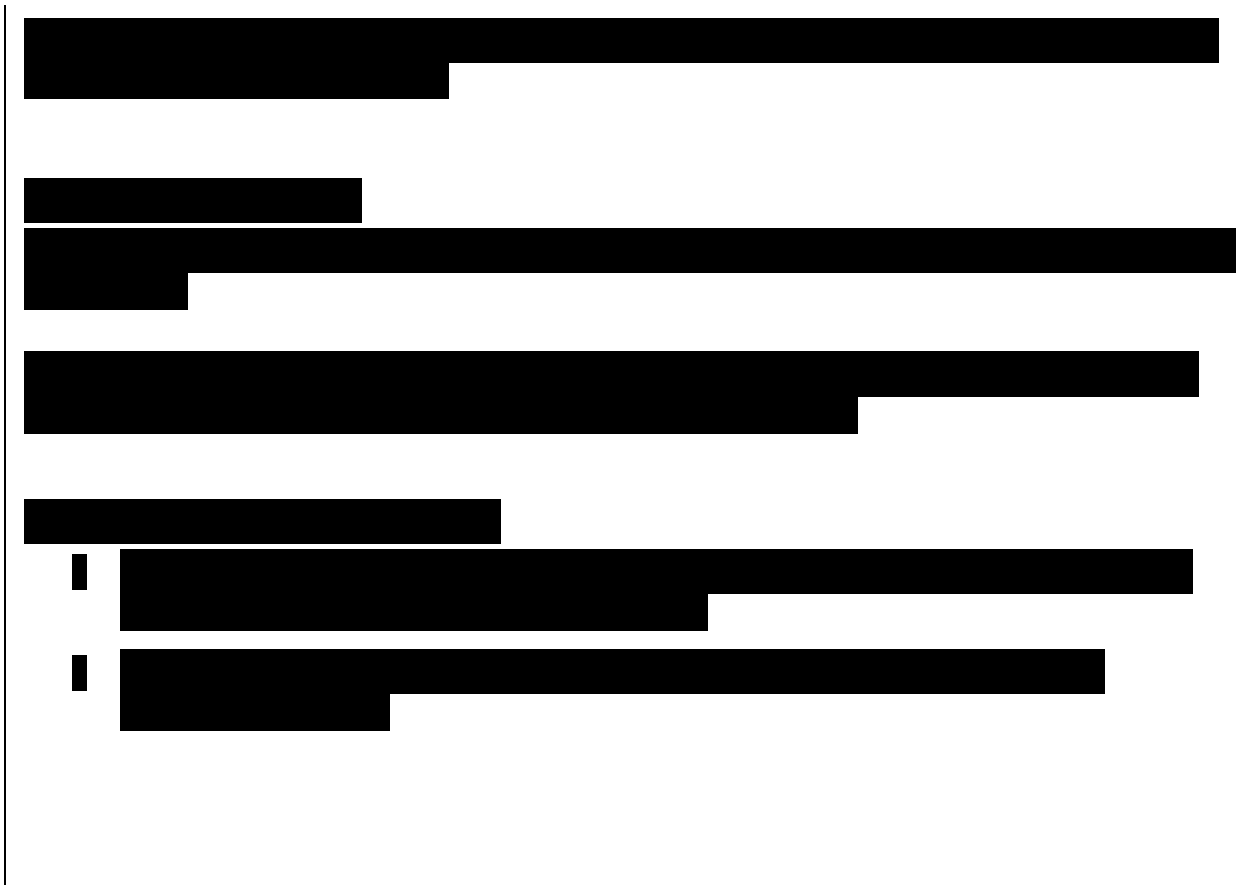

