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RESEARCH**

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MEDICAL REVIEW



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Division of Anesthesia, Analgesia and Rheumatology Products
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CLINICAL REVIEW

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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.

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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.

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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-minute 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 Dentistry¹ 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]

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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]

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[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 █ years old and older. The proposed dosing regimen is based on the amount of local anesthetic-vasoconstrictor injected as follows:

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- 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 █ years of age or <15 kg is not recommended.

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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]

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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 of 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 cartridge 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.

b(4)

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.

b(4)

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 *in-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.

b(4)

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 Enrollment	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 Enrollment	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 Enrollment	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 undergoing 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 █ years of age and older.

b(4)

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

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

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 <i>p</i> -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 <i>p</i> -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)
Apthous 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 $\geq 1\%$ 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 fasciculations 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.

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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 none 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:

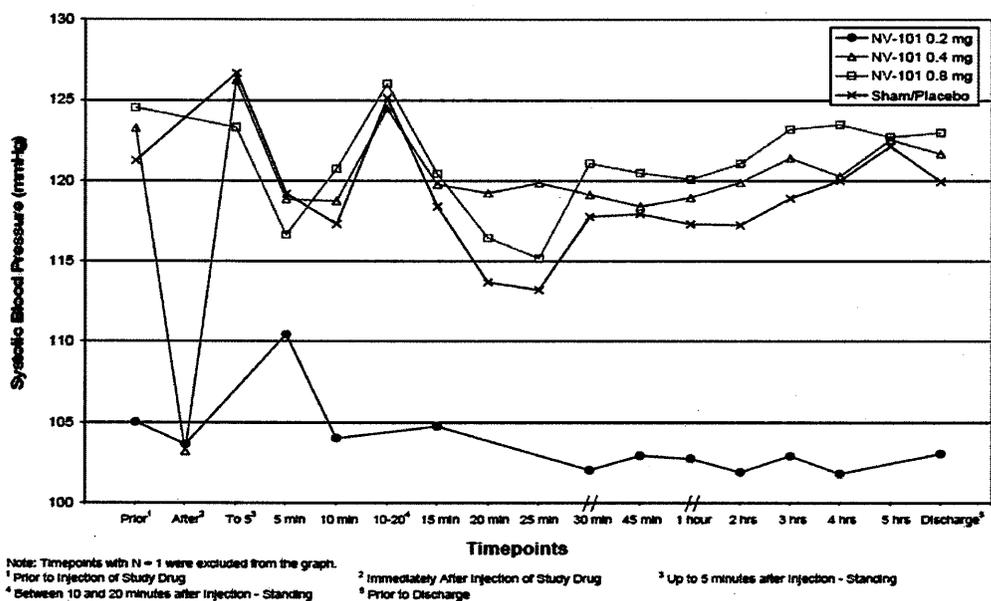
1. comparisons of changes from the baselines in the mean blood pressures and heart rates following study drug administration, which were assessed separately for subjects undergoing and not undergoing dental procedures
2. comparisons of proportions of subjects whose changes from baseline values for blood 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.

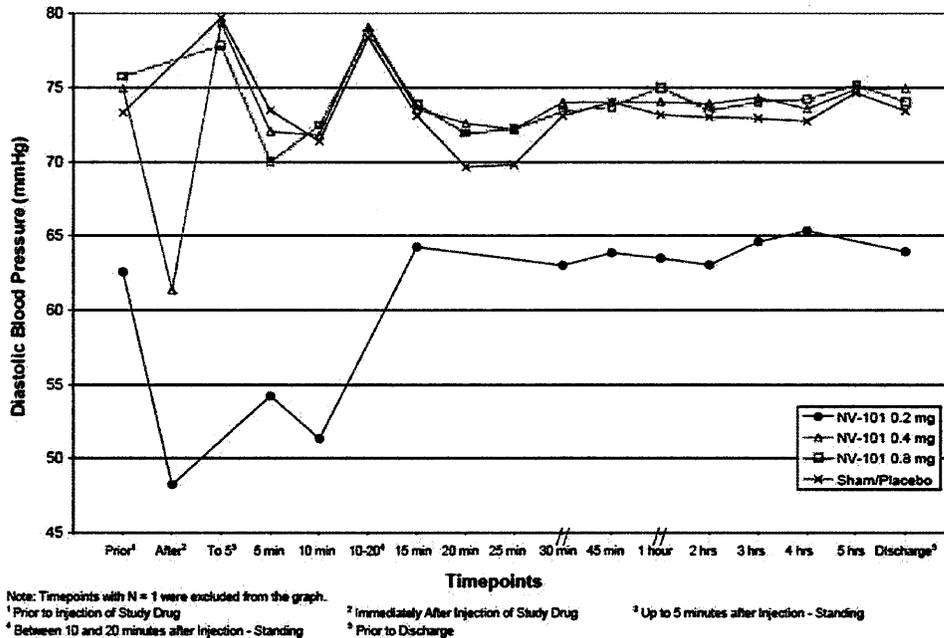
Figure 1: Mean systolic blood pressures over time for dental subjects (Figure 1 from NDA ISS, p.105)



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

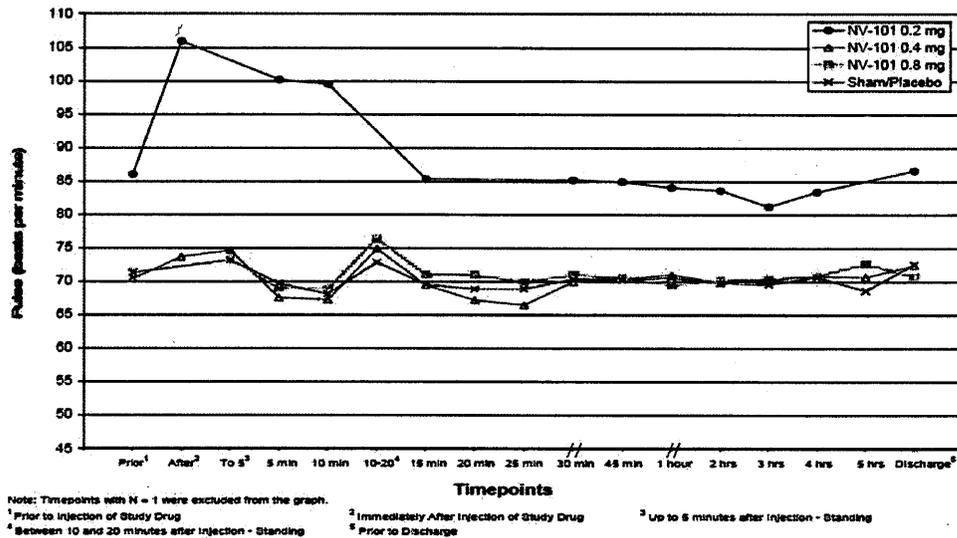
taken only in the NOVA 05-PEDS-PK study with subjects in supine position and under general anesthesia or conscious sedation. These findings suggest no untoward effects of NV-101 on either systolic or diastolic blood pressure in the overall cohort of dental subjects.

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.

b(4)

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)

Pain Category ^C	NV-101 ^A				Control ^B
	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 phenomena 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.