

## 10.1.7 NOVA 03-001

### **“A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of NV-101 in Dental Patients”**

#### 10.1.7.1 Study Design

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

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

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

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

### 10.1.7.2 Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### 10.1.7.3 Discussion and Conclusions

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

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

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

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

## 10.1.8 NOVA 05-PEDS

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

#### 10.1.8.1 Study Design

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

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

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

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

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

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

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

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

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

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

#### 10.1.8.2 Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### 10.1.8.3 Discussion and Conclusions

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

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

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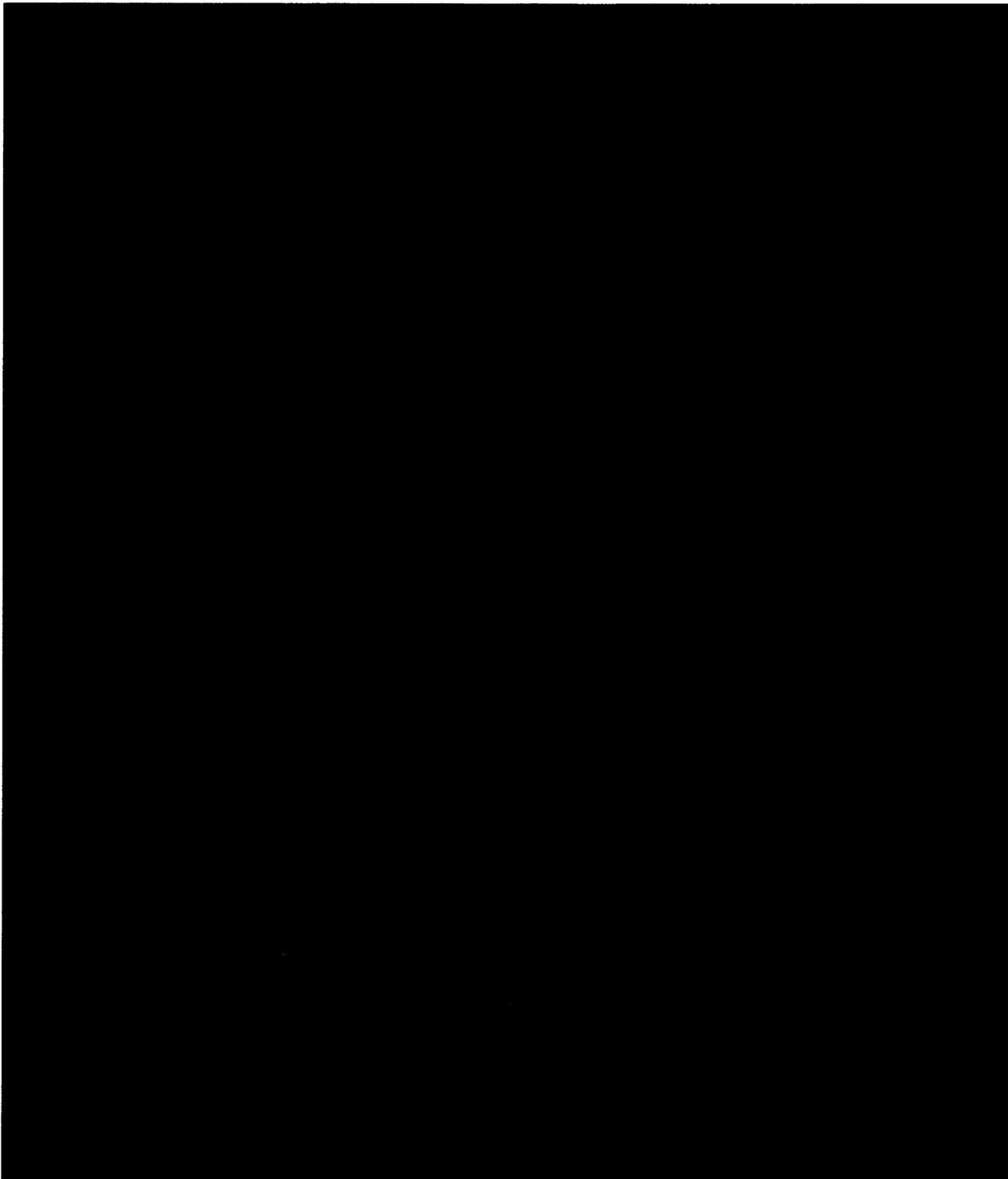
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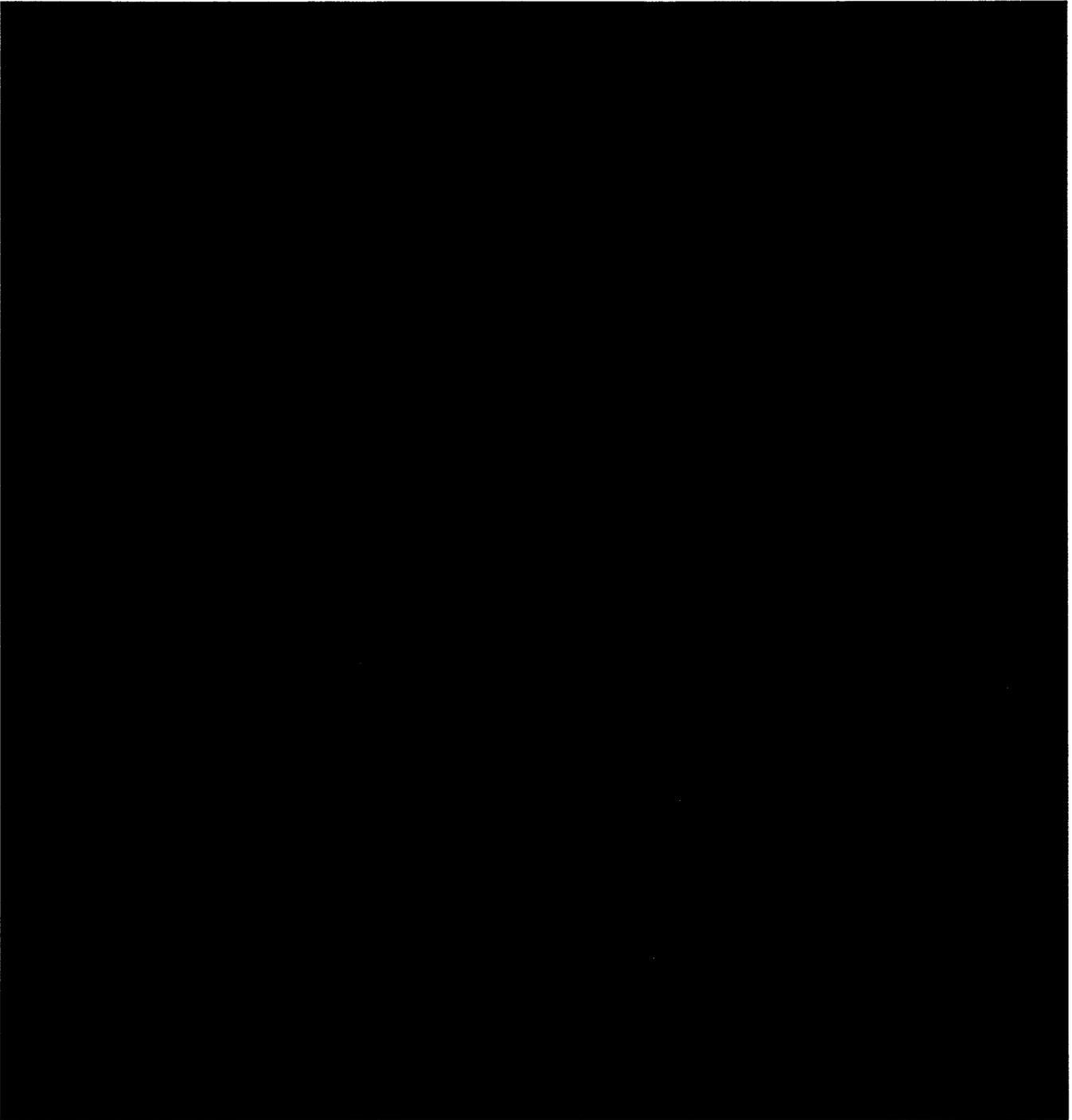
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## **11 APPENDICES**