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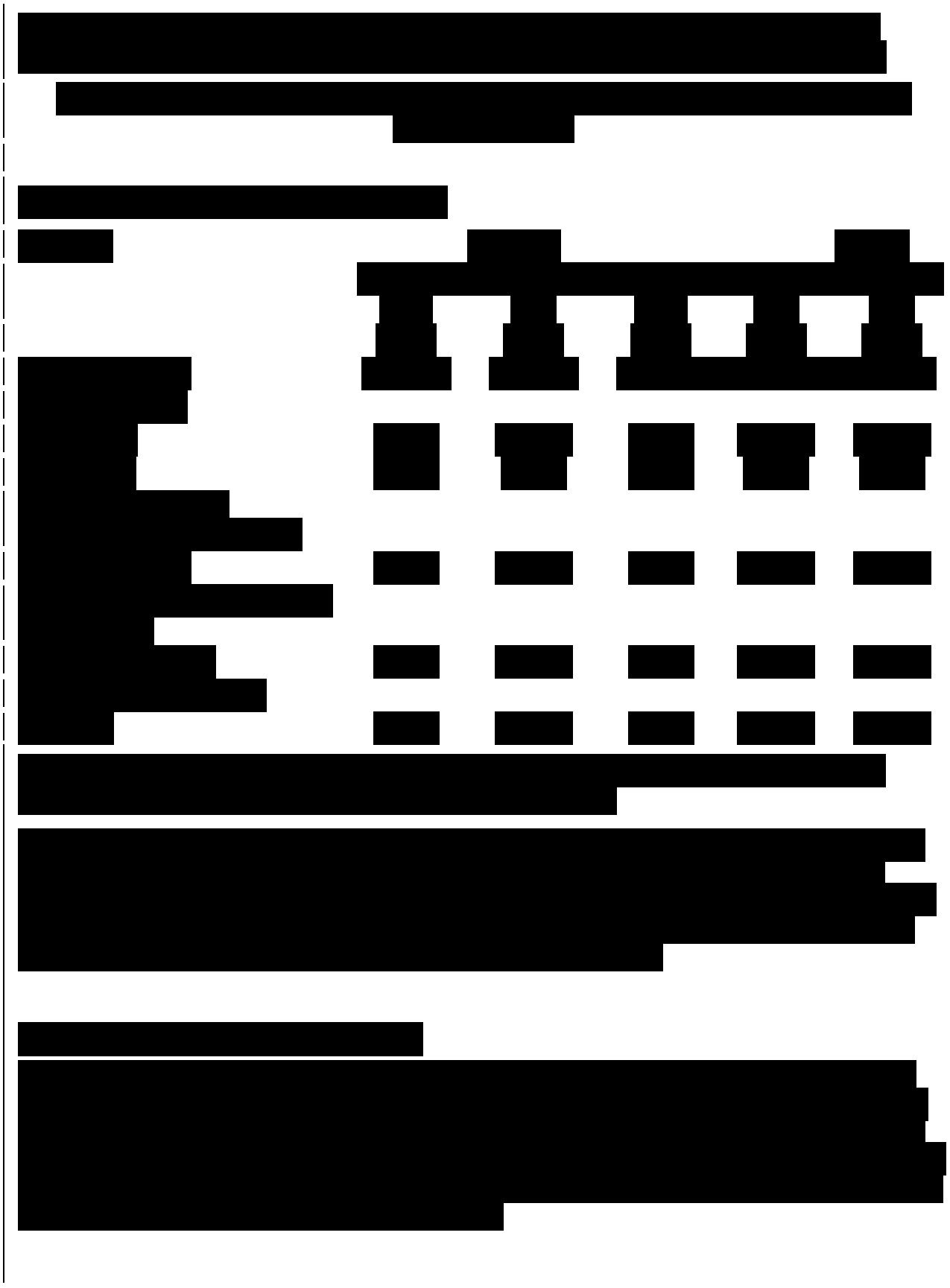

