A200 and A100 would have been evaluated as well as testing A200 to Aw/o and A100 to Aw/o. A carryover effect was not expected by the Sponsor since at least one week would have elapsed between treatment visits.

Means and standard deviation summary tables were to have been provided for vital signs and other continuous variables (blood pressure, pulse, etc.) by the prognostic factors such as age, gender, race, center and sequence group.

10.1.1.8.2 Determination of Sample Size

A total of 63 subjects were to have been enrolled to ensure 54 completed subjects taking into account a possible 15% loss of subjects to follow-up. The sample size had been considered large enough to detect a 15% difference in success rate between the two treatments at a 0.05 significance level and a 0.90 power to detect a difference. An equal number of subjects were to have been enrolled in each of the three sites.

10.1.1.9 Protocol Amendments

There were no protocol amendments for this study.

10.1.1.10 Study Conduct

The final study report indicated that the study was conducted in accordance with the Good Clinical Practice Guidelines, with the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and in compliance with 21 CRF Parts 50 and 56.

The final clinical report was inspected and the findings were reported to Management by the Quality Assurance Unit. Copies of audit certificates were presented in the submission (Appendix 10.1.6, NDA Vol. 16, p. 135-140). During the study the individual study sites were to permit study related monitoring to assure data recording and protocol adherence.

The study was conducted as planned. However, according to the final study report there were 18 protocol deviations for 15 subjects out of a total of 63 patients enrolled. The protocol violations are listed below (Copied from Section 6.2- Protocol Deviations, NDA Vol. 15, p. 51).

Table 10.1.1.10-1 **Subjects Related Protocol Deviations According to the Sponsor**

Subject #	Visit	Incident
22	1	Did not discontinue testing when subject reached 10 minutes without 3 EPT tests > 80.
23	Screening	Enrolled in study with Screening BP 150/90 (exceeded BP in exclusion criteria).
23	2	Did not discontinue EPT testing once 3 EPT < 80 were achieved.
27	Screening	Enrolled in study with Screening BP > 140/90 (exceeded BP in exclusion criteria).
30	1	Median tooth EPT value was 52 although subject passed Screening with 48.
31	2	Pulse was not recorded at the 200 minute testing station.
34	3	EPT measurements missed at 1.5, 2.0, 2.5, 3.0 and 3.5-minute intervals due to syncope AE. Subject resumed at 4.0 minutes after administering O_2 with nasal canula and measurements were stable.
37	3	There was a 2-minute interval from time of initiation of drug administration to EPT testing.
43	1	5 minute BP missed due to subject moving her arm during reading. Subjects to be reminded to remain still during readings.
43	Screening	Assigned subject # at screening instead of treatment 1.

45	Screening	Assigned subject # at screening instead of treatment 1.
47	1	24-hour follow-up call was not completed within 24 hours. Subject contacted on 02/19/04 instead of 02/18/04.
52	3	10.5 and 11.0-minute EPT ratings were recorded in space for 15 and 20 minute EPTs. Anesthesia not achieved and subject dismissed at 11 minutes.
55	1	8.5-minute EPT reading missed due to 8.0 minute reading taking too long because EPT probe lost contact with tooth.
56	2	24-hour follow-up call not completed within 24 hours due to subject's cell phone number being out of service. 24-hour follow-up completed on 04-13-2004 when they came in to clinic.
59	1	7.0-minute reading missed due to EPT probe tip slipping on tooth.
62	2	Study drug for Visit 3 was used at Visit 2.
62	3	Study drug for Visit 2 was used at Visit 3.

Furthermore, there were an additional 24 study related protocol violations in the complete listing of protocol violations (Appendix 10.1.7, NDA Vol. 16, p. 142). In six of the protocol violations there were issues in maintaining adequate room temperature, and there was no record of in which of the sites these violations occurred. In the protocol violation # 3 the standard emergency procedures of the site would be used instead of the procedures set in the protocol but the former were not described anywhere in the submission. The protocol violation # 34 was not clearly described in the table. Most of the other protocol violations were data recording problems which most likely did not affect the overall assessment of efficacy or safety, but raises certain concern of the lack of consistency of the data collection and recording.

The Sponsor sent a clarification response in regards to the maintenance of the room temperature. They all occurred at Novocol Pharmaceutical of Canada, Inc. which is a manufacturing facility and only one of the violations occurred prior to packaging and shipping of the drug product. This protocol violation as well as the other ones did not affect the results of the study. Protocol violation 39 was during the compounding of the drug product: a 20 minute mixing time was not performed as specified in the batch record for A200. According to our chemistry reviewer this would have no impact on the result of the study. Another clarification was for the emergency procedures used by The Forsythe Institute which seemed adequate. The protocol violation # 34 was a recording error with no impact on the data.

10.1.1.10.1 Subject Disposition

There were 63 enrolled patients in this study and all 63 were randomized. Sixty-two of them completed the study in the A200 group and in the Aw/o group. One subject withdrew consent after treatment visit 1 (A100 group) at the Forsythe Institute. There is no mention as to the reason for withdrawal.

10.1.1.11 Demographics/Group Comparability

There was a higher number of males [N= 36/63 (57.1 %)] compared to females [N= 27/63 (42.9 %)]. The ages ranged from 19 to 57 years of age and the mean age was 30 years [<26, 29/63 (46 %); 26-29, 14/63 (22 %); 30-39, 9/63 (14 %); >39, 11/63 (17 %)]. The Sponsor stratifies the population according to ethnicity as Hispanic (6.3 %) and Non-Hispanic (93.7 %). The distribution according to race reveals a higher percentage of Whites (79.4%) as shown in the table below (table with information contained in the section 7.2 Demographic and Baseline Characteristics of the clinical study report, NDA Vol.15, p54).

Table 10.1.1.11-1 **Subjects Demographics** (Data extracted from Section 7.2, NDA Vol.15, p. 54)

Variable	Number (%) of Subjects
Sex	
Male	36 (57.1)
Female	27 (42.9)
Age (years)	
Mean ± SD	30.4 ± 10.0
Range	19 - 57
Ethnicity	
Hispanic	4 (6.3)
Non- Hispanic	59 (93.7)
Race	
Other	2 (3.2)
American Indian or Alaska Native	0 (0)
Asian	5 (7.9)
Native Hawaiian or Other Pacific Islander	1 (1.6)
Black or African American	5 (7.9)
White	50 (79.4)

10.1.1.12 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.1.13 Unplanned Analyses.

A summary of sensory function at baseline and post-injection was presented by treatment group for all subjects who received study drug. According to the sponsor, there was not a statistically significant difference in the success rate based on a subject descriptive rating of 3 (moderate but not complete feeling of numbness) or 4 (side of my mouth is completely numb) at 10 minutes post-dose.

Table 10.1.1.13-1 **Frequency of Successful Anesthesia per Subjective Rating** (Data extracted from Section 7.4 Efficacy Analyses, NDA Vol.15, p. 56)

Treatment Groups	% Success
Aw/o	77.4
A100	87.3
A200	85.5

In addition, the Sponsor states that there were no statistically significant differences when comparing the frequency of successful anesthesia per subjective rating between the treatment groups.

Table 10.1.1.13-2 **Comparison of Frequency of Successful Anesthesia per Subjective Rating Among Treatment Groups** (Data extracted from NDA Vol.16, p.385)

Treatments Compared	*p* value
Aw/o vs. V100	0.1336
Aw/o vs. V200	0.1317
A100 vs. A200	0.7630

10.1.1.14 Sponsor's Efficacy Results

10.1.1.14.1 Primary Efficacy Variables

The primary endpoint was the success rate of subjects with complete anesthesia following intraoral administration for inferior alveolar nerve block anesthesia. The success of the

anesthesia was determined if three consecutive EPT values were ≥ 80, at 30 second intervals, achieved within 10 minutes of the completion of the injection.

According to the Sponsor, there was no difference in the success rate between A200 [N=34/62 (54.8%)] and A100 [N=30/63 (47.6%)], p= 0.2253 using the McNemar test. However, there was a difference in the success rate between the two epinephrine containing drugs and the formulation without epinephrine Aw/o [N=16/62 (25.8%)]: A200 vs. Aw/o, $p< 0.0001$; A100 vs. Aw/o, $p = 0.0196$.

A 95% confidence interval was constructed with a pre-specified non-inferiority margin of 15% for the difference in success rate between A100 and A200. According to the sponsor the confidence interval [-22.3%, 5.6%] did not cover the pre-specified non-inferiority margin of 15%. The unconditional exact test of non-inferiority using the difference of two related binomial proportions resulted in $p = 0.0009603$.

According to the sponsor's evaluation the overall success rate for the three drug formulations was 42.8%. However, site differences were detected between the University of Pittsburgh (43/63 = 68.6%), the University of Pennsylvania (25/63 = 39.7%) and The Forsythe Institute (12/61 = 19.7%). The Sponsor claimed that gender, weight or race had no effect on the success rate.

10.1.1.14.2 Secondary Efficacy Variables

There were two secondary endpoints:

1. Comparison of time of onset and time of duration of anesthesia of the two epinephrine containing formulations by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation and
2. Comparison of the same anesthesia characteristics between the epinephrine containing formulations and the formulation without epinephrine.

The following table has been created using information from the NDA submission:

Table 10.1.1.14.2-1 **Time to Onset and Time of Duration of Three Formulations of Articaine** (Table created with data from the Sponsor's table "Summary of Efficacy Results in Study ART02-001", NDA Vol. 28, p. 37)

	Time to Onset			Time of Duration		
Treatment Groups	N	Mean ± SD	Range	N	Mean ± SD	Range
A200	34/62	4.7 ± 2.6	1.0 - 9.0	34/62	51.2 ± 55.9	3.0 - 218.0
A100	30/63	4.2 ± 2.8	0.5 - 9.0	30/63	61.8 ± 59.0	3.5 - 236.0
Aw/o	16/62	4.3 ± 2.5	0.5 - 8.0	16/62	49.7 ± 44.2	3.5 - 161.0

According to the sponsor, there was no statistical difference in the time to onset or duration of anesthesia between A200, A100 and Aw/o. The following are the *p*-values between the treatment arms for the time to onset (determined by the Sponsor with the): Aw/o vs. A100, $p = 0.8920$; Aw/o vs. A200, $p = 0.2121$; A100 vs. A200, $p = 0.2930$. The following are the *p*-values between the treatment arms for the duration of anesthesia (determined by the Sponsor with the): Aw/o vs. A100, $p = 0.2943$; Aw/o vs. A200, $p = 0.7711$; A100 vs. A200; $p = 0.4461$).

The Sponsor also provided the subject descriptive rating at 10 minutes after injection by treatment arm. The results are as follows:

Table 10.1.1.14.2-2 **Subject Descriptive Rating at 10 Minutes After Injection** (Table created with data from the Sponsor's Response to Request for Additional Information, dated March 9, 2006)

Rating	Aw/o (n=62)	A100 (n=63)	A200 (n=62)
1-No change	7 (11.3%)	5 (7.9%)	4 (6.5%)
2- Slight numbness	14 (22.6%)	8 (12.7%)	7 (11.3%)
3- Mod. Numbness	21 (33.9%)	25 (39.7%)	26 (41.9%)
4- Completely numb	20 (32.3%)	25 (39.7%)	25 (40.3%)

In summary, the Sponsor concluded that:

- There were no statistically significant differences between the efficacy of A100 and A200, or differences in time of onset and duration based on EPT values.
- The confidence intervals showed that the A200 formulation is not inferior to A100 in efficacy.
- The formulation without epinephrine (Aw/o) was inferior to the other formulations in terms of efficacy, but not for time of onset and duration of anesthesia.

10.1.1.15 Discussion of Efficacy Findings in Study

If the success rate from the University of Pittsburgh (which was the highest) is excluded from the calculation of the overall success rate, this would be 29.7% instead of 42.8%. In the other hand, if The Forsythe Institute (which was the lowest) is not included in the calculation of the overall success rate, this would be 54%. The Sponsor agreed that there is a difference in success rate among sites. However, the Sponsor stated that all treatments were given to each subject so they served as their own control and such difference did not invalidate the inference of success by treatment. While I agree that each subject served as their own control, the data revealed that the responses to the active drug were inconsistent for the same patient across different treatment arms regardless of the study site. One would expect the response to the active drug to be consistent for the same patient and with possible differences in time of onset and duration from one treatment to another because of the concentration of epinephrine.