### **11.1 Appendix 1: Metrics for Assessing Sensation and Function**

### 11.1.1 The STAR Questionnaire

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

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

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

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

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

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

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

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

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

## 11.1.2 Functional Assessment Battery and Instructions

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

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

### Definitions:

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

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

Respond to any question.

### Smiling Test

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

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

### Speaking Test

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

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

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

**Drinking Test**

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

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

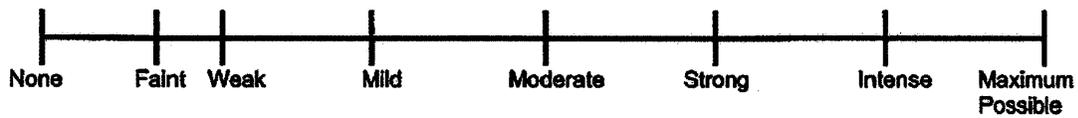
**Drooling Test**

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

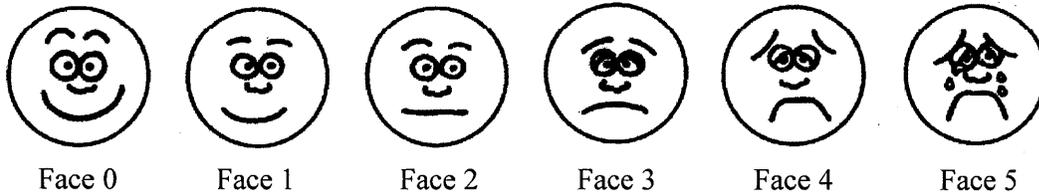
**Rating by observer: rate the presence of drooling that is observed as abnormal under the observer rating; be especially aware of the period immediately following the drinking test; rate any reported presence of drooling within 15 minutes as abnormal under the subject rating.**

### 11.1.3 Heft-Parker Visual Analog Scale

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



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



## References

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

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/s/

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Arthur Simone  
5/5/2008 06:04:42 PM  
MEDICAL OFFICER

Rigoberto Roca  
5/6/2008 09:44:13 PM  
MEDICAL OFFICER  
I concur with Dr. Simone's review.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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## Memorandum

*DATE:* January 16, 2008

*FROM:* Fred Hyman, D.D.S. M.P.H, Dental Officer, DDDP

*THROUGH:* John Kelsey, D.D.S., M.B.A., Dental Team Leader, DDDP

*THROUGH:* Susan Walker, M.D., Division Director, DDDP

*cc:* Julie Beitz, M.D., Office Director, ODE III  
Bronwyn Collier, ADRA, ODE III  
Margo Owen, Supervisory PM, DDDP

*TO:* Dominic Chiapparino, PhD., Project Manager  
Division of Anesthetics, Analgesics and Rheumatology Products

*SUBJECT:* Request for Information about a Local Anesthetic Reversal Agent in  
Pediatric Dentistry

DDDDP Consult #1060

Received Date: January 10, 2008

Requested Completion Date: February 5, 2008

### **Purpose of Consult**

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) is currently reviewing NDA 22-159, phentolamine mesylate solution for submucosal injection (Trade Name: OraVerse). The drug is intended to reverse the soft tissue anesthesia associated with dental injections of local anesthetic agents. In dental practice, the majority of dental restorative work is performed with the aid of local anesthesia, which prevents the patient from experiencing pain that would normally be associated with mechanical removal of dental structure. The loss of sensation created by the local anesthetic generally lingers beyond the time required to complete the procedure. Many patients find the extended loss of sensation unpleasant because it often results in difficulties including unclear speech, drooling, and other discomfort associated with the loss of sensation in the tongue, lips, and cheeks.

Phentolamine is currently being reviewed as an agent that significantly reduces the time for the sensation to return after the dental procedure has been completed. The clinical testing in the trials encompassed two sets of efficacy criteria: 1) a test of the amount of time subsequent to the administration of phentolamine until subjects could feel a physical touch applied to the area under study, and 2) an evaluation of improved function including subjects' abilities to speak clearly and refrain from drooling. Clinical trials were conducted in both adults and children as young as 5 years of age. According to the clinical reviewer in DAARP, the subjective portion of the evaluation was not validated in children. The DAARP review team is requesting assistance from DDDP with the assessment of the risk-benefit ratio of dental anesthesia reversal in children. Specifically, DAARP is requesting citation of published literature for benefits of local anesthesia reversal in children.

### **Request from Division of Anesthesia, Analgesia, and Rheumatology Products**

Following is the verbatim request from DAARP to DDDP:

*Oraverse, (phentolamine mesylate solution for submucosal injection) is currently under review in the Division of Analgesia, Anesthesia and Rheumatology Products as NDA 22-159 with the indication of reversal of local anesthesia in dentistry. Novalar Pharmaceuticals, Inc, the sponsor of this NDA, has claimed that there is a need for this drug in the pediatric population. Is there published literature in which benefits of local anesthesia reversal in children for dental procedures is discussed?*

### **Response**

#### *Summary*

Yes, a literature search reveals that several articles have been published about injury to soft tissue in children by biting and chewing on their lips, tongue and cheeks. In addition, the American Academy of Pediatric Dentistry has issued a guidance document entitled *Guideline on Appropriate Use of Local Anesthesia for Pediatric Dental Patients* in which the authors state that "self-induced soft tissue trauma is an unfortunate clinical complication of local anesthetic use in the oral cavity" and recommend that "residual soft tissue anesthesia should be minimized in pediatric and special health care needs patients to decrease risk of self-inflicted postoperative injuries."

*Statement Support*

American Academy of Pediatrics: Guideline on Appropriate Use of Local Anesthesia for Pediatric Dental Patients.

Young children are often confused by the residual numbness in their tongues, lips and/or cheeks after a dental procedure requiring local anesthesia is completed. Although they are routinely instructed by their dentist to be cautious about injuring these areas while anesthesia is still present, it is not uncommon for children to inadvertently bite and chew on their lips, cheeks and tongue while their normal sensation is absent, resulting in damage to the soft tissue.