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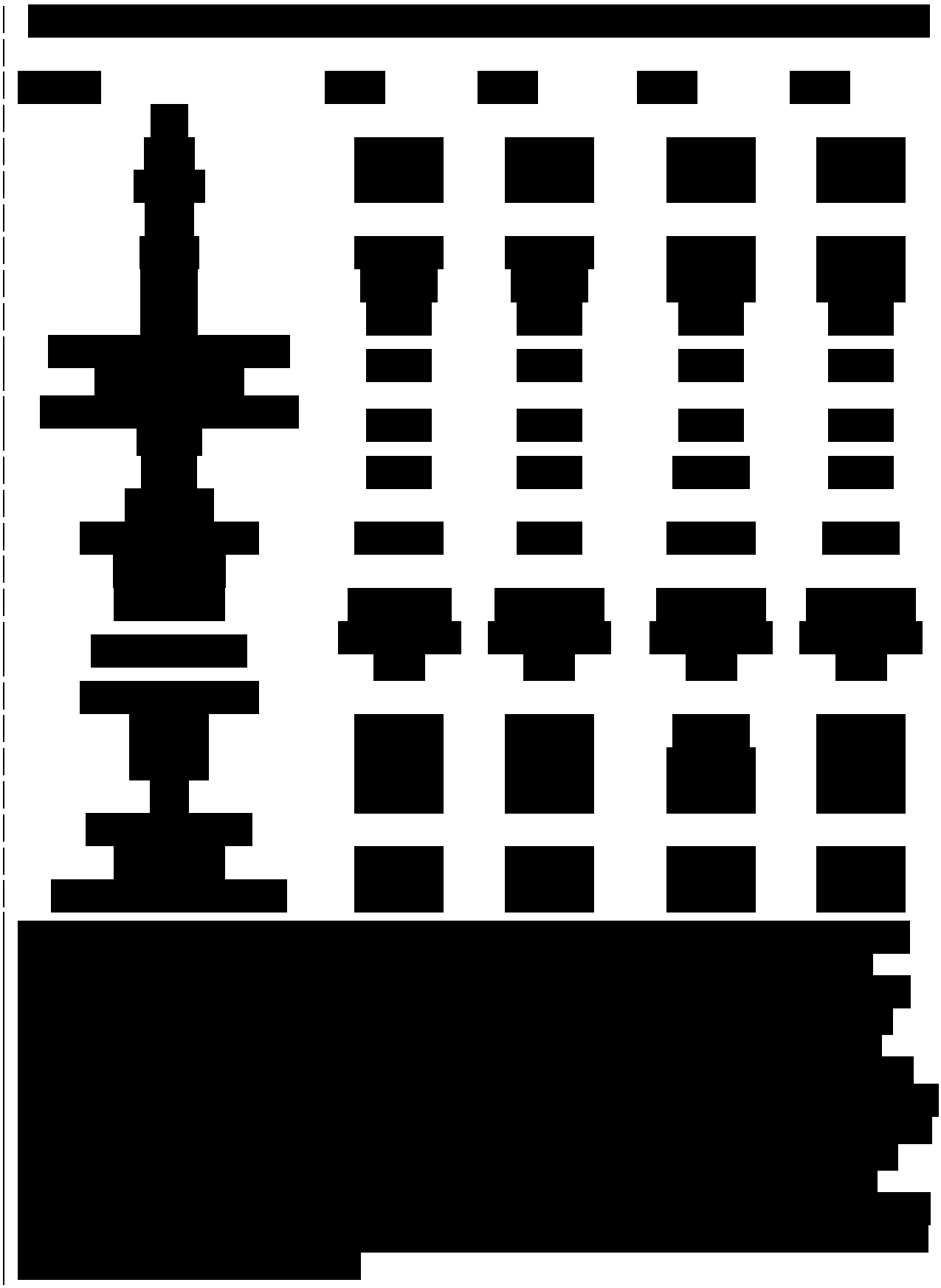