The table below illustrates the responses of some patients, across the treatment arms (data extracted from Appendix 10.2.12. Listing of EPT Values and Subject Descriptive Ratings, Vol.17, p. 7, and Appendix 10.1.5. Randomization Schedule, Vol.16, p. 125)

Table 10.1.1.15-1 **Patients' Success/Failure Responses by Treatment (sample)** [S=success; F=failure]

	Subject #	Aw/o	A100	A200
Un. Pittsburgh	5	S	F	S
	10	F	F	S
Un. Pennsylvania	25	F	S	F
	35	F	S	F
The Forsythe Ins.	51	F	S	F
	57	F	F	S

Some hypotheses to explain the low success rate are:

- the dose used for the mandibular block: in clinical practice sometimes larger doses are required
- ETP testing up to 10 minutes to designate anesthetic success or failure: since the time for T_{max} is 25 minutes, EPT testing for a longer period (up to 15 minutes) could have captured additional "anesthesia successes"
- anesthesia technique variability among the investigators

The Sponsor has been asked to explain the rationale for the disparity among the centers. The response is pending at the time of this review.

The Sponsor stated that the sequence of receiving the three different drug formulations, gender, weight and race had no effect on the success rate, and that the overall success rate was not affected by the age of the subjects. However, the success rate for subjects under 30 years old (49.6%) compared to subjects over 30 years old (24%) was significantly different (p= 0.0006). Patients under 18 and over 65 years old were excluded from the study.

Despite the claim that weight had no impact on the overall success rate it is noteworthy that the success rate in patients above 249 lbs was significantly lower (16.7%), even though there were only 2 patients in this weight range.

It is difficult to make conclusions regarding the effect of ethnicity and race on the success rate because of the uneven representation of all the groups. However, the data indicated that the success rate in Hispanics (16.7%) was lower than on the non-Hispanic population (44.5%).

The Sponsor succeeded in demonstrating that the formulation containing 1:200,000 epinephrine was not inferior to the formulation containing 1:100,000 epinephrine because the success rate was not statistically different between these two treatment groups A200 [N=34/62 (54.8%)] vs. A100 [N=30/63 (47.6%)], p= 0.2253.

The Sponsor was also successful in demonstrating that the two formulations containing epinephrine were superior to the formulation without epinephrine in terms of success rate for inferior nerve block (A200 54.8% vs. Aw/o 25.8%, $p < 0.0001$, A100 47.6% vs. Aw/o 25.8%, $p< 0.0001$).

When analyzing the subjective descriptive ratings at 10 minutes, the rating of 4- "Completely numb" is what best correlates with the EPT value of 80 (profound anesthesia). The incidence of the rating of 4 was low (32.3% for Aw/o, 39.7% for A100 and 40.3% for A200). For A100 and A200 the subjective rating of anesthesia did not always correlate with EPT of 80.

Table 10.1.1.15-2 **Comparison between the subject descriptive rating of anesthesia and EPT ≥ 80** (table created by the reviewer)

	Aw/o	A100	A200
Subject rating - 4 (Completely numb)	32.3 %	39.7 %	40.3 %
EPT ≥ 80 (profound anesthesia)	25.8 %	47.6 %	54.8 %

In summary:

- The A200 formulation is not inferior to the A100 formulation in achieving profound anesthesia following inferior mandibular block.
- The formulations A100 and A200 are both superior to Aw/o in achieving profound anesthesia following inferior mandibular block.
- The addition of epinephrine did not affect the time of onset of any of the three formulations, following inferior mandibular block. All three formulations had similar time to onset.
- The addition of epinephrine did not affect the duration of anesthesia forA100 and A200 compared with Aw/o, following inferior mandibular block. All three formulations had similar duration.

10.1.2 Study ART-02-002: "The efficacy and clinical anesthetic characteristics of 4% articaine HCl with 1:200,000 epinephrine, 4% articaine with 1:100,000 epinephrine, and 4% articaine without epinephrine, when administered for maxillary infiltration anesthesia."

10.1.2.1 Overall Summary of Findings

The Sponsor conducted a randomized, double-blind, active-controlled, cross-over, multicenter, phase 3 study seeking to demonstrate the equivalence in anesthetic efficacy between 4% articaine HCL with 1:200,000 epinephrine (A200) and the previously approved 4% articaine

HCL with 1:100,000 epinephrine (A100). The Sponsor also proposed to compare the anesthetic characteristics (time of onset and duration) between the two formulations containing epinephrine and 4% articaine alone (Aw/o).

Sixty-three subjects were randomized to one of six treatment sequences, so that all were exposed to each of the drug formulations over three treatment visits. The maxillary first premolar tooth on either side was tested with an electric pulp tester (EPT) at each visit to obtain a baseline measure of sensation and was retested every 30 seconds following a mandibular infiltration with 1mL of study drug.

The EPT is a battery-operated instrument designed to evaluate dental pulp sensitivity. It electrically stimulates the pulpal nerve through application of a slowly rising current flow. This test was utilized to assess tooth viability, to obtain a baseline reading, and to assess the onset, duration and level of anesthesia.

The Sponsor demonstrated that articaine 4% with epinephrine 1:200,000 is equivalent to articaine 4% with epinephrine 1:100,000 in that there is no statistically significant difference in the number of subjects who achieved profound anesthesia with the two drugs (A200 93.5% vs. A100 95.2%, p= 0.6547). The Sponsor also demonstrated that the addition of epinephrine to articaine improves efficacy, i.e., increases the success rate of producing profound anesthesia, for both formulations containing epinephrine compared to the articaine alone (A200 93.5% vs. Aw/o 75.8%, p<0.0076, A100 95.2% vs. Aw/o 75.8%, p< 0.0013). Despite the fact that there was no difference in the time to onset of the three formulations, the formulation without epinephrine had a shorter duration compared to the epinephrine containing formulations and the difference was statistically different.

10.1.2.2 Study Plan

The original version of this protocol was dated June 6, 2003. Sixty-three subjects underwent dental anesthesia at three study sites (21 subjects each site)- University of Pittsburgh School of Dental Medicine, University of Pennsylvania School of Dental Medicine and The Forsyth Institute- during the period of December 4, 2003 to May 25, 2004. There were no protocol amendments in this study. Source: NDA Vol. 18, Appendix 10.1.1., p. 217.

10.1.2.3 Objectives

The protocol-specified objectives of the study were:

Primary Objective: Demonstrate the equivalence in anesthetic efficacy between the investigational formulations of 4% articaine HCL with 1:200,000 epinephrine as compared to 4% articaine HCL with 1:100,000 epinephrine.

Secondary Objectives:
1. Compare the time to onset of anesthesia and duration of profound anesthesia between 4% articaine HCL with 1:200,000 epinephrine to 4% articaine HCL with 1:100,000 epinephrine, following maxillary infiltration anesthesia.
2. Demonstrate that the addition of epinephrine to 4% articaine solutions improved the efficacy of anesthesia following administration of a maxillary infiltration injection compared to the formulation with articaine alone.

10.1.2.4 Study Design

This was to be a randomized, double-blind, active controlled, cross-over, multicenter, phase 3 study, designed to compare clinical efficacy and anesthetic characteristics of 4% articaine HCl with 1:200,000 epinephrine (A200), 4% articaine HCl with 1:100,000 epinephrine (A100), and 4% articaine HCl without epinephrine (Aw/o), when injected intraoral to induce maxillary infiltration anesthesia.

One ml of A200 was to provide 40 mg of articaine hydrochloride and 0.005 mg of epinephrine base, A100 was to provide 40mg of articaine hydrochloride and 0.010mg of epinephrine base, and the Aw/o contained only 40mg of articaine hydrochloride.

A total of 63 subjects were to be enrolled and randomized to one of six sequence groups based on a Latin Rectangle design. The sequence groups for study drug were as follows:

- Group 1: A200, A100, Aw/o
- Group 2: A100, Aw/o, A200
- Group 3: Aw/o, A200, A100
- Group 4: A200, Aw/o, A100
- Group 5: A100, A200, Aw/o
- Group 6: Aw/o, A100, A200

At the treatment visits the subjects were to be assigned to the next available subject number in ascending order. After receiving the assigned treatment, each subject was evaluated at pre-determined scheduled times by means of an electric pulp tester (EPT) for time of onset and duration of analgesia.

10.1.2.5 Efficacy Endpoints

Primary Efficacy Endpoint: The success rate of subjects with complete anesthesia following intraoral administration for maxillary infiltration anesthesia.

Secondary Efficacy Endpoints:

1. Comparison of time of onset and time of duration of anesthesia of the two epinephrine containing formulations by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation.
2. Time of onset and time of duration of anesthesia of the two epinephrine containing formulations compared with the articaine formulation not containing epinephrine determined by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation.

10.1.2.6 Population

The subjects were 63 volunteers of both genders, in good general health, between 18 and 65 years of age inclusive. One subject did not complete the study due to a protocol violation. The following were the inclusion and exclusion criteria for the study population.

Inclusion Criteria

1) Subjects had to be between 18 and 65 years of age, inclusive.
2) Females of child bearing potential had to have a negative urine pregnancy test and use adequate means of birth control (abstinence, oral contraceptive steroids, intrauterine device, etc.) for at least one month prior to study entry and during the study.
3) The subjects were to sign the informed consent prior to initiation of any study procedures. The subject had to be able to understand and agree to cooperate with study requirements.
4) The subjects had to have at least one maxillary premolar with normal pulp vitality (determined by EPT testing of 10 - 50 units), free of gross caries, and without dental restorations including full coverage (crowns or "caps").

Exclusion Criteria

1) Any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions.
2) Significant history of cardiac or neurological diseases.
3) Severe or frequent cardiac arrhythmias.
4) Treated or untreated hypertension equal to or greater than 140 mm Hg systolic or 90 mm diastolic.
5) Severe or currently symptomatic bronchial asthma.
6) In the investigator's opinion, the subject was considered an inappropriate candidate for the study due to a concomitant medical or psychiatric condition.
7) The subject had evidence of soft tissue infection near the proposed injection site.
8) The subject was taking nonselective beta-blockers, monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.

9) The subject had taken aspirin, acetaminophen, non-steroidal anti-inflammatories (NSAIDS), opioids or other analgesic agents within 24 hours of administration of study medication.
10) The subject had taken an investigational drug(s) or participated in another study within four weeks prior to initiation of treatment.
11) Female subject who was lactating or pregnant.
12) The subject required sedative premedication (oral, inhalational, or intravenous) to tolerate the injection procedure.

Subjects could be withdrawn from the study for any of the following reasons:

1) An adverse event(s) that warranted termination as judged by the investigator.
2) The subject decided to withdraw from the study for any reason.
3) The subject required treatment with a prohibited medication.
4) EPT measurements outside of normal range at baseline measurement of each treatment visit.

10.1.2.7 Methods and Procedures

The trial was to have been comprised of 4 visits: a one-hour screening visit and three 4-5 hour treatment visits.

The subjects were to have been screened within 8 days prior to the first treatment visit. At the screening visit, a written informed consent was to be obtained. At that time a complete medical history was to be recorded (including record of all medications taken within two weeks prior to the screening visit), as well as a brief physical examination of the head, neck and mouth. The test tooth (maxillary first premolar) was to have been examined to confirm vitality and eligibility. A urine pregnancy test for females was to have been performed at screening and the day of each treatment visit prior to drug administration. The vital signs recorded at the screening visit should have included supine blood pressure, pulse rate, respiratory rate and body weight. With the exception of body weight, all other vital signs were to be measured at the treatment visits prior to administration of the study drug.

During the first treatment visit the patients were to have been randomized to one of the treatment sequence groups described previously in section 10.1.1.4. Before all treatment visits a urine pregnancy test was to have been repeated for females of childbearing potential. Measurements of blood pressure, pulse rate, respiratory rate were to have been performed 10 minutes after administration of the study drug and at the end of the treatment session.

The maxillary infiltration anesthesia was to have been administered on the same side (left or right) for all treatments. The injection volume was 1ml and it was to have been injected slowly with frequent aspirations over a one-minute time span. According to the sponsor, this is the lowest effective dose of articaine which was chosen to simulate clinical practice and to avoid high plasma concentrations of anesthetic. No topical anesthetics were to be applied prior to the

injection and the local anesthesia technique used was to have been the standard intraoral maxillary infiltration injection technique for inducing maxillary infiltration anesthesia (the sponsor referred to the following reference: Moore, PA, Editor, *Manual of Local Anesthesia in Dentistry, 4th Ed.* , Eastman-Kodak Co, Rochester, NY,1996.).

The time of onset and time of duration of anesthesia were to have been determined by measuring changes in the sensory threshold of the dental pulp following electric tooth stimulation using a standard commercially available EPT ([redacted]). This pulp tester is a battery-operated instrument designed to evaluate dental pulp sensitivity. It electrically stimulates the pulpal nerve through application of a slowly rising current flow. When the subject first experiences a threshold sensation, the probe tip is removed from the tooth and an EPT value (0-80) is recorded. Subjects usually report this sensation as an "itch" sensation (pre-pain) or a very mild noxious sensation (pain). Normal response values range from 10-50 units for mandibular canines and premolars. All EPTs were to have been calibrated before and after study completion.