Although this risk is well-known to practicing dentists, there is little published literature on the subject. The best example of a consensus on the topic can be found in a 2006 statement from the American Academy of Pediatric Dentistry (AAPD) entitled, *Guideline on Appropriate Use of Local Anesthesia for Pediatric Dental Patients*. It was written by the Council on Clinical Affairs of the AAPD and is attached to this consult. This document is one of a series of clinical guidelines that was published by AAPD in a compilation entitled Reference Manual 2005-2006. On page 104 of this manual, there is a section entitled Postoperative Soft Tissue Injury, in which the following language appears:

*“Self-induced soft tissue trauma is an unfortunate clinical complication of local anesthetic use in the oral cavity. Most lip- and cheek-biting lesions of this nature are self-limiting and heal without complications, although bleeding and infection possibly may result.”*

The section that follows is entitled Recommendations for local anesthetic complications: Recommendation #4 states:

*“Residual soft tissue anesthesia should be minimized in pediatric and special health care needs patients to decrease risk of self-inflicted postoperative injuries.”*

Other References

A PubMed search that used various combinations of the keywords “*pediatric, dental, local anesthesia, and injury*” revealed three separate articles that had high relevance to the search topic: 1) Maiwald HJ. *Bite-wounds in preschool children as complications of local anesthesia* Dtsch Stomatol. 1970 Feb;20(2):121-3; 2) Ram D, Peretz B. *Administering local anaesthesia to paediatric dental patients* Int J Paediatr Dent, 2002 Mar; 12(2):80-9; and 3) Schulte W, Merk H. *Problems and possibilities of local anesthesia in the child* Dtsch Zahnarztl Z. 1968 Dec;23(12):1336-9. However, none of the articles was in English, so they could not be evaluated for this consult. A search on the Internet using the Google search engine revealed more than ten websites of pediatric dental specialists which contains identical language in warning about care after dental treatment as follows:

*“Care of the Mouth after Local Anesthetic*

*Your child has had local anesthetic for their dental procedure. Often, children do not understand the effects of local anesthesia, and may chew, scratch, suck, or*

play with the numb lip, tongue, or cheek. These actions can cause minor irritations or they can be severe enough to cause swelling and abrasions to the tissue. Please monitor your child closely for approximately two hours following the appointment. It is often wise to keep your child on a liquid or soft diet until the anesthetic has worn off”

**Conclusion:**

Although minimal published literature can be located to substantiate the incidence of oral tissue injury in children resulting from residual local anesthesia after a dental procedure, the consensus among pediatric dentists is that this risk exists. The magnitude of the problem is sufficient that the AAPD issued a warning to dentists about the possibility of self-induced soft tissue trauma in children as a complication of local anesthetic use and advises risk minimization. Use of a product that reduces the duration of post operative local anesthesia would therefore be of medical benefit to the pediatric population.

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/s/

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Fred Hyman  
1/22/2008 12:42:13 PM  
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John Kelsey  
1/24/2008 03:59:56 PM  
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Susan Walker  
1/31/2008 09:10:50 AM  
DIRECTOR

## STUDY ENDPOINT REVIEW

|   |  |
|---|--|
| SEALD ACTION TRACK NUMBER               | 2007.002.A.00082   |
| APPLICATION NUMBER                      | NDA 22-159   |
| LETTER DATE/SUBMISSION NUMBER           | April 9, 2007  |
| PDUFA GOAL DATE                         | February 9, 2008   |
| DATE OF CONSULT REQUEST                 | August 7, 2007   |
| REVIEW DIVISION                         | Division of Anesthesia, Analgesia, and<br>Rheumatology Products (DAARP)  |
| MEDICAL REVIEWER                        | Arthur Simone  |
| REVIEW DIVISION PM                      | Geri Smith   |
| SEALD REVIEWER(S)                       | Ann Marie Trentacosti  |
| REVIEW COMPLETION DATE                  | October 22, 2007   |
| ESTABLISHED NAME                        | Phentolamine Mesylate Solution for Injection<br>(NV-101)   |
| TRADE NAME                              | OraVerse   |
| APPLICANT                               | Novalar Pharmaceuticals, Inc.  |
| ENDPOINT(S) CONCEPT(S)<br>INSTRUMENT(S) | Time to reversal of local dental anesthesia<br>Soft Tissue Anesthesia Recovery (STAR)<br>Questionnaire; Functional Assessment Battery<br>(FAB) |
| INDICATION<br>INTENDED POPULATION(S)    | Reversal of dental soft tissue anesthesia<br>Patients — years of age receiving local dental<br>anesthesia                                      |

b(4)

## STUDY ENDPOINT REVIEW

### 1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding NDA 22-159 and the proposed indication for NV-101 (OraVerse) for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of local anesthetic containing a vasoconstrictor in patients  $\geq$  12 years of age.

b(4)

Based upon the information submitted, we have the following comments:

- Novalar has not included information to ascertain that the lip/tongue palpation tests can be adequately completed by the pediatric population (<12 years of age). It has not been determined if children can comprehend the instructions, questions, and responses. The large number of efficacy assessments excluded from analysis due to lack of patient comprehension (n=37) in Study NOVA-05-PEDS, suggests that the instruments are not appropriate for this age group.
- Although Novalar selected 3 domains: sensory, perception, and function, in order to evaluate the local dental anesthetic effects in their pivotal clinical studies in patients  $\geq$  12 years of age, in the study involving children 4-12 years of age, Study NOVA-05-PEDS, only the domain of sensation was evaluated. Justification has not been submitted to suggest that the omitted perception and function assessments are not important measurements for this pediatric population. In order to adequately assess the efficacy of NV-101 in reversing the effects of dental anesthesia in the pediatric population, it is recommended that Novalar develop age-appropriate instruments which measure the sensation, perception, and function outcomes.
- The use of the 7 questions from the Soft Tissue Anesthesia Recovery (STAR) Questionnaire as a composite score to measure the impact of local dental anesthesia in adults is supported by the instrument development/validation plan submitted. Therefore, the STAR Questionnaire is an acceptable endpoint as utilized in the pivotal clinical trials for evaluating perceived clinical benefit from reversal of dental anesthesia in adults.
- The data from Study NOVA 05-SQV do not support the content validity of the STAR Questionnaire for use in patients 12-17 years of age. In study NOVA 05-SQV, several items rated by the target population in terms of commonality, obtained mean patient rated scores of <1 (1 = somewhat common) Based upon the results of this study, the STAR Questionnaire may need to be revised for use in this age group of patients.
- Novalar has not provided any information concerning the development of the Functional Assessment Battery (FAB) in order to ascertain its content validity. Therefore, SEALD cannot determine the adequacy of this instrument in terms of measuring function as a result of dental anesthesia.

## 2 ENDPOINT REVIEW

In order to establish efficacy of NV-101 in reversing the effects of local anesthesia associated with dental procedures, Novalar selected three domains of transition from anesthesia to normal in their pivotal clinical trials: sensory, perceptual, and functional.

Each domain was assessed by the following endpoints/instrument:

- Sensation: Lip/Tongue Palpation
- Perception: The Soft Tissue Anesthesia Recovery (STAR) Questionnaire:
- Functional: The Functional Assessment Battery (FAB)

The following is a review of each of these endpoints. A copy of the instrument representing each endpoint located in the Appendix.

### Lip/Tongue Palpation:

The return of normal sensation in the lip by lip palpation was the primary endpoint utilized in the pivotal clinical trials. Tongue sensation by palpation was assessed as a secondary endpoint

Lip palpation consisted of soft tapping of the upper or lower lip with the subject's index or middle finger. Subjects rated the degree of lip numbness as either "numb", "tingling", or "normal". Tingling was defined as a sensation of "pins and needles". Palpation of other soft tissues such as nose, chin and tongue were also evaluated.