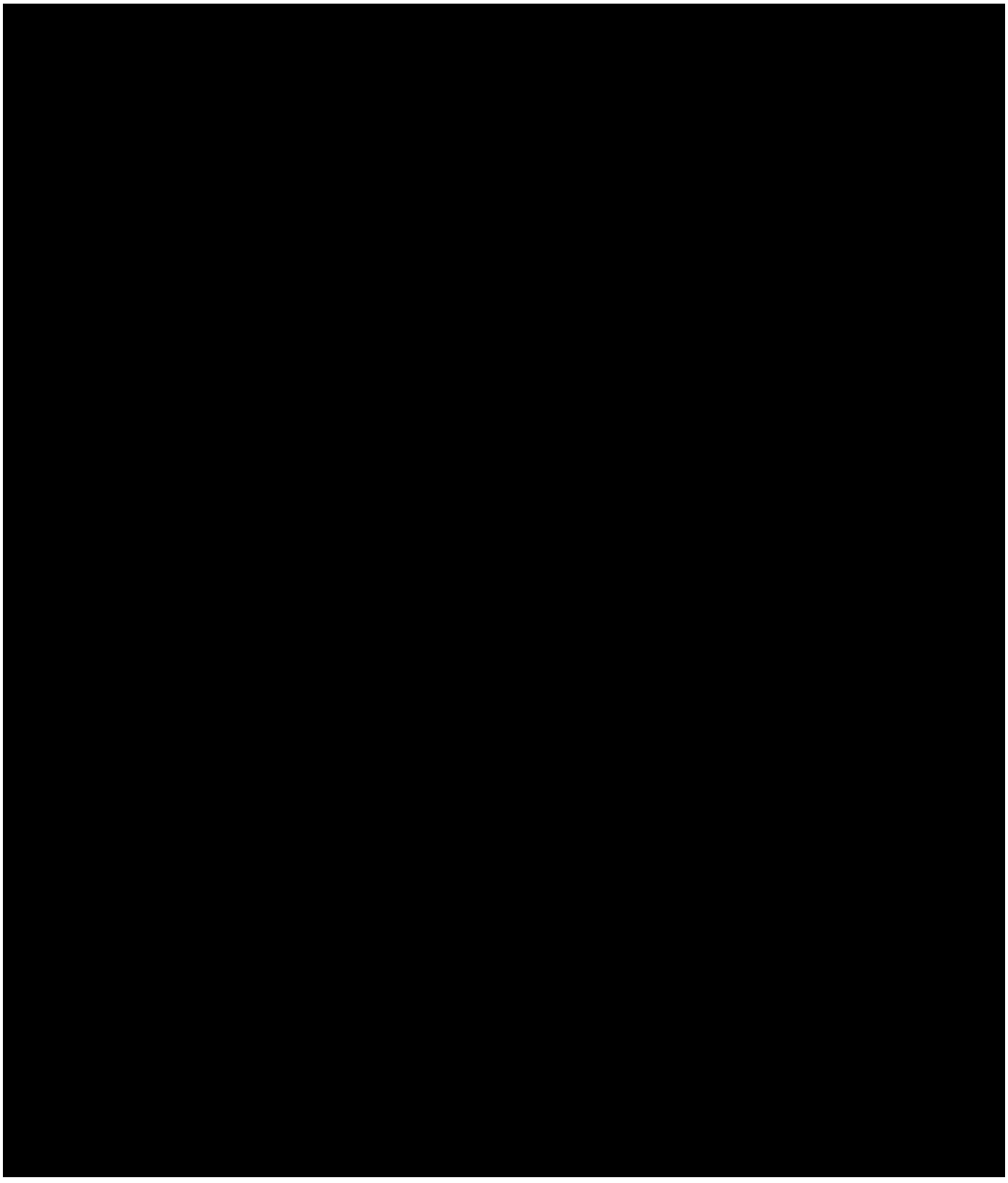