The maxillary first premolar tooth on the anesthetized side of the maxilla was the tooth to be monitored throughout the study session. If the maxillary first premolar had been extracted for orthodontic reasons, the maxillary second premolar was to be used for the testing. The tooth could not have any dental restorations or gross caries and had to present a normal baseline EPT (sensitivity value 10-50 units) at each treatment visit. The site of tooth contact was the midpoint of the incisal third of the labial surface and to assure the electrode contact fluoride gel was to be applied to the probe tip.

Onset time for anesthesia was defined as the time (minutes) from completion of the injection (t=0) to the time when profound anesthesia (EPT $\geq$ 80) was established. If profound anesthesia had not been achieved by 10 minutes, the injection was to be considered an anesthetic failure. Duration of anesthesia was the time from establishment of profound anesthesia (onset) to the initial loss of profound anesthesia. Three consecutive tests (at 5-minute intervals) below maximum threshold (EPT = 80) were to be required to assure that the loss of profound anesthesia had occurred.

The median of three baseline EPT measurements of pulpal sensitivity were to have been determined and recorded prior to anesthetic administration. In order to make onset time suitable for continuous analysis, EPT values were to have been determined at 30-second intervals until success (or failure) was obtained. Three consecutive tests (at 30-second intervals) above maximum threshold (EPT = 80) were to have been required to assure that profound anesthesia had occurred. After this time, testing intervals were to begin again at five or ten minutes post injection and were extended to 5 minutes. For example, if onset had occurred at 4 minutes, EPT testing was to have been performed at 0.5, 1, 1.5, 2, 2.5,3, 3.5, 4, 4.5 and 5 minutes and then at 10, 15, 20, 25 minutes, etc., until loss of profound anesthesia was detected.

A descriptive report of anesthetic characteristics was to have been simultaneously elicited. At baseline and immediately following post-injection EPT testing, subjects were to be asked to select one of the following categories of sensory function: 1) no change or alteration in sensation, 2) slight feeling of numbness, 3) moderate but not complete feeling of numbness, and 4) side of

my mouth is completely numb. An 8 by 11.5- inch card with these categories was to have been presented to the subject to permit rapid selection of their responses.

Adverse events were to have been assessed immediately following the anesthetic testing procedure and at a phone interview 24 hours later. Immediately following the procedure, an investigator assessment would have had included: unexpected pain upon injection, positive aspiration during injection, discomfort at the injection site, swelling at the site of injection (hematoma), rash or other abnormal skin reaction, syncope or any other adverse events that had not been mentioned. At the end of the treatment, assessments of adverse events were to have been recorded and the subjects discharged from the sites.

Follow-up procedures would have consisted of an interview by phone call approximately 24 hours after the anesthetic efficacy testing had been completed, to determine whether the subject had had any adverse effects after discharge. The investigator or site personnel would have elicited any adverse events by asking the subject whether the subject noticed any changes in his or her health since the previous day testing session. A positive response to this question would have been followed by other questions regarding location and description of the changes. Also, other likely adverse reactions would have been inquired upon, such as swelling, headache, infection, pain, gingivitis, numbness and tingling. If adverse events occurred, the Adverse Event Form in the CRF was to be completed by the investigator. If the subjects could not be reached at the follow-up call, follow-up information was to be reported as soon as it was received from the subject.

The subject would have completed the study if he or she received three study medications and participated in all follow-up telephone calls. All who received study medication were to have been evaluated for safety.

The following is the study schematic:

Table 10.1.2.7-1 **Study Schematic for ART-02-002** (NDA Vol.18, p.35)

Study Schematic				
Procedure	Screening Visit[a]	Treatment Session 1[b]	Treatment Session 2[b]	Treatment Session 3[b]
Informed Consent Signed	X			
Complete Medical History	X			
Brief Physical Exam	X			
Urine Pregnancy Test (females only)	X	X	X	X
Vital Signs	X	X[c]	X[c]	X[c]
Randomization		X		
Study Drug Administration		X	X	X
Drug Accountability		X	X	X
Efficacy Measurement		X	X	X
Adverse Event Assessment[d]		X	X	X
Telephone Follow-up[e]		X	X	X

a. Within eight days prior to the treatment visit. Screening and Treatment 1 may be done on the same day.

b. One to three weeks after previous treatment visit. Will confirm inclusion and exclusion criteria are met prior to each treatment.

c. To be conducted at the following times: prior to administration of study drug (all), five minute interval for the entire EPT session (supine blood pressure and pulse rate only) and immediately following the testing procedure (all). Does not include body weight.

d. Immediately following the testing session.

e. Approximately twenty-four hours following discharge from the site.

Appears This Way
On Original

10.1.2.8 Analyses Plan

10.1.2.8.1 Analyses of Efficacy

The frequency of successful anesthesia was to have been summarized for the three formulations. A binomial test was to have been used to determine the effect of treatments on success rate. McNemar tests were to have been performed to compare treatment A200 vs. A100, treatment A200 vs. Aw/o, and treatment A100 vs. Aw/o. According to the sponsor, the sites could be pooled together since each treatment had a similar probability of success across all sites and the dentists had all been given injection training to validate the assumption of equal success probabilities.

Time of onset and duration of anesthesia were to have been summarized using means and standard deviations for each of the treatments. If the assumptions of normality had not been met, appropriate normalizing transformations were to be used. The structure of the linear models would have had Treatment (A100, A200, Aw/o) as a fixed factor, Time Period (1 ,2, 3) as a fixed factor, Sequence (1, 2, 3, 4, 5, 6) as a fixed factor, Center (site1, site2, site3) as a fixed factor, and Subject nested in Center x Sequence.

Multiple comparison tests (e.g., Tukey Kramer) were to have been used in the linear model to determine significance between A200 and A100, A200 and Aw/o, and A100 and Aw/o. Multiple comparison tests of the following were to have been performed: treatment A200 vs. A100, treatment A200 vs. Aw/o, and treatment A100 vs. Aw/o. In this case, the likely insignificant difference between A200 and A100 would have been evaluated as well as testing A200 to Aw/o and A100 to Aw/o. A carryover effect was not expected by the Sponsor since at least one week would elapse between treatment visits.

10.1.2.8.2 Determination of Sample Size

A total of 63 subjects were to have been enrolled to ensure 54 completed subjects taking into account a possible 15% loss of subjects to follow-up. The sample size had been considered large enough to detect a 15% difference in success rate between the two treatments at a 0.05 significance level and a 0.90 power to detect a difference. An equal number of subjects were to have been enrolled in each of the three sites.

10.1.2.9 Protocol Amendments

There were no protocol amendments for this study.

10.1.2.10 Study Conduct

The final study report indicated that the study was conducted in accordance with the Good Clinical Practice Guidelines, with the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and in compliance with 21 CRF Parts 50 and 56.
The final clinical report was inspected and the findings were reported to Management by the Quality Assurance Unit and copies of audit certificates were presented in the submission (Appendix 10.1.6, NDA Vol.19, p.176-181). During the study the individual study sites were to permit study related monitoring to assure data recording and protocol adherence.

The study was conducted as planned. However, according to the final study report there were 47 protocol deviations for 29 subjects, of the 63 patients enrolled. The protocol deviations are listed below (from Section 6.2- Protocol Deviations, NDA Vol. 18, p. 49).

Table 10.1.2.10-1 **Subject Related Protocol Deviations According to the Sponsor**

Subject #	Visit	Incident
17	3	Study coordinator accidentally signed in the Performed By section for the EPT test at 15 minutes. All EPT tests were performed by Dr. Boynes.
22	1	Section 4.0 - did not continue testing until they had 3 EPT tests < 80.
23	1	Subject was enrolled in study with Screening BP > 140/90 and therefore did not meet inclusion criteria.
23	2	Section 6.5 -10 minute subjective rating missed.
25	1	Subject was enrolled in study with Screening BP 145/73 and therefore did not meet inclusion criteria.
27	1	Section 6.5 - extra EPT test done at 8.5 minutes. Subject was numb after 5 minutes; next test should have been at 10 minutes.
27	3	Section 6.5 - extra EPT test done at end of session that was < 80 for a total of 4.
29	2	One EPT value prior to treatment was 53 (over 10-50 units range in protocol) however median was 45.
31	1	HH:mm time format not followed.
31	2	Initials not recorded for every EPT value.

32	2	5.0 minute EPT value and subject rating was not recorded. Subject was numb from 2 to 90 minutes.
33	3	2.5 minute EPT value was not recorded. 5.0 minute EPT rating was 80.
35	1	EPT result and subject rating were recorded on line for 4.0 minutes in CRF instead of 5.0 minutes.
39	3	Initials not recorded for 0.5 to 10 minute EPT evaluations.
43	1	Assigned patient # at screening instead of Treatment 1.
43	1	Section 6.5 - at 4.5 min the subject rating was missed.
43	2	Section 6.5 - 10 min EPT and subject rating missed.
44	1	Assigned patient # at screening instead of Treatment 1.
45	1	Assigned patient # at screening instead of Treatment 1.
45	3	24-hour follow-up call was not completed within 24 hours. Calls were made for 3 days without reaching patient until 02/17/04 (Treatment 3 on 02/13/04).
45	1, 2, 3	On 01/16/04, 02/06/04 and 02/13/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
46	1	After Screening it was determined that subject had participated in a one day study on 01/09/04. Subject re-appointed for 4 weeks out from that date.
46	3	3 minute EPT test missed due to vitality scanner reading 0.0 despite tip being in contact with tooth surface.
47	1	Assigned patient # at screening instead of Treatment 1.
47	1, 2, 3	On 01/15/04, 02/05/04 and 02/20/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
48	1	Assigned patient # at screening instead of Treatment 1.
48	1, 2, 3	On 01/20/04, 02/02/04 and 02/09/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
49	1, 3	On 01/13/04 and 02/05/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.

50	1	Section 6.4 - at 10 min the vitals were taken 2 minutes late due to machine not detecting BP first time.
50	2	24 hour follow-up call not done within 24 hours. Obtained T2 24 hour call information during T3 24 hour follow-up call.
50	3	On 02/09/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
50	3	CRF entry for 24-hour follow-up Question 2 Other was not completed.
51	1	EPT and subject rating were not performed at 5.0 minutes post-dose.
52	2	On 02/05/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
52	3	The final vital signs were not recorded post-treatment. They were taken but operator failed to write them down.
52	3	The second pre-dose EPT test was 62 which is outside the normal range of 10-50 units listed in the protocol.
52	3	On 02/12/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
53	1, 2	On 01/26/04 and 02/02/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
54	1, 2	On 02/03/04 and 02/12/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
54	3	On 02/19/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
55	1	Assigned patient # at screening instead of Treatment 1.
56	2	On 02/18/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
56	3	Third visit only 6 days after Treatment 2 on 02/18/04. No impact expected due to washout period of drug and medical history and brief physical exam revealed no issues at injection site.
57	1, 2	On 02/10/04 and 02/17/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
58	2	On 02/17/04 the EPT and subject rating were not performed at 5.0 minutes post-dose.
59	3	Unable to reach subject for 24-hour follow-up call despite leaving two messages on answering machine. 24 hour call completed on Mar-12-2004.
61	1	Missed 30 minute EPT reading due to subject having a coughing fit.

Furthermore, there were an additional 21 protocol violations (Appendix 10.1.7 of the NDA submission). In 7 of the protocol violations there were issues in maintaining adequate room temperature, and in six of them there was no record of in which sites these violations occurred, in resemblance to several of the protocol violations that occurred in Study ART-02-001. In the protocol violation # 3 the standard emergency procedures of the site (The Forsythe Institute) would be used instead of the procedures set in the protocol but the former were not described anywhere in the submission. In the protocol violation #65 a 20 minute mixing time was not performed which could potentially affect the efficacy of the drug tested. These protocol violations were the same as in Study ART 02-001 and were addressed by the Sponsor through a clarification response (refer to Section 10.1.1.10). Most of the other protocol violations were data recording problems which most likely did not affect the overall assessment of efficacy or safety, but raises concerns of the lack of consistency of the data collection and recording.

10.1.2.10.1 Subject Disposition

Sixty-three subjects were enrolled and randomized. Sixty-two of them completed the study as per protocol. One subject did not complete the study as per protocol due to a protocol violation and received only A100 treatment. There is no description as to what protocol violation led to this subject's withdrawal. All subjects were included in the efficacy and safety analyses.

10.1.2.11 Demographics/ Group Comparability

In this study there was a higher number of females [N= 35/63 (55.6%)] compared to males [N= 28/63 (44.4%). The ages ranged from 20 to 55 years of age and the mean age was 30 years (< 26, 27/63 (42.8 %); 26-29, 11/63 (17.4 %); 30-39, 16/ 63 (25.4 %); >39, 9/63 (14.3%). The Sponsor stratifies the population according to ethnicity as Hispanic (12.7%) and non-Hispanic (87.3%). The distribution according to race reveals a higher percentage of Whites (63.5%) as shown in the table below (constructed with data from section 7.2 Demographic and Baseline Characteristics of Clinical Study Report ART 002-002, NDA Vol.18, p. 52).