### *Comments:*

*Novalar has not included information to ascertain that the lip palpation can be completed by the pediatric population. It has not been determine if children can comprehend the instructions, questions, and responses.*

### The Soft Tissue Anesthesia Recovery (STAR) Questionnaire:

The STAR Questionnaire was developed to quantify the patient's perceived clinical benefit of reversal of soft tissue anesthesia. The development process was described in "Development and Validation of the Soft Tissue Anesthesia Recovery (STAR) Questionnaire" by \_\_\_\_\_ and included in this submission. The survey was developed in a two-step process. Item generation was obtained through open-ended interviews with expert dental clinicians and results were summarized and item domain identified. A sample of 15 dental patients then completed an open-ended interview and an item rating survey that required them to rate items generated by expert clinicians according to how common the experience and relevance to soft tissues anesthesia (STA). In the second step, item reduction, a list of items was presented to two sets of expert panels, who reduced the item list.

b(4)

In part 2 of the study, the questionnaire was validated by administering a set of 12 questions to 100 adult patients undergoing dental procedures where a local anesthetic containing a vasoconstrictor was used. Patients completed the STAR Questionnaire at five time points: 1)

## STUDY ENDPOINT REVIEW

baseline: in the dental treatment center prior to receiving any treatment; 2) within 5 minutes of the completion of the dental procedure; 3) 30-45 minutes after completion of the procedure (in the dental treatment center); 4) 120 minutes after completion of the procedures (completed after leaving the dental treatment center); and 5) within 5-7 hours of leaving the dental office (i.e., a time by which they would not be expected to be experiencing STA).

Evaluation of the STAR questionnaire's reliability, validity and responsiveness to change included the following analyses:

- Factor analysis to investigate a possible underlying multidimensional structure and to determine whether or not there are items that do not significantly contribute to the underlying dimension(s)
- Internal consistency reliability using Cronbach's coefficient alpha
- Calculation of the test-retest reliability (test stability), chosen a priori as score correlation between 5 and 30 minutes, using both the Spearman correlation coefficient and the intraclass correlation coefficient (ICC)
- Concurrent validity using correlational analyses with other variables in the database
- Convergent Validity using the SF-36 Bodily Pain and other scales and the patient self-ratings of numbness and other sensations recorded post-baseline. As this was developed to be a targeted questionnaire, more responsive than generic measures, stronger correlations of the new instrument were expected with numbness ratings than with SP-36 scores.

The relationship between STAR change scores and sensation ratings on self-palpation from the patient were examined as evidence of responsiveness to change. Patients performed self-palpation of their lip, tongue, cheek, chin and nose immediately prior to each of their five assessments with the STAR.

Although the entire STAR Questionnaire was administered in the pivotal clinical studies (all 12 questions), the STAR scoring for the efficacy analysis was based on 7 of the 12 questions (questions # 2 [uncomfortable], 3 [biting], 4 [drinking], 6 [speaking], 7 [smiling], 8 [drooling], 11 [appearance to others]). The scoring using the STAR-7 responses only, was determined *a priori*.

The STAR Questionnaire was administered in clinical studies NOVA 04-100 and NOVA 04-200 at screening, before randomization to study drug, and every 30 minutes for 5 hours after study drug administration.

*Comments: The STAR Questionnaire was developed prior to the publishing of the 2006 draft FDA Guidance for Industry: "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims". In response to a special protocol assessment of the pivotal clinical trials, in 2005, DAARP informed Novalar that they concurred with the use of the STAR-7 as a basis for analyzing the clinical impact of soft tissue anesthesia.*

*Overall, the development of the STAR Questionnaire has been consistent with the principles of the 2006 draft FDA Guidance for Industry: "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims". Although the STAR-7 version was*

## STUDY ENDPOINT REVIEW

recommended by the FDA, Novalar chose to administer the entire instrument, STAR-12, but only use the response to the 7 FDA recommended questions in obtaining an overall score. Since this choice of scoring was selected a priori, it is acceptable.

In considering the interpretation of the STAR-7, it would have been helpful, but not necessary, if the sponsor included a global question, in order to ascertain if the patient felt that the recovery from anesthesia was complete.

Study NOVA 05-SQV was conducted to evaluate the content validity of the STAR Questionnaire in adolescents (ages 12 to 17 years) undergoing dental procedures. In the study, 15 patients with lingering soft tissue anesthesia were interviewed. The study consisted of 3 parts. In part 1, patients were read the items of the STAR Questionnaire and asked how common the items (rating options were 0=Not at all; 1=Somewhat; 2=Very much; 3=Extremely). In Part 2, patients were asked if the items were appropriate and if not, how they would change them. (rating options were 0=Not at all; 1=Somewhat; 2=Very much; 3=Extremely). In Part 3, patients were asked if they had any other concerns that were important to them but not addressed. Results of Part 1 and 2 are delineated in Table 1.

Table 1. Study NOVA 05-SQV Item Rating:

| Item  | How <b>common</b> is this problem?<br>Not at all = 0<br>Somewhat = 1<br>Very much = 2<br>Extremely = 3 |   | How <b>relevant</b> is this question?<br>Not at all = 0<br>Somewhat = 1<br>Very much = 2<br>Extremely = 3 |   |
|---|--|---|---|---|
|   | I feel like my lip, tongue or cheek is swollen   | 0 = 1 (6.7%)<br>1 = 4 (26.7%)<br>2 = 8 (53.3%)<br>3 = 2 (13.3%) | Mean = 1.73<br>Median = 2<br>SD = .8<br>Range = 0-3   | 0 = 2 (13.4%)<br>1 = 8 (53.3%)<br>2 = 5 (33.3%)<br>3 = 0 (0%) |
| I am uncomfortable with how my lip, tongue or cheek feels                                       | 0 = 4 (26.7%)<br>1 = 8 (53.3%)<br>2 = 3 (20%)<br>3 = 0 (0%)  | Mean = .93<br>Median = 1<br>SD = .7<br>Range = 0-2              | 0 = 2 (13.3%)<br>1 = 7 (46.7%)<br>2 = 5 (33.3%)<br>3 = 1 (6.7%)   | Mean = 1.33<br>Median = 1<br>SD = .82<br>Range = 0-3          |
| I am concerned about biting my lip, tongue or cheek   | 0 = 5 (33.4%)<br>1 = 3 (20%)<br>2 = 5 (33.3%)<br>3 = 2 (13.3%)   | Mean = 1.27<br>Median = 1<br>SD = 1.1<br>Range = 0-3            | 0 = 1 (6.7%)<br>1 = 5 (33.3%)<br>2 = 5 (33.3%)<br>3 = 4 (26.7%)   | Mean = 1.8<br>Median = 2<br>SD = .94<br>Range = 0-3           |
| I have trouble drinking from a glass or cup   | 0 = 5 (33.3%)<br>1 = 7 (46.7%)<br>2 = 2 (13.3%)<br>3 = 1 (6.7%)  | Mean = .93<br>Median = 1<br>SD = .88<br>Range = 0-3             | 0 = 1 (6.7%)<br>1 = 8 (53.3%)<br>2 = 3 (20%)<br>3 = 3 (20%)   | Mean = 1.53<br>Median = 1<br>SD = .92<br>Range = 0-3          |
| I have trouble eating   | 0 = 8 (40%)<br>1 = 8 (53.3%)<br>2 = 1 (6.7%)<br>3 = 0 (0%)   | Mean = .87<br>Median = 1<br>SD = .62<br>Range = 0-2             | 0 = 1 (6.7%)<br>1 = 5 (33.3%)<br>2 = 5 (33.3%)<br>3 = 4 (26.7%)   | Mean = 1.8<br>Median = 2<br>SD = .94<br>Range = 0-3           |
| I have trouble speaking clearly   | 0 = 10 (66.6%)<br>1 = 4 (26.7%)<br>2 = 1 (6.7%)<br>3 = 0 (0%)  | Mean = .4<br>Median = 0<br>SD = .83<br>Range = 0-2              | 0 = 4 (26.7%)<br>1 = 4 (26.7%)<br>2 = 6 (33.3%)<br>3 = 2 (13.3%)  | Mean = 1.33<br>Median = 1<br>SD = 1.05<br>Range = 0-3         |
| I have trouble smiling  | 0 = 3 (20%)<br>1 = 6 (40%)<br>2 = 4 (26.7%)<br>3 = 2 (13.3%)   | Mean = 1.33<br>Median = 1<br>SD = .98<br>Range = 0-3            | 0 = 3 (20%)<br>1 = 8 (53.3%)<br>2 = 3 (20%)<br>3 = 1 (6.7%)   | Mean = 1.13<br>Median = 1<br>SD = .83<br>Range = 0-3          |
| I am concerned about drooling   | 0 = 9 (60%)<br>1 = 2 (13.3%)<br>2 = 3 (20%)<br>3 = 1 (6.7%)  | Mean = .73<br>Median = 0<br>SD = 1.03<br>Range = 0-3            | 0 = 2 (13.3%)<br>1 = 7 (46.7%)<br>2 = 2 (13.3%)<br>3 = 4 (26.7%)  | Mean = 1.53<br>Median = 1<br>SD = 1.06<br>Range = 0-3         |
| I am concerned about how long my numbness will last   | 0 = 2 (13.4%)<br>1 = 6 (40%)<br>2 = 5 (33.3%)<br>3 = 2 (13.3%)   | Mean = 1.47<br>Median = 1<br>SD = .92<br>Range = 0-3            | 0 = 0 (0%)<br>1 = 9 (60%)<br>2 = 3 (20%)<br>3 = 3 (20%)   | Mean = 1.6<br>Median = 1<br>SD = .83<br>Range = 1-3           |
| I am concerned about my ability to speak at work, home or school                                | 0 = 8 (53.3%)<br>1 = 5 (33.3%)<br>2 = 1 (6.7%)<br>3 = 1 (6.7%)   | Mean = .87<br>Median = 0<br>SD = .9<br>Range = 0-3              | 0 = 2 (13.3%)<br>1 = 7 (46.7%)<br>2 = 4 (26.7%)<br>3 = 2 (13.3%)  | Mean = 1.4<br>Median = 1<br>SD = .91<br>Range = 0-3           |
| I am concerned about the way my mouth might look to others                                      | 0 = 4 (26.7%)<br>1 = 5 (33.3%)<br>2 = 3 (20%)<br>3 = 3 (20%)   | Mean = 1.33<br>Median = 1<br>SD = 1.11<br>Range = 0-3           | 0 = 2 (13.4%)<br>1 = 9 (60%)<br>2 = 2 (13.3%)<br>3 = 2 (13.3%)  | Mean = 1.27<br>Median = 1<br>SD = .88<br>Range = 0-3          |
| The numbness I feel now would cause me to avoid social activities (e.g. going out with friends) | 0 = 11 (73.3%)<br>1 = 4 (26.7%)<br>2 = 0 (0%)<br>3 = 0 (0%)  | Mean = .27<br>Median = 0<br>SD = .46<br>Range = 0-1             | 0 = 5 (33.3%)<br>1 = 4 (26.7%)<br>2 = 6 (40%)<br>3 = 0 (0%)   | Mean = 1.07<br>Median = 1<br>SD = .88<br>Range = 0-2          |

## STUDY ENDPOINT REVIEW

In Part 3 of the study, patients were allowed to nominate any other symptoms or concerns that were important to them other than those specifically named in the survey. Below is a summary of every symptom named by these 15 patients. Each line represents a single mention by a single patient.

- Nose got numb
- Whole cheek wasn't numb, area around hp only
- Lip felt more swollen than it actually was Nervous about the study but it was fine
- Why did the numbness last so long this time?

Patients were allowed to offer suggestions for appropriate wording. All 15 patients found the items to be worded appropriately and no participant offered suggestions to change any items.

The study report concluded that the current adult STAR is appropriate for adolescent patient and does not lack any important or relevant content areas. However, after reviewing the original STAR items, only one item (#10) was chosen for modification: "or school" was added ("I am concerned about my ability to speak at work, home, or school").

*Comments: The data do not support the conclusion that the STAR does not lack any important or relevant content areas. In considering whether an item is common or relevant, the item should be at least somewhat common or relevant (rating of  $\geq 1$ ). However, this was not observed with all items of the instrument. Some of the items were noted to have mean common averages of  $< 1$  (somewhat common). Items with a  $< 1$  common rating included "I am concerned about drooling" (0.73 common rating) and I have trouble speaking clearly (0.4 common rating). In addition, none of the items received mean relevant scores of  $> 2$  or very relevant. The results of the study suggest that not all of the items of the STAR Questionnaire (including some of the 7 which were utilized to obtain a composite score in the clinical trials) may be appropriate for the 12 to 17 year old age group and that the content validity of the instrument for this population has not been fully established.*

### The Functional Assessment Battery (FAB):

The FAB is a test which includes both patient and observation assessments. The FAB was designed to measure the functional effects of local anesthesia and consisted of 4 individual tests: smiling, speaking, drinking, and drooling. Eating was not included because of the safety concern (accidental injury). Drinking was tested using the 3-ounce water test. Speaking was tested by the Fisher-Logemann test which uses the standard sentences that require articulation of sounds requiring normal motor/sensory function of the tongue. Smiling and drooling were assessed by a visual observation tool. The FAB was considered abnormal if 1 or more of the individual tests was considered abnormal.

The ability of the FAB to assess the presence of functional impairment, as well as its correlation with the STAR questionnaire was tested in Study NOVA 05-FAB-1. The study was designed in 2 stages: stage 1 evaluated the prevalence of an abnormal FAB at the end of the dental procedure in 12 subjects; stage 2 further evaluated the prevalence of an abnormal FAB at the end of the dental procedure and explored the temporal relationship of the FAB to STAR-7 score of zero and lip sensation in 40 subjects.

## STUDY ENDPOINT REVIEW

Prior to the dental procedure, there was complete agreement between subject and observer.

- At 5 minutes after the completion of the dental procedure, agreement between subject and observer was 67% for normal ratings and 95% for abnormal ratings for smiling;
- agreement was 0% for normal ratings and 59% for abnormal ratings for speaking;
- agreement was 50% for normal ratings and 50% for abnormal ratings for drinking;
- agreement was 92% for normal ratings and 91% for abnormal ratings for drooling.
  
- At 1 hour after the completion of the dental procedure, agreement between subject and observer was 0% for normal ratings and 86% for abnormal ratings for smiling;
- agreement was 50% for normal ratings and 50% for abnormal ratings for speaking; agreement was 73% for normal ratings and 77% for abnormal ratings for drinking;
- agreement was 100% for normal ratings and 100% for abnormal ratings for drooling
  
- At 2 hours after the completion of the dental procedure, agreement between subject and observer was 73% for normal ratings and 77% for abnormal ratings for smiling;
- agreement was 75% for normal ratings and 50% for abnormal ratings for speaking;
- agreement was 63% for normal ratings and 25% for abnormal ratings for drinking;
- agreement was 93% for normal ratings and 89% for abnormal ratings for drooling.