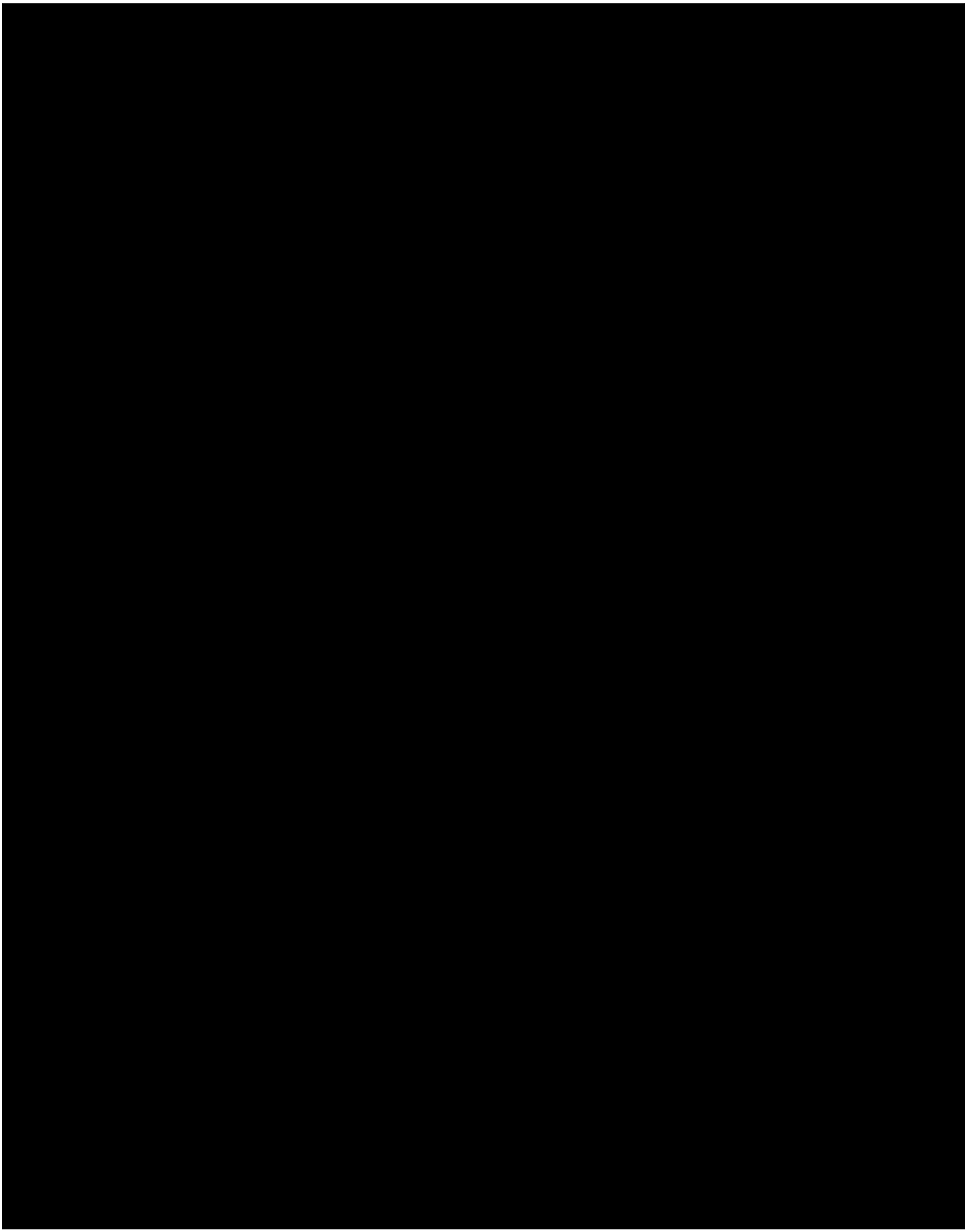
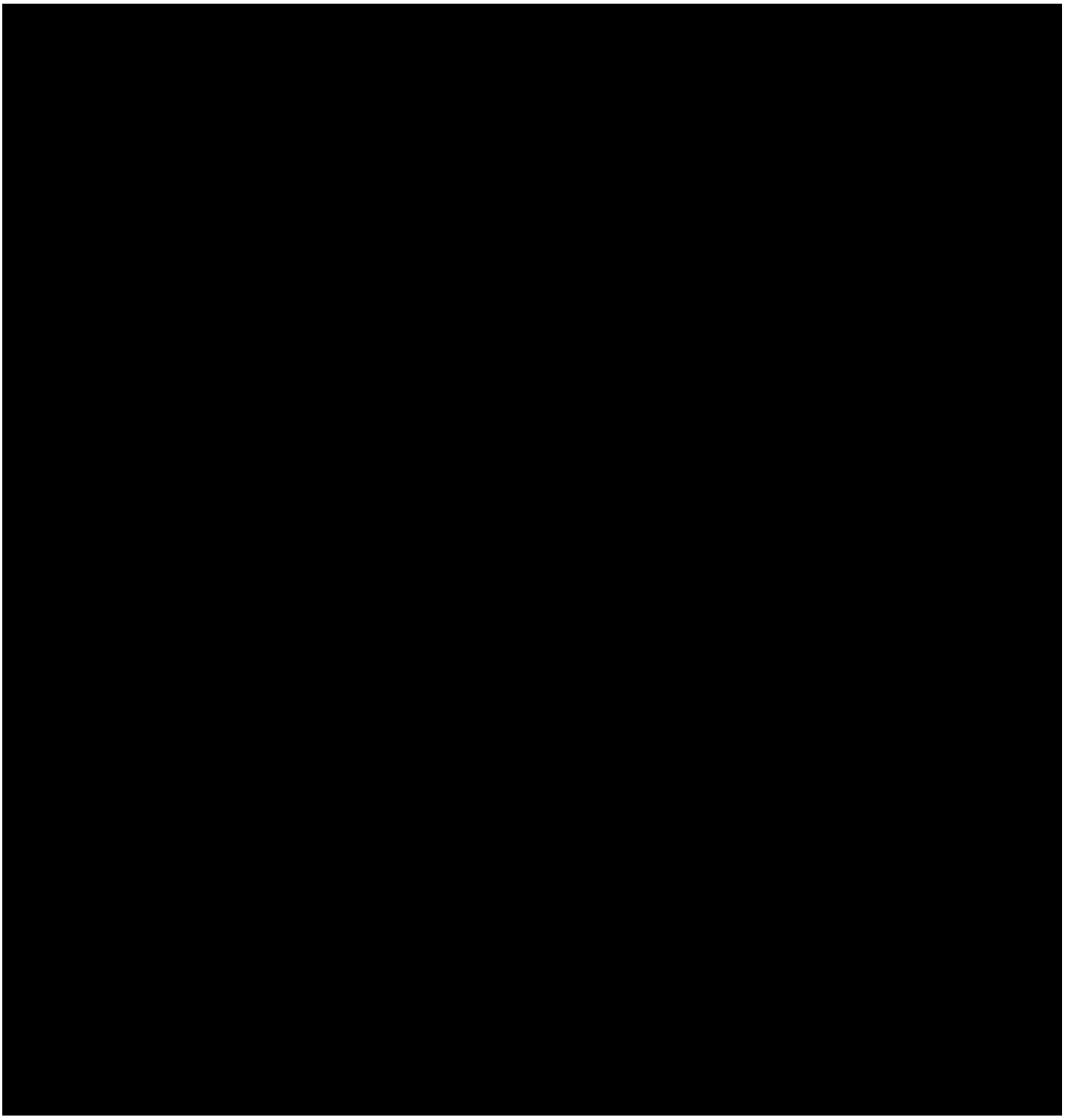