Table 10.1.2.11-1 **Subject Demographics**

Variable	Number (%) of Subjects
Sex	
Male	28 (44.4)
Female	35 (55.6%)
Age (years)	
Mean ± SWD	30.4 ± 8.4
Range	20-55
Ethnicity	
Hispanic	8 (12.7)
Non-Hispanic	55 (87.3)
Race	
Other	6 (9.5)
American Indian or Alaska Native	0 (0)
Asian	7 (11.1)
Native Hawaiian or Other Pacific Islander	0 (0)
Black or African American	10 (15.9)
White	40 (63.5)

10.1.2.12 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.2.13 Unplanned Analyses

There were no unplanned analyses for this study.

10.1.2.14 Sponsor's Efficacy Results

10.1.2.14.1 Primary Efficacy Variables

The primary endpoint was the success rate of subjects with complete anesthesia following intraoral administration for maxillary infiltration anesthesia. The success of the anesthesia was

determined if three consecutive EPT values were ≥ 80, at 30 second intervals, achieved within 10 minutes of the completion of the injection.

According to the Sponsor, the difference in the success rate between A200 [N=58/62 (93.5%)] and A100 [N=60/63 (95.2%)] was not statistically different, p=0.65 using the McNemar test. However, there was a statistically significant difference in the success rate between A200 and Aw/o [N=47/62, (75.8%)], p= 0.0013 and between A100 and Aw/o, p= 0.0076.

A 95% confidence interval was constructed with a pre-specified non-inferiority margin of 15% for the difference in success rate between A100 and A200. The confidence interval [-7.1%, 10.9%] does not cover the pre-specified non-inferiority margin of 15%. The unconditional exact test of non-inferiority using the difference of two related binomial proportion results in a p = 0.0047.

The overall success rate for the three drug formulations was 88.2%. The success rates were similar across the study sites: University of Pennsylvania, 90.2%, University of Pittsburgh, 88.9%, and The Forsythe Institute, 85.7%.

According to the Sponsor, gender, age, weight or race did not have any effect on the success rate.

10.1.2.14.2 Secondary Efficacy Variables

There were two secondary endpoints:

1. Comparison of time of onset and time of duration of anesthesia of the two epinephrine containing formulations by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation and
2. Comparison of the same anesthesia characteristics between the epinephrine containing formulations and the formulation without epinephrine.

Table 10.1.2.14.2-1 **Time to Onset and Time of Duration of Three Formulations of Articaine** (table generated with data extracted from NDA Vol. 18, p. 56)

	Time to Onset			Time of Duration		
Treatment Groups	N	Mean ± SD	Range	N	Mean ± SD	Range
A200	58/62	3.1 ± 2.3	0.5 – 9.5	58/62	41.6 – 21.1	3.5 – 103.0
A100	60/63	3.0 ± 2.1	0.5 – 9.0	60/63	45.0 – 23.6	5.0 - 99.5
Aw/o	47/62	3.0 ± 2.0	0.5 – 9.5	47/62	13.3 – 6.8	2.0 – 38.0

The Sponsor also provided the subject descriptive rating at 10 minutes after injection by treatment arm. The results are as follows:

Table 10.1.1.14.2-2 **Subject Descriptive Rating at 10 Minutes After Injection** (Table created with data from the Sponsor's Response to Request for Additional Information, dated March 9, 2006)

Rating	Aw/o (n=62)*	A100 (n=63)	A200 (n=62)*
1-No change	1 (1.6%)	0 (0%)	0(0%)
2- Slight numbness	8 (12.9%)	3 (4.8%)	0(0%)
3- Mod. Numbness	14 (22.6%)	10 (15.9%)	14(22.6%)
4- Completely numb	38 (61.3%)	50(79.4%)	47(75.8%)

* missing one recorded value (1.6%)

10.1.2.15 Discussion of Efficacy Findings in Study

The success rate was similar across the three study sites. The overall success rate was 88.2%.

The sponsor claimed that the sequence in which the drug was received, gender, age, weight or race had no effect on the success rate. The difference in the success rate according to treatment sequence, gender, age, weight categories was not statistically significant and was confirmed by the statistical reviewer.

This reviewer cannot draw any relevant conclusions in regards to the efficacy of this drug among races since there was a higher representation of Whites, compared to the numbers of African American and Asian subjects and lack of representation of Native Hawaiian/ Pacific Islander and American Indian or Alaska Native. The same is to be said in regards to ethnicity. The Hispanic population (12.7%) is under-represented compared to the non-Hispanic population (87.3%).

The primary efficacy endpoint was the success rate in achieving complete anesthesia and the Sponsor succeeded to demonstrate that the formulation containing 1:200,000 epinephrine is not inferior to the formulation containing 1:100,000 epinephrine because the success rate in achieving profound anesthesia was not statistically different between these treatment groups [A200 58/62 (93.5%) vs. A100 60/63 (95.2%), p= 0.6547].
One of the secondary endpoints was a comparison of anesthetic characteristics (time to onset and duration) between the two formulations containing epinephrine. The Sponsor succeeded to demonstrate that there was no difference in the time to onset between A200 and A100, p= 0.8597 and duration of anesthesia, p= 0.6503.

Another secondary endpoint was the comparison of the success rate of the epinephrine containing formulations and the formulation without epinephrine. The Sponsor demonstrated that the formulations containing epinephrine had a higher success rate than the formulation without epinephrine: A200 (58/62, 93.5%) vs. Aw/o (47/62, 75.8%), p = 0.0076 and A100 (60/63, 95.2%), p = 0.0013.

Despite the fact that there was no difference in the time to onset of the epinephrine containing formulations and the formulation without epinephrine (A200 vs. Aw/o, p= 0.9945, A100 vs. Aw/o, p= 0.8268) there was a statistically significant difference in the duration of anesthesia (A200 vs. Aw/o, p <0.0001; A100 vs. Aw/o, p< 0.0001). This demonstrates that the addition of epinephrine to articaine prolongs the duration of anesthesia when used for maxillary infiltration.

In Study ART 02-002, less patients reported being completely numb in comparison to the rate of profound anesthesia by EPT. A rating of 4-"Completely numb" should correlate to an EPT of 80:

Table 10.1.2.15-1 **Comparison between the subject descriptive rating of anesthesia and EPT ≥ 80** (table created by the reviewer)

	Aw/o	A100	A200
Subject rating - 4 (Completely numb)	61.3 %	79.4 %	75.8 %
EPT ≥ 80 (profound anesthesia)	75.8 %	95.2 %	93.5 %

For all treatment arms the subjective rating of anesthesia did not correlate with EPT of 80. A higher percentage of patients met the criteria for profound anesthesia and did not translate as the subject being completely numb by the subjects' perception.

In summary:

- The A200 formulation is not inferior to the A100 formulation in achieving profound anesthesia following maxillary infiltration.
- The formulations A100 and A200, both are superior to Aw/o in achieving profound anesthesia following maxillary infiltration.
- The addition of epinephrine did not affect the time of onset of any of the three formulations, following maxillary infiltration. All three formulations had similar time to onset.
- The addition of epinephrine prolonged the duration of anesthesia forA100 and A200 compared with Aw/o, following maxillary infiltration. The formulations A100 and A200 lasted longer than the Aw/o.

10.1.3 Study ART-02-003: "A comparison of the hemostatic efficacy of 4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine when administered intraorally to induce maxillary anesthesia required for periodontal surgery"

10.1.3.1 Overall Summary of Findings

The Sponsor conducted a randomized, double-blind, active-controlled, cross-over, multicenter, phase 3 study with the main objective of demonstrating a difference in the visualization of the surgical field with A200 compared to the active control, A100.

Forty-two patients that required bilateral (split-mouth) periodontal surgery of equal complexity were randomized to one of two treatment sequences, so that they were all exposed to both drugs over two surgical sessions. Each patient received up to 4 cartridges (6.8ml) of anesthetic for maxillary infiltration.

At the conclusion of the surgical procedure the surgeon assessed his or her ability to visualize the surgical field using a seven point categorical scale. This scale requested a response to the question: "How clear was your visualization of the surgical field?" A response to one of the following seven categories was requested: 1) Very unclear, 2) Moderately unclear, 3) Slightly unclear, 4) Neither clear nor unclear, 5) Slightly clear, 6) Moderately clear, and 7) Very clear. The Sponsor determined as a clear surgical fields all ratings of 5 and above. This reviewer however did not agree with the inclusion of the rating "slightly clear" into the proposed analyses, since it cannot be precisely distinguished from "slightly unclear". Nevertheless, if one takes into consideration only the ratings of "moderately" and "very clear" the clear surgical fields would be 26/42 (61.9%) for A100 and 20/42 (47.6%) for A200, which is statistically significant (p=0.0455) and provides evidence that A100 provides better visualization of the surgical field than A200.

[redacted]

10.1.3.2 Study Plan

The second amended protocol was dated June 21, 2004. Forty-two patients underwent dental anesthesia at three study sites- University of Pittsburgh School of Dental Medicine, University of

Pennsylvania School of Dental Medicine, and The Forsythe Institute- during the period of April, 19 to November 3, 2004. There were two protocol amendments in this study. Source: NDA submission, Appendix 10.1.1, Vol. 21, p.237.

10.1.3.3 Objectives

The protocol-specified objectives of this study were:

Primary objective: To compare the surgeon's ability to visualize the surgical field when using A200 as compared to the control formulation A100 by utilizing a categorical rating system.

Secondary objectives:
1. Demonstrate a significant difference in surgical blood loss (volume), measured from the start of surgery until the last suture was placed, between A200 and the approved formulation of A100.
2. Demonstrate a significant difference in the surgeon's rating of bleeding compared to his or her experience and expectation when using A200 as compared to the control formulation of A100.
3. Determine if there is a significant difference in success of controlling blood loss and visualization between A200 and A100.
4. Determine the adequacy of anesthesia for the surgical procedure through patient report of the level of anesthesia and pain control.

10.1.3.4 Study Design

This was a randomized, double-blind, active controlled, cross-over, multicenter, phase 3 study, designed to compare the hemostatic efficacy of 4% articaine with 1:200,000 epinephrine (A200) to the standard currently marketed anesthetic 4% articaine with 1:100,000 epinephrine (A100) when administered intraoral to induce maxillary infiltration anesthesia for outpatient periodontal surgery.

A total of 42 patients requiring matched maxillary bilateral periodontal surgeries were enrolled. These patients were to be randomly assigned to one of two treatment sequence groups such that each would have received A200 on one side of the mouth during one of the surgical sessions and A100 on the other side at the other surgical session or vice-versa. The patients received up to a maximum of 4 cartridges of anesthetic (6.8ml) per procedure. At the conclusion of the surgical procedure the surgeon assessed his or her ability to visualize the surgical field using a seven point categorical scale: "The Visualization of Surgical Field Scale", as the primary efficacy endpoint. Other endpoints were evaluated and will be described in more detail in section 10.1.3.7 Methods and Procedures.

10.1.3.5 Efficacy Endpoints

Primary Efficacy Endpoint: The surgeon's rating of the ability to visualize the surgical field after anesthesia with A200 or A100, using a seven point categorical scale, "The Visualization of Surgical Field Scale". A clear surgical field was defined as a rating of 5 (slightly clear), 6 (moderately clear) or 7 (very clear) on the Visualization of Surgical Field Scale.

Secondary Efficacy Endpoints:
1. The comparison of the total amount of blood loss after injection of A200 or A100, from the time of the initial incision to the time the final suture was placed.
2. The comparison of the surgeon's rating of bleeding using a seven point categorical scale, "The Expectation of Blood Loss Scale".
3. The success rate of acceptable visualization of the surgical field.
4. The rate of failure to achieve adequate surgical hemostasis.
5. The comparison of the level of anesthesia after injection of A200 or A100, prior to injection, immediately prior to surgery and following the placement of the last suture by soliciting responses from the patient.

10.1.3.6 Population

The subjects were 42 volunteer patients of both genders, between 21 and 65 years inclusive. The patients enrolled had moderate to severe periodontal disease and needed bilateral (split-mouth) periodontal surgery of equal complexity. All patients completed the study.