Study report conclusions from Stage 1 are noted below:

- FAB defines a deficit in one or more functions in the vast majority of subjects over the first 2 hours after completion of the dental procedure.
- The functional deficit measured by FAB changes over time.
- Subject ratings of abnormal tend to be higher than observer ratings of abnormal.
- Agreement between subject and observer ratings is higher for smiling and drooling than for drinking and speaking
- Agreement between subject and observer ratings is higher at 5 minutes and 1 hour than at 2 hours.

As noted in the study report, Stage 2 results showed that:

- The median time for the return of normal function for subject-rated assessments was 2:30 for mandibular dental procedures (range of 0:00 to 4:30) and 3:00 for maxillary procedures (range of 0:00 to 4:30).
- The median time for the return of normal function for observer-rated assessments was 2:30 for mandibular dental procedures (range of 1:00 to 4:00) and 2:30 for maxillary procedures (range of 1:30 to 5:00).
- The median time for the return of normal lip sensation was 2:55 for mandibular dental procedures (range of 0:50 to 5:00) and 3:35 for maxillary procedures (range of 2:00 to 4:40).
- The median time for the STAR-7 score to return to zero was 2:45 for mandibular dental procedures (range of 0:30 to 5:00) and 3:30 for maxillary procedures (range of 1:00 to 4:30).

Statistically significant ( $p < 0.05$ ) correlations were found for all possible pairs of time to event endpoints. The highest estimated Pearson correlation coefficient (R) was 0.84, which occurred between the time to normal lip sensation and subject-rated time to normal function endpoints.

## STUDY ENDPOINT REVIEW

The percentage of variation explained (as measured by R squared) among the pairs of endpoints ranged from 35% to 71%.

*Comments: Novalar has not provided any information concerning the development of the FAB, especially with respect to the content validity, in order to adequately establish that the instrument represents a relevant, comprehensive, and complete measurement of functioning following local dental anesthesia. It is unclear how the direction, items, and response options were generated. For example, the speech test requires the patient to read 3 sentences, which were obtained from the "Therapist's Manual for the Fisher-Logemann Test of Articulation Competence". The observer is required to listen for articulation or words or speech sounds containing "r", "l" and "s" in order to discern abnormalities. It is unclear if the observer has received any speech training in order to adequately score the patient's articulation response.*

*Combining patient-reported with observer assessments into a single instrument and score does not accurately describe either the patient's experience or observer's observations. The general lack of agreement between the patient's and observer's scores in drinking and speaking noted in Study NOVA 05-FAB-1 exemplifies the fact that patients and observers have different perspectives of a treatment effect. It is usually recommended that each effect is evaluated by a separate instrument.*

*In addition, the content validity of the FAB has not been evaluated in children 12-17 years through the use of qualitative interviews and focus groups.*

### 2.1 Claim Structure

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

### 2.2 Endpoint Model

To measure the effect of NV 101 on soft tissue anesthesia, Novalar chose 3 domains to evaluate: perceptual (perception of altered physical appearance), sensory (lack of sensation), and functional (diminished ability to speak, smile, drink, and control drooling).

## 3 EFFICACY STUDIES

On April 9, 2007, Novalar Pharmaceuticals submitted NDA 22, 159 to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). NDA 22-159 is a 505(b) (2) application for the proposed indication of NV-101 (OraVerse) 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 patients \_\_\_\_\_ years of age. b(4)

NDA 22, 159 includes two pivotal phase 3 efficacy/safety studies in subjects  $\geq 12$  years of age; studies NOVA 04-100 NOVA 04-200. Phase 2 Study NOVA 05-PEDS was performed in children 4 to 11 years of age.

The following is a brief review of these three pivotal studies.

## STUDY ENDPOINT REVIEW

### Studies NOVA-04-100/NOVA-04-200:

Studies NOVA-04-100 and NOVA-04-200 had similar study designs and were both randomized, blinded, controlled studies designed to evaluate the efficacy, pharmacodynamics, and safety of NV-101 when used for the reversal of soft tissue anesthesia. Study NOVA-04-100, enrolled subjects undergoing mandibular anesthesia, while Study NOVA-04-200 enrolled subjects undergoing maxillary anesthesia.

In Studies NOVA-04-100 and NOVA-04-200, eligible subjects were randomized with respect to both the type of anesthetic/vasoconstrictor and study drug (NV-101 or sham). Following completion of the dental procedure, subjects who met all eligibility criteria were randomized to receive NV-101 or sham (control) in a 1:1 allocation ratio. Study drug was administered at the same site(s) as the local anesthetic by the same Investigator who administered local anesthetic. Assessments for efficacy, pharmacodynamics, and safety were conducted by the observer during a 5-hour observation period. The subject and the member of the investigative team who observed soft tissue anesthesia recovery and performed safety assessments were blinded to the treatment received. Subjects were discharged after 5 hours and contacted by study staff for telephone follow-up within 2 days of study drug administration.

The primary efficacy endpoint for both studies was the time to observed recovery of normal sensation in the lip as measured by subjects using a 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 2 consecutive reports of normal sensation of the lip.

Secondary efficacy endpoints were as follows: 1) time to perceived recovery (score of zero) using 7 items of the Soft Tissue Anesthesia Recovery questionnaire (STAR-7); 2) time to observed normal function (smiling, speaking, drinking, and absence of drooling) as measured by subjects and observers using the functional assessment battery (FAB); and 3) time to observed normal sensation of the tongue as measured by subjects using a standardized tongue palpation procedure.

All assessments were performed over a 5-hour observation period. Lower lip palpation was to be done every 5 minutes starting 10 minutes after administration of study drug. The STAR questionnaire was given every 30 minutes after the study drug. The FAB was performed every 5 minutes starting 10 minutes after the administration of study drug until recovery of normal function and every 30 minutes thereafter. Tongue palpation was to be performed every 5 minutes starting 10 minutes after the administration of study drug. For all time-to-event endpoints, recovery of normal sensation/function was defined as findings of normal sensation at 2 consecutive time points.

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 2 consecutive assessments of normal sensation of the lower lip. The recovery of normal lip sensation also was considered to have occurred if the lip sensation test was rated normal at the subject's final evaluation and the rating from the preceding assessment was other than normal (i.e., not done, numb, or tingling). Subjects

## STUDY ENDPOINT REVIEW

were right-censored at the time of the subject's last lower lip sensation rating. No imputation was used for missing lip sensation data.

The STAR-7 score was calculated by adding the responses pertaining to item # 2 (uncomfortable), 3 (biting), 4 (drinking), 6 (speaking), 7 (smiling), 8 (drooling), 11 (appearance to others) 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 2 consecutive STAR-7 scores of zero. This event was also considered to have occurred if the subject's last reported STAR-7 score was zero and the score from the preceding assessment was greater than zero or missing. Subjects who did not meet these criteria before the end of the 5-hour observation period were right-censored at the last time the subject completed the STAR questionnaire. The last observation carried forward (LOCF) method was used to impute missing item responses.