11 APPENDICES

11.1 Appendix 1: Metrics for Assessing Sensation and Function

11.1.1 The STAR Questionnaire

Following are some concerns that some people have said are important after getting medication to numb their mouth. By circling one (1) number per line, please indicate how much of a problem each statement is for you right now. **If any of the questions ask about something you are not in a position to do right now (e.g., eating, drinking), please answer to the extent to which you think it would be a problem for you.**

	Not at all	A little bit	Some -what	Quite a bit	Very much
I feel like my lip, tongue or cheek is swollen	0	1	2	3	4
I am uncomfortable with how my lip, tongue or cheek feels	0	1	2	3	4
I am concerned about biting my lip, tongue or cheek	0	1	2	3	4
I have trouble drinking from a glass or cup	0	1	2	3	4
I have trouble eating	0	1	2	3	4
I have trouble speaking clearly	0	1	2	3	4
I have trouble smiling	0	1	2	3	4
I am concerned about drooling	0	1	2	3	4
I am concerned about how long my numbness will last	0	1	2	3	4
I am concerned about my ability to speak at work or home	0	1	2	3	4
I am concerned about the way my mouth might look to others	0	1	2	3	4
The numbness I feel now would cause me to avoid social activities	0	1	2	3	4

Instructions for administration of the STAR questionnaire are provided on the next page. Items 2, 3, 4, 6, 7, 8 and 11 were evaluated separately as the STAR-7 score.

The coordinator or study staff person will read the following instructions to each subject on the day of testing before the anesthetic has been given but after they have made their first rating of lip and other tissue sensations.

"It is very important to both the integrity and quality of this research that you answer the Soft-Tissue Anesthesia Recovery (STAR) questionnaire 11 times today. This short questionnaire is based on the sensations and potential problems that a typical dental patient may have because their lip or some other part of their face or mouth is numb after they leave the dentists office. You will probably have numbness in your lip and possibly other places in or around your mouth because of the local anesthetic you will receive today. This numbness will continue after the dentist finishes the procedure you are scheduled for, and may last as long as five hours. Your answers to the questionnaire will help us understand how much people are bothered by the numbness, how numbness might influence the way people spend their time after leaving the dental clinic, and if it impairs the way you function at work, speak or other regular activities of daily living."

"Please answer the questions the way you feel at the exact moment you are taking the questionnaire. It is very important to think about the effects you are having now and not how you either felt earlier or believe you will feel in a few hours. Your answers may be different each time you take the questionnaire. Here is the questionnaire. Please answer all the questions now and, if you have questions about this, please ask me."