Inclusion Criteria
1) Patients were to be 21 to 65 years of age, diagnosed with moderate to severe periodontal disease that required bilateral periodontal surgery. The planned surgeries should have had involved gingival flap procedures and be of equivalent severity (free gingival graft procedures were not permitted). Criteria for matching included equal number of teeth involved ± one tooth); and equal mean level of attachment loss (± 2 mm).
2) Females of child bearing potential must have had a negative urine pregnancy test and must have been using adequate means of birth control (abstinence, oral contraceptive steroids, intrauterine device, etc.) for at least one month prior to study entry and during the study.
3) Clinical laboratory values within normal range as determined by the reference laboratory.
4) Signed informed consent prior to initiation of any study procedures. The patient must have been able to understand and agree to cooperate with study requirements.

Exclusion Criteria
Patients with the following were not eligible for participation in the study:
1) Any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions.

2) Significant history of cardiac or neurological diseases.
3) Severe or frequent cardiac arrhythmias.
4) Treated or untreated hypertension equal to or greater than 140 mm Hg systolic or 90 mm Hg diastolic.
5) Severe or currently symptomatic bronchial asthma.
6) In the investigator's opinion be considered an inappropriate candidate for the study due to a concomitant medical or psychiatric condition.
7) Evidence of acute soft tissue infection near the proposed injection site.
8) Current use of nonselective beta blockers, monoamine oxidase (MAD) inhibitors, tricyclic anti-depressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.
9) Current use of warfarin, dicumarol, heparin, aspirin or any medication that inhibits blood coagulation.
10) Previous use of an investigational drug(s) or participation in another study within four weeks prior to initiation of treatment.
11) Female patients must not have been lactating or pregnant.
12) Consumption of more than 3 alcoholic beverages per day or 21 per week on a regular basis.

Patients could have been withdrawn from the study for any of the following reasons:
1) An adverse event(s) that warranted termination as judged by the investigator.
2) The patient decided to withdraw from the study for any reason.
3) The patient required treatment with a prohibited medication.

No patients dropped out of the study or were replaced.

10.1.3.7 Methods and Procedures

The trial consisted of four visits: a one-hour screening visit, and two 2-4 hour surgical visits, each followed by a 24-hour telephone call and a 7-day post-operative visit.

The patients were to be screened within 4 weeks of the first surgical session. At the screening visit, a written informed consent was to be obtained as well as a medical history. Patients received a brief medical exam, laboratory assessments and vital signs (blood pressure, pulse rate, respiratory rate) were recorded. The vital signs were also recorded prior to administration of the study drug, ten minutes after administration of the study drug and immediately following the surgical procedure.

During the first surgical session, the patients were to be randomized to one of the study drugs. Before the treatment sessions a urine pregnancy test was to be performed for females of childbearing potential.

The matched bilateral surgeries were to be performed during two separate surgical visits scheduled at 3- 5 week intervals. The assigned study drug was to be injected immediately prior

to each surgery. Injection volumes were dependent upon the site and extent of the surgical procedure. According to the Sponsor the lowest effective dose of articaine had been selected to simulate clinical practice and to avoid high plasma concentrations of the anesthetic. The maximum recommended dose for 4% articaine 1:100,000 epinephrine is 7mg/kg of body weight, which corresponds to a maximum of 7.2 dental cartridges for a healthy 70kg adult. For maxillary periodontal procedures being studied in this protocol, a maximum of four cartridges of anesthetic (6.8 mL) was permitted. According to the Sponsor, local anesthesia technique uses approximately one-half cartridge of anesthetic per tooth to induce maxillary infiltration anesthesia (the Sponsor refers to two references: Moore, PA *(ed), Manual of Local Anesthesia in Dentistry,* 4th ed., Eastman-Kodak Co, Rochester, NY, 1996 and Malamed, SF, *Handbook of Local Anesthesia,* 4th ed., Mosby-Year Book Inc., St. Louis, 1997). Palatal infiltrations or Greater Palatine blocks use an additional one-half to one cartridge. Infiltration anesthesia included 0.10 mL injections into all dental papilla to be incised. Topical anesthetic ( ) was applied to the mucosa prior to all anesthetic injections.

The surgeon assessed his or her ability to visualize the surgical field using a seven point categorical scale: The **Visualization of Surgical Field** Scale. This assessment was completed at the conclusion of each of the surgical procedures. This scale requested a response to the question: "How clear was your visualization of the surgical field?" A response to one of the following seven categories was requested: 1) Very unclear, 2) Moderately unclear, 3) Slightly unclear, 4) Neither clear nor unclear, 5) Slightly clear, 6) Moderately clear, and 7) Very clear.

Surgical blood loss was determined from the time of the initial incision to the time the final suture was placed. All free-flowing blood, saliva and irrigation solutions were collected into a separate canister attached to a portable vacuum system ( ). Pre-weighed dry sterile gauze (2 inch by 2 inch) used during the procedure were placed in a tared container immediately after removal from the mouth and weighed. The volume of absorbed blood/saliva/irrigation solution/ultrasonic scaler solution was estimated from the increase in weight (1.0 g =1.0 ml). At the end of each procedure, the volumes of irrigation solution and ultrasonic scaler solution used were recorded. These volumes were subtracted from the total volume of the collected aspiration, including gauze solution. The difference is an estimate of the blood loss during surgery as saliva volumes were not expected to vary with different anesthetics therefore any observed difference in volume should be solely due to a difference in blood volume.

Another endpoint was the surgeon's rating of the blood loss using a seven point categorical scale: "The **Expectation of Blood Loss** Scale". This assessment was completed at the conclusion of each of the surgical procedures. This scale requested a response to the question: "Based on your past experience performing periodontal surgery, how well did the local anesthetic limit bleeding?" A response to one of the following seven categories was requested: 1) Much worse than expected, 2) Moderately worse than expected, 3) Slightly worse than expected, 4) Equal to expected, 5) Slightly better than expected, 6) Moderately better than expected, and 7) Much better than expected.

The **hemostatic success rate** was to be determined if at any time during the surgical procedure, the surgeon felt that the hemostatic efficacy of the study anesthetic was clearly inadequate, the field was very unclear and bleeding was considered much worse than expected. The surgeon would have declared the study anesthetic a failure in terms of bleeding control and that an alternative anesthetic was to be administered. The alternative anesthetic was to be one cartridge of 2% lidocaine hydrochloride with 1:50,000 epinephrine. Failure was therefore defined as the decision that an alternative anesthetic agent was required to allow adequate visualization of the surgical field.

Lastly, **a patient report of the level of anesthesia** was elicited prior to injection, immediately prior to surgery and following placement of the final suture. Patients were asked to select one of the following categories describing their anesthesia: 1) normal sensation, 2) slight feeling of numbness, 3) moderate but not complete feeling of numbness, and 4) side of my mouth is completely numb. An 8 by 11.5-inch card with these categories was presented to the patient to permit rapid selection of their responses.

Adverse events were to have been assessed immediately following the anesthetic testing procedure and at a phone interview 24 hours later. Immediately following the procedure, an investigator assessment would have had included: unexpected pain upon injection, positive aspiration during injection, discomfort at the injection site, swelling at the site of injection (hematoma), rash or other abnormal skin reaction, syncope or any other adverse events that had not been mentioned. At the end of the treatment assessments of adverse events were to have been recorded and the subjects discharged from the sites.

Follow-up procedures would have consisted of an interview by phone call approximately 24 hours after the anesthetic efficacy testing had been completed to determine whether the subject had had any adverse effects after discharge. The investigator or site personnel would have elicited any adverse events by asking the subject whether the subject noticed any changes in his or her health since the previous day testing session. A positive response to this question would have been followed by other questions regarding location. If adverse events occurred, the Adverse Event Form in the CRF was to be completed by the investigator. If the subjects could not be reached at the follow-up call, follow-up information was to be reported as soon as it was received from the subject. At the seventh day post-operative visit, after suture removal, post-operative recovery and wound healing were to be assessed. Specific oral complications such as swelling, headache, infection, pain, gingivitis, numbness or tingling, persistent bleeding, poor wound healing or any other adverse events were again inquired. If adverse events occurred, these were to be recorded by the investigator on the Adverse Event Form in the CRF.

The subject would have completed the study if he or she received two study medications and participated in all follow-up telephone calls and post-operative visits and all who received study medication were to have been evaluated for safety.

The following is the study schematic excerpted from NDA Vol.21, p. 35:

Table 10.1.3.7-1 **Study Schematic for ART 02-003**

Study Schematic					
Procedure	Screening Visit[a]	Surgical Session #1	Session #1 7-day Follow-up	Surgical Session #2	Session #2 7-day Follow-up
Informed Consent Signed	X				
Complete Medical History	X				
Brief Physical Exam	X	X[b]		X[b]	
Clinical Laboratory Evaluation	X	X[c]		X[c]	
Vital Signs	X	X[d]		X[d]	
Randomization		X			
Study Drug Administration		X		X	
Drug Accountability		X		X	
Efficacy Measurements		X		X	
Adverse Event Assessment		X	X	X	X
Telephone Follow-up[e]		X		X	

a. Within four weeks prior to the first surgical session. Screening and Surgical Session 1 could have been done on the same day.

b. Before study medication and following end of surgical treatment.

c. Laboratory assessments limited to urine pregnancy tests for female patients.

d. Performed at the following times: prior to administration of study drug, ten minutes following study drug administration and immediately following the surgical procedure. Included blood pressure, pulse and respiration rate.

e. Twenty-four hours following discharge from the site.

10.1.3.8 Analyses Plan

10.1.3.8.1 Analyses of Efficacy

Tables were to be provided for all categorical responses such as visualization of surgical field, expectation of blood loss and success rate by treatment. A binomial test was used to compare the percentage response rates for clarity of surgical field, blood loss expectation and success rate. McNemar's test was performed to compare Treatment A200 vs. A100

Summaries of mean and standard deviation were to be provided on the quantity of blood loss for each treatment. If the assumptions of normality were not met, appropriate normalizing transformations were used. The structure of the linear model has Treatment (A200, A100) as a fixed factor, Time Period (1, 2) as a fixed factor, Sequence (1,2) as a fixed factor, Side of Mouth (L, R) as a fixed factor, Center (site1, site2, site3) as a fixed factor, and Patient nested in Center x Sequence. Analysis of variance was used to determine significance between A200 and A100. A carryover effect was not expected because of the washout period between treatment visits. Non-parametric tests were used if necessary.

If the assumptions of normality were not met, appropriate normalizing transformation was to be used. Means and standard deviation summary tables were to be provided for vital signs and other continuous variables (blood pressure, pulse, etc.) by the prognostic factors such as age, gender, race, center and sequence group.

According to the Sponsor the sites could be pooled together since each treatment had a similar probability of success across all sites and all dentists were given injection training to validate the assumption of equal success probabilities.

10.1.3.8.2 Determination of Sample Size

According to the Sponsor 80% of the procedures using A100 were expected to have a clear surgical field compared to 50% of the procedures using A200. The sample size calculation was based on a 0.05 significance level and a 0.80 power to detect a 30% difference between the two treatment groups. Since this study used a crossover design, 36 treated patients would be required. Therefore, 42 patients were enrolled, to allow for a possible 15% loss to follow-up.

10.1.3.9 Protocol Amendments

There were two protocol amendments in this study. The first amendment had the following changes (excerpted from Section 5.0 Protocol Amendments, Vol. 21, p. 48):
1. Provided a justification for not performing a 24-hour hematocrit assessment.
2. The clinical laboratory used by the University of Pittsburgh study site, from University of Pittsburgh Medical Center Chemistry and Hematology Lab, to Quest Diagnostics Inc.
3. The method used to measure blood loss, from a colorimetric to a volumetric determination, to permit less potential variation in results between the three sites.
4. Update first patient description of anesthesia category.
5. The 24-hour patient telephone call has been revised to separate adverse reactions to the anesthetic from expected reactions following periodontal surgery.
6. Labeling and packaging procedures were updated to reflect procedures used to package drug at Novocol.
7. To consistently reference the post-injection vitals check at ten minutes.
8. Allow for study sites to follow the emergency procedures at their institution, in case of an adverse event following administration of local anesthetic.

The second amendment included changes related to (excerpted from Section 5.0 Protocol Amendments, Vol. 21, p. 49):
1. Number of patients to have surgery at each study site.
2. Remove the reference to COSTART terminology for adverse events.

10.1.3.10 Study Conduct

The final study report did indicate that the study was conducted in accordance with the Good Clinical Practices Guidelines, with the Ethical Principals for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and in compliance with 21 CFR Parts 50 and 56.

The final clinical report was inspected and the findings were reported to Management by the Quality Assurance Unit and copies of audit certificates were presented in the submission (Appendix 10.1.6, NDA Vol.22, p. 173-178). During the study the individual sites permitted study related monitoring to assure data recording and protocol adherence.

The study was conducted as planned. However, according to the final study report there were 19 protocol deviations for 16 patients that impacted the data in the study. The protocol deviations are listed below (from Section 6.2- Protocol Deviations, Vol.21, p. 50 of the NDA submission).