The time to return of normal function was calculated by the number of minutes elapsed from the administration of study drug to the first of 2 consecutive assessments in which both the subject and the observer rated smiling, speaking, and drinking as normal and drooling as not present. The return of normal function was also considered to occur if all functional tests were rated normal or not present for the subject's last functional assessment battery and 1 or more of these tests from the preceding assessment was rated other than normal (i.e., not done or abnormal). Subjects who did not meet these criteria before the end of the 5-hour observation period were right-censored at the last time the subject completed the FAB with none of the individual subject or observer rated assessments missing. The LOCF method was used to impute missing item responses.

The primary analysis of the primary efficacy endpoint used the ITT analysis data set, with hypothesis testing using a 2-sided significance level of 0.05. The primary analysis of the secondary endpoints time STAR-7 score of zero, time to normal function, and time to recovery of normal tongue sensation used the corresponding mITT analysis data set. The analysis of the offset of the treatment effect (pharmacodynamic endpoint) in the lower lip and tongue used the ITT analysis data set and the mITT tongue sensation analysis data set, respectively.

To maintain an upper boundary on the overall experiment-wise type I error rate of 0.05, hypothesis testing of the time-to-event secondary efficacy endpoints followed a closed testing procedure. Provided the null hypothesis associated with the primary analysis of the primary efficacy endpoint was rejected at the 2-sided 0.05 level of significance, inferential comparisons between treatment groups for 1 or more of the secondary endpoints were performed in the indicated rank order of importance: 1) time to STAR-7 score of zero; 2) time to recovery of normal function; 3) time to recovery of normal sensation of the tongue. Inferential testing of the secondary efficacy endpoints was to proceed in a sequential step-down manner, provided the null hypothesis associated with the previously tested secondary endpoint was rejected at the 2-sided significance.

As noted by Novalar, the median time to recovery of normal sensation in the lower lip was reduced by 85 minutes (54.8%). The median times to recovery for patients randomized to NV-101 or control were 70 minutes and 155 minutes, respectively. The median time to recovery of

## STUDY ENDPOINT REVIEW

normal sensation in the upper lip was reduced by 82.5 minutes (62.3%). Patients randomized to NV-101 or control recovered in 50 minutes and 132.5 minutes, respectively. The differences between these times for both studies was found to be highly significant (stratified log-rank  $p < 0.0001$ ).

Novalar also noted that in both studies, the secondary endpoints were all significantly reduced in the NV-101 group relative to the control group ( $p < 0.0001$ ). In NOVA 04-100 (mandibular), NV-101 accelerated: a) the recovery of the perception of normal appearance and function (STAR) by 60 minutes (40%), b) the recovery of normal function (FAB) by 60 minutes (50%), and c) the recovery of normal sensation in the tongue by 65 minutes (52%). In NOVA 04-200 (maxillary), the STAR was reduced by 60 minutes (50%) and FAB by 45 minutes (42.9%).

### Study NOVA-05-PEDS:

Study NOVA 05-PEDS was primarily a safety study. Study NOVA-05-PEDS was a multicenter, randomized, blinded, controlled study designed to evaluate the safety and efficacy of NV-101 in dental patients 4 to 11 years of age. Study NOVA 05-PEDS enrolled subjects undergoing either maxillary or mandible anesthesia.

After obtaining informed consent from the parent or legal guardian and, as appropriate, written or verbal assent from the subject, pediatric dental patients scheduled to undergo a restorative or periodontal maintenance procedure were screened for eligibility. Eligible subjects were randomized to NV-101 or control (sham injection) in a 2:1 allocation ratio, respectively, and stratified according to the location of the dental procedure (mandible or maxilla) and study site.

Study drug (NV-101 or sham) was administered by submucosal injection at the same site(s) as the local anesthetic by the same Investigator who administered local anesthetic. The Investigator who administered injections of anesthetics and study drug may or may not have conducted the dental procedure. Subjects were observed for up to 4 hours after administration of study drug by a member of the investigative team distinct from the Investigator who administered the anesthetic and study drug. Subjects were discharged after their observation period, and contacted by study staff for a 24-hour telephone follow-up.

As a primary objective, the study evaluated the safety and tolerability of NV-101 as measured by the incidence and severity of adverse events, incidence, severity and duration of oral pain as measured by the Wong Baker FACES Pain Rating Scale, clinically significant changes in vital signs and oral cavity assessments, and analgesics required for oral pain.

As secondary objectives for subjects 6 to 11 years of age who were trainable in standardized palpation procedures, the study determined if NV-101 accelerates the time to normal lip sensation as measured by a standardized palpation procedure. In addition, the study determined if NV-101 accelerates the time to normal tongue sensation in mandibular procedures as measured by a standardized palpation procedure. This study was not prospectively powered to detect treatment differences in the secondary efficacy endpoints. Hypothesis testing of the secondary efficacy endpoints was performed using a 2-sided significance level of 0.05.

## STUDY ENDPOINT REVIEW

The study was considered complete when approximately 150 subjects had been randomized to study drug (NV-101 or sham) and had completed the procedures of the protocol. Although the study enrolled and analyzed 152 patients for safety, only 115 were analyzed for efficacy. For the modified Intent to Treat analysis a total of 37 subjects were either 4 or 5 years old or 6 to 11 years old and were not trainable in the standardization palpation procedure and therefore, excluded for the efficacy analysis.

*Comments: The design of NOVA 05-PEDS with respect to providing efficacy determinations is problematic in several respects. First, as noted in the protocol, the study was primarily a safety study and not prospectively powered to detect treatment differences in the secondary efficacy endpoints. Although Novalar had chosen 3 domains of efficacy: sensory, perception, and function, in their pivotal clinical studies in patients  $\geq 12$  years of age, in this pediatric study, only the domain of sensation has been evaluated by the lip and tongue palpation procedure. It can be surmised that all three domains are equally important to consider in evaluating local anesthesia effects in children as well as adults. Justification has not been submitted to suggest that the omitted perception and function assessments are not important measurements for this pediatric population.*

*In addition, Novalar has provided no information to support the content validity of the lip/tongue palpation test for use in the pediatric population. The comprehension of the instruction/responses of the palpation tests has not been provided. It is doubtful that the test is easily understood by this target group, since the 37 subjects were excluded from the efficacy analysis because they could not be trained in the procedure.*

*In order to adequately assess efficacy, it is recommended that Novalar develop age specific efficacy instruments which measure sensation, perception, and function, based upon qualitative interviews with subjects, parents, and specialists in the field.*

## **4 BACKGROUND**

The U.S. IND for NV-101 was filed in June 2002. A Special Protocol Assessment (SPA) was submitted by Novalar in December 2004 for Studies NOVA 04-100 and NOVA 04-200. In their February 2005 response to the SPA request and based upon comments provided in a SEALD consult in November 2004, DAARP informed Novalar of the following:

- The Division agrees with the use of the STAR-7 as a basis for analyzing the clinical impact of soft tissue anesthesia. In addition, as the protocol makes reference to multiple versions of the STAR questionnaire, one version, i.e., STAR-7, STAR-3 or STAR-Eating, Drinking, Speaking, Smiling, Drooling, should be selected as a secondary endpoint, and the remaining versions should be defined as exploratory only.
- It is anticipated that hastening the return of normal sensation by approximately one hour, or reducing the duration of numbness compared to control by 35%, will be clinically meaningful. The relevance of such a finding, however, will be based on the results of your analysis of the STAR-7 data and the findings of the eating, drinking, speaking, smiling and drooling assessments. Although a significant difference between the two treatment groups in terms of time to recovery of normal sensation will be required to demonstrate efficacy, the number of the supportive efficacy endpoints which differ between treatment groups and the magnitudes of those differences will play a significant role in the overall benefit-risk assessment.