[*The staff member hands one copy of the STAR to the subject, who then answers the questionnaire by marking with pen and the staff member collects the completed form and checks for completion and proper method of marking answers*]

You will be given the same questionnaire again in approximately 30 minutes.

"We greatly appreciate your volunteering to help us in this research project."

11.1.2 Functional Assessment Battery and Instructions

Four functions will be tested in a standardized sequence at specified times in the protocol: smiling, speaking, drinking, and drooling.

- Smiling, speaking, and drinking will be rated as normal or abnormal by both an observer and the subject
- Drooling will be rated as present or absent by the observer (actually observed) and by querying the subject regarding drooling in time since last assessment.

Definitions:

- Normal for each function will be defined as same as or equivalent to performance of test prior to dental procedure (baseline)
- Abnormal for each function will be defined as not normal, i.e., different from baseline; examples are given under instructions for rating of each test
- Presence of drooling will be interpreted as abnormal for that function
- "Normal function" will be defined as normal ratings for all four functions
- "Abnormal function" will be defined as one or more abnormal ratings

Overall instruction: "These tests are meant to evaluate your ability to perform various functions; you may decline or "opt out" of any test for any reason. You should rate each test as normal or abnormal. Think of this rating in terms of true or false; normal = true and abnormal = false; your first impression is probably correct. The order of these tests will always be the same: 1) smiling, 2) speaking, 3) drinking, and 4) drooling. Any questions?"
Respond to any question.

Smiling Test

Instruction to subject: "Give me a big smile; rate any change from normal feeling when you smile as abnormal"

Rating by observer: look for symmetry; rate any asymmetry as abnormal

Speaking Test

Instruction to subject: "Please read these 3 sentences out loud at your usual pace; if certain words are difficult to say, sound funny to you, or are slurred, rate this test as abnormal"

1. Suzie sewed zippers on two new dresses at Bessie's house.
2. She usually rushes to push the garage door closed.
3. Ruth caught a cold because she wouldn't wear her new, warm, wool coat.

Rating by observer: listen for articulation of words or speech sounds; words containing "r", "l" and "s" are often affected; if certain words or speech sounds are slurred or not understandable, circle those words on the source document and rate as abnormal.

Drinking Test

Instruction to subject: "Drink these 3 ounces of water from this glass (or cup) without interruption; rate any difficulty in drinking as abnormal"

Rating by observer: observe drinking and then observe for 1 additional minute; rate any cough, choking, or interruption to breathe as abnormal; rate any leakage or spillage as abnormal under drooling.

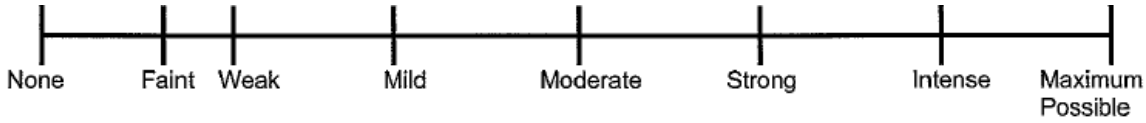
Drooling Test

Instruction to subject: "I will observe you for drooling while doing certain tests at the selected times during the study period; I will ask you if you have noticed any drooling within 15 minutes of these tests"

Rating by observer: rate the presence of drooling that is observed as abnormal under the observer rating; be especially aware of the period immediately following the drinking test; rate any reported presence of drooling within 15 minutes as abnormal under the subject rating.

11.1.3 Heft-Parker Visual Analog Scale

Pain in three locations was to be rated by subjects using the Heft-Parker visual analog scale (VAS: the site of administration of the study drug, the site of the dental procedure, and the side of the mouth on which the dental procedure was performed. The scale used in the clinical trials was to have been 170 mm in length and look like the one below.



11.1.4 Wong-Baker Pain Rating Scale (W-B PRS)

References

[1] American Academy of Pediatric Dentistry Council on Clinical Affairs: Guideline on Appropriate Use of Local Anesthesia for Pediatric Dental Patients; Pediatric Dentistry 27 (7 Reference Manual): 101-106.

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/s/

Arthur Simone
5/5/2008 06:04:42 PM
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Rigoberto Roca
5/6/2008 09:44:13 PM
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I concur with Dr. Simone's review.