Table 10.1.3.10-1 **Patient Related Protocol Deviations**

Patient #	Visit #	Incident
1	2	7 day visit done at 9 days due to work scheduling conflict for the Memorial Day holiday.
2	1 and 2	7 day visit done at 9 days due to work scheduling conflict for the Memorial Day holiday.
6	1	7 day visit done at 9 days due to work scheduling conflict for the Memorial Day holiday.
8	2	Treatment 2 was scheduled at a 2-week interval instead of 3-5 week interval due to scheduling conflicts with participants.
9	1	7 day visit done at 8 days due to work scheduling conflict.
9	2	Treatment 2 was scheduled at a 2-week interval instead of 3-5 week interval due to scheduling conflicts with participants.
15	Screening	Failure to keep hematology log for date and time samples drawn
15	1	Patient had visit on 8th day instead of 7 due to July 4th holiday.
17	2	Patient moved to Florida and was not able to visit clinic for 7-day follow-up visit and suture removal. Dr. Johnson completed visit by telephone.
18	Screening	No lab results for June 18 screening visit due to wrong tubes used for blood draw. No hematology log was completed for June 28 blood draw.
19	2	Patient had visit on 6th day instead of 7 due to leaving for holiday on 7 days post-op.
28	2	Peridex should have a Stop Date of 11/02/2004 in Recent/Concomitant Medications.
31	2	Estimated blood loss produced a negative result of -8.6mL.

31	2	Patient had a pre-treatment BP > 140/90 and should have been retested prior to surgery.
34	2	Estimated blood loss produced a negative result of -7.0mL.
35	Screening	Tooth ranges listed on page 6 of Screening should have been 15-17 and 26-27 as listed by Dr. Goodson on the assessment form to meet inclusion criteria instead of 14-17 and 26-27 listed in error on the CRF.
36	1	Patient took Excedrin and due to washout period the interval was greater than 4 weeks between Screening and Treatment 1.
37	2	Surgical visit was 6 weeks and 5 days after first surgery instead of 3-5 weeks due to scheduling conflict with patient.
38	1	7 day follow-up visit was done 8 days after surgery due to scheduling conflict with patient.

In addition to the protocol deviations listed above there were an additional 15 protocol deviations. Six of them were related to room temperature control which had occurred in other studies as well (ART02-001 and ART 02-002). Two protocol violations occurred at the Forsythe Institute where the blood loss resulted in negative values, likely due to swallowing of the fluids. Other violations were in regards to the treatment visit and follow-up dates that did not occur within what was specified in the protocol. Lastly, there were a few protocol violations for lack or erroneous data recording. These protocol violations were unlikely to affect the study results but overall raise concerns in terms of the accuracy of the data collection and recording.

10.1.3.10.1 Subject Disposition

Forty-two patients were enrolled and all of them completed the study as per protocol. Each one of them received a dose of A100 and a dose of A200.

10.1.3.10.2 Demographics/ Group Comparability

There was a higher incidence of males (26/42, 61.9%) as compared to females (16/42, 38.1%). The ages ranged from 22 to 65 years of age and the mean age was 46.6 ± 9.7 [22 - <40, 7/42 (16%); 40 – 49, 17/42 (40%); 50 – 59, 17/42 (40%); > 59, 1/42 (2.4%)]. The population

distribution according to ethnicity was: Hispanic (1/42, 2.4%) and non-Hispanic (41/42, 97.6%). The patient distribution according to race was: Whites 32/42 (78%), Black or African American 7/42 (17.1%), Asian 2/42 (4.9%); America Indians, Alaska Natives and Native Hawaiian or other Pacific Islanders were not represented (See Table 3 below with information extracted from Section 7.2 Demographics and Baseline Characteristics of the submitted clinical study report, Vol. 21, p. 53).

Table 10.1.3.10.2-1 **Patient Demographics**

Variable	Number (%) of patients
Sex	
Male	26 (61.9%)
Female	16 (38.1%)
Age (years)	
Mean ± SD	46.3 ± 9.7
Range	22 - 65
Ethnicity	
Hispanic	1 (2.4%)
Non-Hispanic	41 (97.6%)
Race	
Other	0 (0)
America Indian or Alaska Native	0 (0)
Asian	2 (4.9%)
Black or African American	7 (17.1%)
Native Hawaiian or Other Pacific Islander	0 (0)
White	32 (78%)

10.1.3.11 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.3.12 Unplanned Analysis

There were no unplanned analyses for this study.

10.1.3.13 Sponsor's Efficacy Results

10.1.3.13.1 Primary Efficacy Variables

The primary endpoint was the surgeon's rating of the ability to visualize the surgical field after anesthesia with A200 or A100, using a seven point categorical scale. A clear surgical field was defined as a rating of 5 (slightly clear), 6 (moderately clear) or 7 (very clear) on the Visualization of Surgical Field Scale. Secondary Efficacy Variables

According to the Sponsor the blood loss during surgery had a mean of 70.2ml for A200 and 54.9ml for A100 resulting in a statistically significant difference in the blood loss between the two formulations (p= 0.0175). The Sponsor noted that there was a statistically significant difference between study sites: at The Forsythe Institute (p= <0.0001) there were negative values as a result of the patients swallowing some of the fluid to be measured and there were larger volumes collected at the University of Pittsburgh.

According to the Sponsor, the surgeon's expectation of blood loss was ranked as equal to or less than expected in 85.71% of the time with A100 and 71.43% of the time with A200 resulting in a statistically significant difference (p=0.0339) between the two formulations.

The Sponsor also claimed that both formulations had a 100% success rate in terms of acceptable visualization and adequate surgical hemostasis (need for an alternative anesthetic containing a higher concentration of epinephrine), since none of the surgeons had to use the alternate anesthetic formulation (2% lidocaine hydrochloride with 1:50,000 epinephrine) to complete the surgeries due to poor hemostasis and visualization of the surgical field.

The Sponsor concluded that there were statistically significant differences between A100 and A200 treatment groups in terms of visualization of the surgical field, expectation of blood loss and the volume of blood loss. In addition, the Sponsor poses that there was no difference in the success rate of hemostasis between the two formulations.

10.1.3.13.2 Secondary Efficacy Variables

The Sponsor provided upon request (response sent March 9, 2006) the subject descriptive ratings of anesthesia collected prior to surgery and after the last suture but did not submit an analyses of the data. The ratings are displayed in the table below.

Table 10.1.3.13.2-1- **Subject Descriptive Ratings of Anesthesia in Study ART 02-003**

	Prior to surgery (n=42)		End of surgery (n=42)	
Ratings	A100	A200	A100	A200
1-Normal sensation	0 (0%)	0 (0%)	0 (0%)	1 (2.4%)
2-Slight numbness	1 (2.4%)	0 (0%)	8 (19.0%)	9 (21.4%)
3- Moderate numbness	10 (23.8%)	16 (38.1%)	16 (38.1%)	16 (38.1%)
4- Completely numb	31 (73.8%)	26 (61.9%)	18 (42.9%)	16 (38.1%)

10.1.3.14 Discussion of Efficacy Findings in Study

The Sponsor claimed that there was a statistically significant difference in the **surgeon rated visualization scale**. The success rate for this primary endpoint was the sum of all the ratings "slightly clear", "moderately clear", "very clear". The validation of the "Visualization of Surgical Field Scale" and the "Expectation of Blood Loss Scale" has been requested to the Sponsor and is pending at the time of this review.

In this reviewer's opinion, the difference between a rating of "slightly unclear" and "slightly clear" is not well characterized, and may not be clearly distinguishable, one from the other. Another component of the rating system "neither clear or unclear" is also non-specific. Therefore, if one only analyzes the results of the ratings "moderately clear" and "very clear", the overall success rate would be 48/84 (57.1%). The rating for A100 would be 26/42 (61.9%) and for A200, 20/42 (47.6 %), p=0.0455, which is statistically significant and provides evidence that A100 allows better visualization than A200.

If analyzing only the ratings for truly poor visualization, "very unclear" and "moderately unclear", the total for A100 would be 0 (0%) and for A200 would be 5/42 (11.9%), p= 0.0253 which is also statistically significant and provides evidence that A100 allows better visualization than A200.

There was not a statistically significant difference in the surgeon's visualization between genders when considering the ratings for moderately clear and very clear: males 30/52 (57.7 %), females 18/32 (56.2 %), p= 0.896.

In terms of the visualization rates by age the Sponsor claimed that there was no difference in efficacy among the age groups which was confirmed by the statistical reviewer. It is noteworthy that there was only one patient in the age group >59; patients > 65 were excluded from the study.

The Sponsor also claimed that there was no effect of weight. When analyzing the different weight groups there was not a statistical difference among them .One cannot make a definitive conclusion in regards to the group > 249 lbs because of the small number of patients in this group (n=2).

Table 10.1.3.14-1 **Mean Blood Loss by Site by Treatment** (data generated from the SAS datasets, by the statistical reviewer)

Site	Number of treatments	Blood loss by treatment	
Un. of Pittsburgh	20	A100	78.62 ml
	20	A200	95.78 ml
Un. of Pennsylvania	14	A100	42.09 ml
	14	A200	53.84 ml
The Forsythe Institute	6	A100	26.66 ml
	8	A200	35.01 ml

The difference between each treatment in each center loses the statistical significance due to the low numbers in each treatment arm; however there is a trend in favor of less blood loss with A100. The statistical significance can only be detected when all treatments are analyzed together.

The Sponsor claimed that the **success rate of acceptable visualization** (hemostasis) was 100% since none of the surgeons had to use lidocaine with 1:50,000 epinephrine to control bleeding, despite ratings of "very unclear" (n=1 visit) and "moderately unclear" (n=3 visits) for the A200 formulation. Despite poor visualization, the surgeons did proceed without using another anesthetic with vasoconstrictor which may suggest that more hemostasis may not be crucial to conduct a surgical procedure.

The Sponsor did not present an analysis of the **patient's rating of the level of anesthesia** but submitted the data upon request. There were a higher percentage of patients in the A100 arm who rated the level of anesthesia as 4-"Completely numb" compared to the A200 arm, both before and after surgery. At the end of surgery the percentage of ratings of 4 decreased by 50% which correlated with the expected decrease in the level of anesthesia but more patients in the A100 treatment arm were still "completely numb". It is noteworthy that all patients had surgery despite subjective ratings of 2 and 3. The data provided did not allow this reviewer to know whether the patients who rated their level of anesthesia < 4 received additional study drug to proceed with the surgery of whether they tolerated the procedure regardless of their rating. In this study patients were allowed to receive up to 4 cartridge of anesthetic. It is possible that patients' perception of pain is variable and not all situations require complete numbness of the surgical area but several patients rated their level of anesthesia as 1 and 2. The values are displayed in the table below (table created by the reviewer with data submitted by the Sponsor on March 09, 2006).

Table 10.1.3.14-2 Subject Descriptive Rating Prior and After the Last Suture Placed

	Prior to surgery		After surgery	
Ratings	A100	A200	A100	A200
1 Normal sensation	0 (0%)	0 (0%)	0 (0%)	1 (2.4%)
2 Slight numbness	1 (2.4%)	0 (0%)	8 (19.0%)	9 (21.4%)
3 Moderate numbness	10 (23.8%)	16 (38.1%)	16 (38.1%)	16 (38.1%)
4 Completely numb	31 (73.8%)	26 (61.9%)	18 (42.9%)	16 (38.1%)

In summary:

- It seems appropriate to state that there is a statistically significant difference in visualization between A100 and A200, in favor of the former formulation based on the visualization rating.
- There seems to be some evidence that there is less blood loss with the A100 formulation than with the A200 formulation, however, since the blood loss volumes could not be precisely estimated, a claim of less blood loss cannot be formally made.
- The difference in expectation of blood loss cannot be supported by the data presented.

10.1.4 Study ART-03-001: " Peak plasma articaine concentrations and cardiovascular responses following intraoral administration of 4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine

10.1.4.1 Overall Summary of Findings

The Sponsor conducted a randomized, double-blind, active controlled, single site, pharmacokinetic (PK) study to evaluate the differences in C_{max} as well as other parameters between A200 and A100. The Sponsor also was seeking to demonstrate cardiovascular differences between the two formulations.

Fourteen healthy adults were randomized to one of two treatment sequences so that each was exposed to 11.9 ml of A100 and A200 over two treatment sessions. These subjects underwent several blood draws as well as concomitant monitoring with an acoustic tonometer (——————————————————) and an automated blood pressure monitor. The acoustic tonometer is a wristwatch like device whose waveform is calibrated by the oscillometric method with the blood pressure cuff used in the opposite arm and is a non-invasive method of obtaining cardiovascular parameters.

The Sponsor demonstrated that the pharmacokinetic profile of the two drugs was not statistically different.