## 5 APPENDICES

### 5.1 Lip Sensation Rating:

Guidance to the experimenter is in bold type. Instructions for the coordinator to convey to the subject are in normal type.

**A. Determine which quadrant of this subject's mouth will be anesthetized.**

You will be asked to rate the sensation in your (upper or lower) lip as either numb, tingling, or normal.

Numb means "no feeling."

Tingling means that you feel a sensation that is like pins and needles touching your lip.

Normal means that it feels normal to you.

Tapping your (upper or lower) lip with your finger will help you decide how you should rate the sensation there. Here are instructions on how to use your finger to judge the sensations in your (upper or lower) lip.

1. Use only the pad of your index or middle finger.
2. Use light pressure. Don't press so hard that you push your lip flat against your teeth. Just lightly depress the surface of your (upper or lower) lip.
3. Use the same amount of pressure each time you tap.
4. Tap to one side or the other rather than in the middle.
5. Tap 3 times in rapid succession (complete all taps within 2-3 seconds).

**B. At this point, show them what the pad of their finger is by circling the pad of your index finger with the tip of your other index finger while you explain that this is the finger pad.**

**C. Demonstrate the proper technique for tapping the upper or lower lip by touching your own lip 3 times using proper pressure and explain that this is the proper technique.**

**D. Demonstrate improper technique by pressing your upper or lower lip, as applicable against your teeth, holding that position so the subject can clearly discern what you are doing, as you explain that this is the wrong way to tap.**

Later today, you will be rating the sensation in the part of your (upper or lower) lip that covers the place where the dentist will perform the dental procedure you need. This part of your lip will be numbed by the anesthetic. However, the opposite side of your mouth should not be numbed by the anesthetic and should always have normal sensation. While you are rating sensations in your upper or lower lip later today, you may tap the opposite side of your (upper or lower) lip as a reference, to remind yourself how normal sensation feels.

**At this time, demonstrate how you will tap the part of your (upper or lower) lip that will be numbed by the anesthetic.**

## STUDY ENDPOINT REVIEW

Now tap your (upper or lower) lip on the opposite side of your mouth.

**E. Ask the subject to point to the quadrant of their mouth where the dental procedure will be performed and verify that their response is correct. If incorrect, teach the subject which is the proper quadrant and then ask them to demonstrate how they will tap the part of their upper or lower lip that will be numbed by the anesthetic. Repeat these instructions as necessary, but if they cannot correctly apply instructions 1 through 5 after five tries, they cannot be enrolled in the study.**

The anesthetic may also make your tongue numb. Tap your tongue in the same way you tapped your lip. Using the pad of your finger, tap the side of your tongue 3 times using the same light pressure. Don't tap the tip of your tongue. If you are tapping your lip on the left side, then tap the left side of your tongue. You may need to stick your tongue out to do this comfortably. You need not open your mouth wide to reach the side of your tongue.

Follow the instructions above each time you are asked to rate your sensation. You will tap many times in the next few hours. You must use the same amount of pressure each time you tap. You must use the same amount of pressure in the second hour as you did in the first hour, and in each hour after that.

### 5.2 The Star Questionnaire

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

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

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

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

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

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

## STUDY ENDPOINT REVIEW

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

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

## 5.3 Functional Assessment Battery and Instructions

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

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

### Definitions:

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

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

### Smiling Test

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

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

### Speaking Test

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

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

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

## STUDY ENDPOINT REVIEW

### **Drinking Test**

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

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

### **Drooling Test**

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

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

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/s/

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Ann Marie Trentacosti  
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FDA, Center for Drug Evaluation and Research,  
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### Clinical Review and Evaluation for Filing of New NDA

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|                             |   |
|-----------------------------|---|
| <b>NDA# (serial):</b>       | 22-159 (N-000)  |
| <b>Drug Name (generic):</b> | NV-101 (phentolamine mesylate for injection)  |
| <b>Sponsor:</b>             | Novalar Pharmaceuticals, Inc.   |
| <b>Indication:</b>          | For the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection fo a local anesthetic containing a vasoconstrictor |
| <b>Type of Submission:</b>  | new NDA   |
| <b>Date of Submission:</b>  | April 9, 2007   |
| <b>Date of Receipt:</b>     | April 9, 2007 (as eCTD)   |
| <b>PDUFA Filing Date:</b>   | June 8, 2007  |
| <b>Project Manager:</b>     | Geri Smith  |
| <b>Reviewer:</b>            | Arthur Simone, MD, PhD  |

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#### Clinical Filing Questions and Responses:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?

Yes. Review of the contents of the clinical section reveals it to be complete in terms of content and organization.

2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?

Yes. The NDA was submitted electronically in Common Technical Document (eCTD) format. The tables of contents, as well as the hyperlinks, allow for appropriate navigation of the document and access to the various sections.

3. On its face, is the clinical section of the NDA legible so that substantive review can begin?

Yes. Text and tables are legible and navigable.

4. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?

Three studies involved 92 healthy adult subjects not undergoing dental procedures (NOVA 02-01, NOVA 02-02, and NOVA 02-03). These studies assessed and evaluated various doses of the commercially available formulation of phentolamine mesylate for reversal of soft tissue anesthesia following injection of local anesthetic. Of the 92 enrolled subjects, 63 (68.5%) were treated with commercially available phentolamine mesylate and 29 (31.5%) were treated with control (placebo injection).

5. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?

Yes. The final Phase 3 protocols, NOVA 04-100 and NOVA 04-200, incorporated the advice provided by the Agency and appear to be both adequate and well controlled, based on superficial review.

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?

Yes. The efficacy studies provide placebo-controlled, randomized, trial data that will allow assessment of both the efficacy and the clinical benefit for reversing dental anesthesia.

7. Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?

Yes. NOVA 04-100 evaluates efficacy for mandibular dental procedures, and NOVA 04-200 evaluates efficacy for maxillary dental procedures.

8. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

On the basis of the proposed labeling and discussions with the Division, the efficacy studies appear adequate and well controlled.

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?

Line listings of patient data are in a format that is suitable for review and appear to include the types of data needed for an adequate review of safety and efficacy.

10. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?

This is not applicable. All studies conducted in relation to the proposed indication were conducted in the United States.

11. Has the application submitted all additional required case records forms (beyond deaths and drop-outs) previously requested by the Division?

Not applicable.

12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?

Yes.

13. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?

The applicant has assessed safety in accordance with recommendations made by the Division. This included assessment of safety related to the hemodynamic effects associated with phentolamine as well as the administration of the drug into the soft tissues of the oral cavity following administration of local anesthesia.

14. Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?

A draft label along with proposed carton and container labels were submitted with the application. They appear to be consistent with the requirements of 21 CFR §201.56 and 201.57.

15. Has the applicant submitted all special studies/data requested by the Division during the presubmission discussions with the sponsor?

The Sponsor has addressed the issues raised by the division during pre-submission discussions, particularly, those related to associating the reversal of soft tissue anesthesia with a clinical benefit.

16. From a clinical perspective, is this NDA fileable? If "no," please state below why it is not?

This NDA is fileable.

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

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Arthur Simone  
6/11/2007 04:21:00 PM  
MEDICAL OFFICER

Rigoberto Roca  
6/11/2007 04:29:08 PM  
MEDICAL OFFICER