10.1.4.2 Study Plan

The original version of this protocol was dated June 22, 2004. Fourteen healthy subjects were enrolled in a single site -University of Pennsylvania School of Dental Medicine- during the period between November 24, 2004 and February 16, 2005. There were no protocol amendments in this study. Source: NDA submission, Appendix 10.1.1., Vol. 23, p.292.

10.1.4.3 Objectives

The protocol-specified objective was:

Primary Objective: Evaluate possible differences in peak articaine plasma concentrations (C_{max}) following administration of the maximum recommended doses of 4% articaine HCl with 1:200,000 epinephrine (A200) as compared to the marketed formulation of the 4% articaine HCl with 1:100,000 epinephrine (A100).

10.1.4.4 Study Design

This was a randomized, multiple dose, double-blind, active controlled, crossover, single site, phase 3 PK study, designed to determine the peak plasma concentration of articaine and the cardiovascular responses of A200 as compared to A100.

Fourteen healthy adults were enrolled and randomized to receive one of two treatment sequences such that each subject would receive both drugs over the two study sessions. The treatment doses were 7 cartridges (11.9ml) of either A100 or A200. At each visit patients were subjected to predetermined blood draws and cardiovascular measurements that were assessed by means of an acoustic tonometer and an automated blood pressure monitor.

10.1.4.5 Efficacy Endpoints

Primary Efficacy Endpoint: The peak plasma concentrations of articaine.

Secondary Efficacy Endpoints:
1. The time to peak plasma concentrations of articaine.
2. Subject rating of anesthetic efficacy.

10.1.4.6 Population

The subjects were 14 healthy volunteers of both genders, 21 to 65 years of age. Thirteen subjects completed the study. One subject withdrew consent.

Inclusion Criteria

1) Subjects had to be between 21 and 65 years of age.
2) Subjects had to weigh between 150 and 200 pounds.
3) Females of child bearing potential must had a negative urine pregnancy test and must have been using adequate means of birth control (abstinence, oral contraceptive steroids, intrauterine device etc.) for at least one month prior to study entry and during the study.
4) Signed informed consent prior to initiation of any study procedures. The subject had to be able to understand and agree to cooperate with study requirement.
5) Clinical laboratory values within normal range as determined by the reference laboratory.

Exclusion Criteria

1) Any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions.
2) History of cardiac or neurological diseases.
3) Severe or frequent cardiac arrhythmias.
4) Treated or untreated hypertension equal to or greater than 140 mm Hg systolic or 90 mm Hg diastolic.
5) Severe or currently symptomatic bronchial asthma.
6) In the investigator's opinion was considered an inappropriate candidate for the study due to a concomitant medical or psychiatric condition.
7) Evidence of soft tissue infection near the proposed injection sites.
8) Current use of nonselective beta-blockers, monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants, phenothiazines, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.
9) Use of an investigational drug(s) or participation in another study within four weeks prior to initiation of treatment.
10) Female subjects that were pregnant or breastfeeding.
11) Subjects that required sedative pre-medication (oral, inhalational, or intravenous) to tolerate the injection procedure.
12) Known or self-reported alcohol or drug dependence.
13) Tobacco use (cigarettes, cigars, pipe smoking, smokeless tobacco, etc.).

Subjects could be withdrawn from the study for any of the following reasons:
1) An adverse event(s) that warranted termination as judged by the investigator.
2) The subject decided to withdraw from the study for any reason.
3) The subject required treatment with a prohibited medication.

10.1.4.7 Methods and Procedures

The trial comprised of 3 visits: a one-hour screening visit and two 3-hour treatment visits.

The subjects were to be screened within 8 days prior to the first treatment visit. At the screening visit, a written informed consent was to be obtained, as well as a complete medical history which included a record of all medications taken within two weeks prior to the screening visit. A brief physical exam was performed in addition to a urine pregnancy test for female subjects of childbearing potential, clinical laboratory evaluation (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count and INR- International Normalized Ratio) and measurement of vital signs (supine blood pressure, pulse rate, respiratory rate and blood pressure). With the exception of body weight, all other vital signs were reassessed prior to receiving each treatment drug and immediately at the end of each treatment session.

During the first treatment session subjects were to be randomly assigned to one of two treatment sequence groups (A100 followed at one to three weeks with A200; or A200 followed at one to three weeks with A100) such that approximately 6 completed subjects received each treatment sequence.

Subjects were required to fast for six hours prior to scheduled testing sessions, with clear liquids allowed until one hour prior to the testing visit. Blood samples were to be collected at baseline (T 0) immediately prior to the local anesthetic injections and at 8, 10, 15, 20, 25, 30, 40, 50, 60, 90 and 120 minutes following initiation of the administration of the first injection. Liquid Chromatography Tandem Mass Spectrometry (LC-MSIMS) was used to determine articaine plasma concentrations. Plasma samples were analyzed for articaine using a validated analytical method according to Good Laboratory Practices (GLP). Stability studies and assay quantification limits were established and reported by [redacted] (refer to Analytical and Pharmacokinetic Report, NDA Vol.25, p.1, Appendix 10.1.9, for analytical and validation reports).

The maximum dose of articaine had been selected to simulate clinical situations where 7 cartridges of anesthetic would be required (i.e., four third molar extractions) and to assess plasma concentrations of anesthetic with different concentrations of epinephrine. The anesthetic volume used for all sessions and formulations was 7 cartridges (11.9 ml). The maximum recommended dose for 4% articaine 1:100,000 epinephrine is 7 mg/kg of body weight (corresponding to a maximum of 7.2 dental cartridges for a healthy 70 kg adult).

At time 0, the seven cartridges of study drug were to be administered to the following sites: one cartridge for the right maxillary infiltration of the first molar (1.0 minute); one cartridge for the left maxillary infiltration of the first molar (1.0 minute); one cartridge for right maxillary first premolar infiltration (1.0 minute); one cartridge for the left maxillary first premolar infiltration (1.0 minute); one cartridge for the right inferior alveolar nerve block (1.0 minute); one cartridge for the left inferior alveolar nerve block (1.0 minute); one-half cartridge for the right mandibular buccal -infiltration (0.5 minute); and one-half cartridge for the left mandibular buccal infiltration

(0.5 minute). The maxillary infiltration and mandibular block injections were to be administered in the same order for all treatments. Injections were to have been given using an aspirating dental syringe and a 30 gauge short disposable needle for maxillary injections and a 27 gauge long needle for mandibular injections. Only one dentist was to provide all of the injections for a given subject. Injection volume was 1.7 ml (one cartridge) for all seven cartridges. Each cartridge was to be injected slowly, with frequent aspirations over a one-minute time span. The local anesthesia technique to be used was the standard intraoral injection technique for inducing maxillary and mandibular anesthesia (the Sponsor refers to two references: Moore, PA (ed), *Manual of Local Anesthesia in Dentistry,* 4th ed., Eastman-Kodak Co, Rochester, NY, 1996 and Malamed, SF, Handbook of Local Anesthesia, 4th ed., Mosby-Year Book Inc., St. Louis, 1997). A topical anesthetic ( ) was applied to injection sites prior to administration.

Upon arrival for each study session, an acoustic tonometer ( ) was to be fitted over the radial artery of one arm and an automated blood pressure monitor was to be placed on the opposite arm. The acoustic tonometer is a wristwatch like device whose waveform is calibrated by the oscillometric method with the blood pressure cuff on the opposite arm (the Sponsor refers to the following reference: Cohn JN, Finkelstein S, McVeigh G, et al. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension,* 1995; 26: 503-508).

According to the Sponsor cardiovascular measurements obtained through this non-invasive method correlate closely with invasive arterial measures (obtained through arterial puncture) of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), estimated cardiac output (CO), large artery elasticity index (C1), small artery elasticity index (C2), and systemic vascular resistance (SVR). Non-invasively measured C2 tends to be somewhat overestimated but the correlation coefficient is still significant. The Sponsor states that the device has clearly demonstrated differences not only in blood pressure recordings but also large artery and small artery compliance between hypertensive and normotensive individuals and between those that did and those that did not experience major cardiovascular events such as stroke, myocardial infarction, coronary artery bypass graft (the Sponsor refers to the following reference: Grey E, Bratelli C, Glasser SP, et al. Reduced small artery but not large artery elasticity is an independent risk marker for cardiovascular disease. *Am J Hyperten* 2003; 16: 265-269). The cardiovascular measures of HR, SBP, DBP, MBP, SV, CO, CI, C2 and SVR were determined at baseline immediately prior to administration of the anesthetic injections and every 10 minutes after initiation of the injections (i.e., pre-dose, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 minutes after time 0). Maximum change from baseline (beats/min, mm Hg, cc/beat, L/min, mL/mm Hg, dynes-sec-cm5) was to have been determined for each subject per session.

A descriptive report of anesthetic characteristics was to be simultaneously elicited. At baseline and following blood sampling, subjects were to be asked to select one of the following categories of sensory function: 1) normal sensation, 2) slight feeling of numbness, 3) moderate but not complete feeling of numbness, and 4) my mouth is completely numb. An 8 by 11.5-inch card with these categories was presented to the subject to permit rapid selection of their responses.

Follow-up telephone calls were to be made within 24 hours of each of the two treatment sessions by the investigator or site personnel to determine any adverse reactions that may have had occurred after discharge. The representative would have elicited any adverse events by asking the subject a yes/no question: "Have you noticed any changes in your health since yesterday's testing session?" A positive response was to be followed by a series of specific questions regarding location and description of the changes. A description of all adverse events was to be recorded on the appropriate Adverse Event Form in the CRF. An immediate return visit to the investigator's site would have been arranged if any adverse reaction was considered severe or requiring treatment, however, none were required during the study.

The subject would have completed the study if he or she received two study medications and participated in all follow-up calls. All subjects who received study medication were evaluated for safety.

The following is a study schematic (copied from Section 3.5.1 A Schematic of Clinical Events, NDA Vol. 23, p. 38-39).

Table 10.1.4.7-1 **Study Schematic for ART03-001**

Procedure	**Screening Visit**	**Testing Session 1[a]**	**Testing Session 2[b]**
Informed Consent Signed	X		
Complete Medical History	X		
Brief Physical Exam	X		
Urine Pregnancy Test (females only)	X	X	X
Vital Signs	X	X[c]	X[c]
Clinical Lab Evaluation	X		
Randomization		X	
Study Drug Administration		X	X
Drug Accountability		X	X
Blood Draws		X	X
Subject Rating of Anesthesia		X	X
Adverse Event Assessment[d]		X	X
Telephone Follow-up[e]		X	X

a. Within eight days of the confirmation of meeting study requirements.

b. One to three weeks after previous treatment visit. Confirm inclusion and exclusion criteria were met prior to each treatment.

c. BP, HR and respiration rate were to be conducted at the following times: prior to administration of study drug and immediately following the testing session (does not include body weight). BP, HR, SV, CO, C1, C2 and SVR to follow each blood sampling time point.

d. Immediately following the testing session.

e. Approximately twenty-four hours following discharge from the site.

10.1.4.8 Analyses Plan

10.1.4.8.1 Analyses of Efficacy

C_{max}, T_{max}, heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, stroke volume, cardiac output, large artery elasticity index, small artery elasticity index and systemic vascular resistance were to be summarized using means and standard deviations for each of the treatments. ———————————————, Section 9.0 Data Analysis, describes the pharmacokinetic and statistical analysis performed for C_{max} and T_{max} as well as AUC_t, $AVC_{inf,}$, kel and $T_{½}$ (refer to Appendix 10.1.9, Vol.25, p.1).

Paired t-tests were used to evaluate heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, stroke volume, cardiac output, large artery elasticity index, small artery elasticity index and systemic vascular. If the assumptions of normality were not met, appropriate normalizing transformations or the Wilcoxon Signed-Rank Test were used. Graphs and summary tables of plasma concentration across time were to be generated to visualize the difference between the two treatments and sequence groups.

10.1.4.8.2 Determination of Sample Size

According to the Sponsor, the maximum plasma concentration (C_{max}) for 6 subjects given 240 mg of articaine provides a mean value of 1,170 ng/ml (+/- 342.9 SD ng/ml) and time to maximum concentration (T_{max}) of 0.28 hours (+/- 0.098 SD hours).

For power of 0.8, the minimal detectable C_{max} difference between A200 and A100 was 392.2 ng/ml and for power of 0.5, the minimal C_{max} difference that could be detected is 274.4 ng/ml.

For power of 0.8, the minimal detectable T_{max} difference between A200 and A100 is 6.7 minutes (0.11 hours) and for power of 0.5, the minimal T_{max} difference that could be detected was 4.7 minutes (0.08 hours).

Fourteen subjects were enrolled to provide 12 completed subjects.

10.1.4.9 Protocol Amendments

There were no protocol amendments for this study.

10.1.4.10 Study Conduct

The final study report did indicate that the study was conducted in accordance with the Good Clinical Practices Guidelines, with the Ethical Principals for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and in compliance with 21 CFR Parts 50 and 56.

The final clinical report was inspected and the findings were reported to Management by the Quality Assurance Unit. Copies of audit certificates were presented in the submission (Appendix 10.1.6, NDA Vol.24, p. 94-97). During the study the individual sites permitted study related monitoring to assure data recording and protocol adherence.

The study was conducted as planned. According to the final study report there were 22 protocol deviations for 10 subjects that impacted the data in this study. Seven of them were lack of blood draws due to loss of IV and three of them the blood samples were collected in wrong tubes. Seven were missed cardiovascular measurements. The list of deviations is listed below (from Section 6.2 Protocol Deviations, NDA Vol. 23, p.53 and 54.

Table 10.1.4.10-1 **Protocol Deviations from Study ART 03-001** (NDA Vol. 23, p. 53)

Subject #	Visit #	Incident
1	1	Missed 50-minute CV measurement due to loss of tonometer position.
1	1 and 2	Blood samples were collected into SST tubes instead of Vacutainer tubes with sodium heparin anticoagulant.
1	2	Missed 90-minute blood draw due to loss of IV.
1	2	A different dentist did the injections at visit 2 due to subject schedule.
2	1	Extra CV measurements taken at 25-minutes post-dose.
2	1 and 2	Blood samples were collected into SST tubes instead of Vacutainer tubes with sodium heparin anticoagulant.
3	1	Blood samples were collected into SST Tubes instead of with sodium heparin anticoagulant.
4	2	Missed 60-minute CV measurement due to loss of tonometer position.
5	1	Missed 120-minute blood draw due to loss of IV.
5	1	Missed 10-minute CV measurement due to loss of tonometer position.
7	Screening	Subject enrolled with a body weight > 200 pounds.
7	1	Incorrect year of date was signed for error code correction at the bottom of page 10 of CRF.
7	1 and 2	Extra CV measurements taken at 15 minutes post-dose.
7	2	Missed 60-minute CV measurements due to loss of tonometer position.
8	2	Missed 90-minute blood draw due to loss of IV.
10	1	Missed 8-minute blood draw due to loss of IV.
10	1	Missed 10-minute blood draw due to loss of IV.
10	1	Missed 15-minute blood draw due to loss of IV.
10	1	Missed 20-minute blood draw due to loss of IV.

10	2	Missed 10-minute CV measurement due to loss of tonometer position.
11	Screening	Subject enrolled with INR outside of range however subinvestigator determined they were not clinically significant.
14	Screening	Subject enrolled with hemoglobin and RBC out of range however subinvestigator determined they were not clinically significant.

There were additional 7 protocol violations that were mostly recording issues and not directly subject related.

10.1.4.10.1 Subject Disposition

Fourteen patients were enrolled and randomized. Only one did not complete the study due to consent withdrawal (participated in the A100 treatment only). There was no description in regards to reason for withdrawal. Twelve of the subjects were included in the efficacy analyses of the subjects (one did not complete the study as mentioned above and other was missing many blood samples). All were included in the safety analyses.

10.1.4.11 Demographics/ Group Comparability

There was a predominance of males: of the 14 patients enrolled, only one was female. The ages ranged from 24-38 years with a mean of 30.4 ± 10.0. The distribution by race was 28.6% (4/14) Hispanic and 71.4% (10/14) non –Hispanic. The distribution by race was : Whites 50% (7/14), African American 14.3% (2/14), American Indian or Alaskan Native 7.1% (1/14); Asians, Native Hawaiian or Other Pacific Islanders were not represented. Below is a table with the subjects' demographics.

Table 10.1.4.11-1 **Subjects' Demographics** (Data extracted from Section 7.2 Demographics and Baseline Characteristics, NDA Vol.23, p. 55)

Variable	Number (%) of Subjects
Sex	
Male	13 (92.9)
Female	1 (7.1)
Age (years)	
Mean ± SD	28.5 ± 3.4
Range	24-38

Variable	Number (%) of Subjects
Ethnicity	
Hispanic	4 (28.6)
Non- Hispanic	10 (71.4)
Race	
Other	0 (0)
American Indian or Alaska Native	1 (7.1)
Asian	0 (0)
Black or African American	2 (14.3)
Native Hawaiian or Other Pacific Islander	0 (0)
White	7 (50.0)

10.1.4.12 Treatment Compliance

Study treatment was administered under direct supervision of study staff; therefore, treatment compliance was assured.

10.1.4.13 Unplanned Analyses

There were no unplanned analyses for this study.

10.1.4.14 Sponsor's Efficacy Results

10.1.4.14.1 Primary Efficacy Variables

According to the Sponsor, after injection of A200 and A100 the systemic absorption of articaine was rapid with mean T_{max} of 0.37h for A200 and 0.36h for A100. The mean C_{max} for A200 was 2145ng/ml and 2037ng/ml for A100. The A200 elimination rate constant was 1.0022 h-l and the corresponding $T_{½}$ was 0.74 hours. For A100 the elimination rate constant was 1.0534 h-l and the corresponding $T_{½}$ was 0.73 hours. The area under the plasma concentration versus time curve (AUC_{inf}) was 2440 and 2479 ng*h/mL for A200 and A100, respectively. According to the Sponsor, there were no significant differences between A200 and A100 found for any of the pharmacokinetic parameters.

Table 10.1.4.14-1 **Primary Pharmacokinetic Parameters for A200 and A100 Following an 11.9ml Dose of Articaine** (extracted from NDA Vol. 23, p. 58)

Parameter	Geometric Mean Arithmetic Means (CV%) 4% Articaine		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intrasubject CV (%)
	with Epinephrine 1:100,000 (n=12)	with Epinephrine 1:200,000 (n=12)			
AUC_t (ng*h/mL)	1860.90 1988.54(38)	1901.81 2012.54 (36)	97.85	83.77-114.30	21
AUC_{inf} (ng*h/mL)	2247.52 2478.72 (50)	2275.76 2440.44 (42)	98.76	84.78-115.04	21
Cmax (ng/mL)	1957.95 2036.67 (31)	2064.24 2145.00 (29)	94.85	79.77-112.78	24
Tmax (h)	- 0.36 (30)	- 0.37 (46)	-	-	-
kel (1/h)	- 1.0534 (30)	- 1.0022 (26)	-	-	-
Thalf (h)	- 0.73 (36)	- 0.74 (28)	-	-	-

CV%: % coefficient of variation; AUC_t: Area under the plasma concentration time curve from time 0 to time of last measurable plasma concentration; AUC_{inf}: Area under the plasma concentration-time curve from time 0 to infinity; Cmax: maximum measured plasma concentration over the sampling time period; Tmax: time of maximum measured plasma concentration; kel: apparent first-order elimination rate constant, or terminal rate constant calculated from the semi-log plot for the plasma concentration versus time curve; Thalf: the apparent elimination half-life.

10.1.4.14.2 Secondary Efficacy Variables

The Sponsor presents the subject report of anesthesia that was evaluated at some time under 10 minutes following administration of study drug and at sometime within 120 minutes following administration of study drug. According to the Sponsor the number of subjects that reported a rating of 4 at some time under 10 minutes was A100 6/13 (46.15 %) vs. A200 8/13 (61.54 %), p= 0.4142. The Sponsor also reports that the anesthetic rating of 4 at some time between 4 and 120 minutes was A100 12/13 (92.31 %) and for A200 12/13 (92.31 %).

The Sponsor sent data on the subject descriptive rating of anesthesia at several time points upon request (response sent on March 9, 2006) but did not provide an analysis of the data.

A table containing the subject descriptive ratings is displayed below.

Table 10.1.4.14.2-1 **Subject Descriptive Ratings at 8, 15, 30, 60 and 120 minutes post-injection** (table created by the reviewer with data provided by the Sponsor in "Response to Request for Additional Information", dated March 9, 2006)

	8 min		15 min		30 min		60 min		120 min	
Ratings	A100	A200	A100	A200	A100	A200	A100	A200	A100	A200
1- No change	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
2- Slight numbness	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
3- Mod. numb	**7 (50.0%)**	**7 (53.8%)**	**3 (21.4%)**	**5 (38.5%)**	**1 (7.1%)**	**2 (15.4%)**	**1 (7.1%)**	**1 (7.7%)**	**2 (14.3%)**	**3 (23.1%)**
4- Compl. numb	**7 (50.0%)**	**6 (46.2%)**	**11 (78.6%)**	**8 (61.5%)**	**13 (92.9%)**	**11 (84.6%)**	**13 (92.9%)**	**12 (92.3%)**	**12 (85.7%)**	**10 (76.9%)**

10.1.4.15 Discussion of Efficacy Findings in Study

The pharmacokinetic study demonstrated that the lower dose of epinephrine has minor impact in the systemic levels of articaine. For a detailed analysis of this study please refer to the Clinical Pharmacology Review.

In regards to the subject reported level of anesthesia, it is no surprise that over 92% of the subjects reported a rating of 4 – "my mouth is completely numb" at some time of the study, given the large dose of anesthetic. This reviewer would like to point out that the number of subjects exposed to A100 was 14 and not 13 (Refer to the section 10.1.4.10.1 Subject Disposition). The difference in the success rate may reflect the fact that some patients may not achieve profound anesthesia by 10 minutes and may require a longer waiting period after injection. The data suggests that the maximum effect was between 30 and 60 minutes indicating that many patients will require a longer waiting period than 10 minutes to achieve more profound anesthesia.

10.2 Listings of Adverse Events

The following is a listing of the adverse events collected from regulatory authorities worldwide between 1998 and 2004: injection site nerve damage, injection site pain, injection site paresthesia, injection site inflammation, injection site edema, injection site induration, injection

site necrosis, injection site ulcer, dental necrosis, tissue sloughing, ulceration, bone exposure, tissue hardening, facial palsy, numbness of L lip, numbness of chin, tingling, burning, prolonged numbness, numbness on side of the body, hypoesthesia, paresthesia, nerve damage, neurotoxicity, anaphylactic reaction, pruritus, hives, allergic reaction, erythematous rash, mucosal burning sensation, oral mucosa discoloration, blanching over an extended area of the right side of the face, bruising, skin discoloration, blistering, subcutaneous emphysema, chest tightness, high blood pressure, hypotension, blood pressure fluctuation, vasovagal attack, acute circulatory failure, sweating attack, syncope, pallor, tachycardia, palpitations, dyspnea, suffocation, cyanosis, feeling hot, flushing, adrenergic syndrome, pyrexia, dizziness, lightheadedness, tremor, sleepiness, insomnia, confusion, amnesia, malaise, sedation, headache, loss of consciousness, convulsions, epilepsy, hiccups, Horton disease aggravated, pain, leg pain, pain in nose, pain exacerbated, post-operative pain, white tongue, pain on the tongue, hypoesthesia of the tongue, taste loss, taste disturbance, oral pain, speech disorders, dysphagia, cough suppression, anxiety, agitation, mood alteration, excitability, weakness, fatigue, malaise, swelling, tongue edema, mouth edema, swelling with discoloration, face edema, muscle weakness, eye irritation, vision blurred, orbital pain, lacrimation increase, dry lip, dry mouth, reaction of pain electric shock, nausea, vomiting, shivering, sneezing, hair loss, delayed recovery from anesthesia, increased drug effect, drug ineffective.

A search in AERS performed by this reviewer, using only the term "articaine" since approval, resulted in 33 case reports. Most of the reports provide scant narrative details. The adverse events reported were: hypoesthesia oral (12), hypoesthesia (6), paresthesia (5), paresthesia oral (1), anesthetic complication (5), post-procedural complication (2), pain in jaw (2), gingival disorder (2), injection site reaction (2), convulsion (2), tremor (2), dizziness (2), feeling abnormal (2), blister (2), face edema (2), hyperhydrosis (2), medication error (2), burning sensation (2), bone disorder (2), blood pressure increase (2), glossodynia (2), tongue blistering, angioneurotic edema, hypersensitivity, drug hypersensitivity, conjunctivitis, dermatitis, mucosal erosion, multi-organ failure, Stevens Johnson Syndrome, toxic epidermal necrolysis, chest pain, cardiac arrest, cardio-respiratory arrest, speech disorder, hypogeusia, dysgeusia, neurotoxicity, loss of consciousness, muscle twitching, muscle tightness, myalgia, feeling jittery, nystagmus, retching, salivary hypersecretion, malaise, sedation, anxiety, confusional state, nervousness, CNS stimulation, pyrexia, body temperature increase, urinary incontinence, hyperventilation, pulmonary edema, respiratory distress, hyperesthesia, local anesthesia, pain, injection site pain, oral pain, ear pain, gingival pain, gingival bleeding, gingivitis, glossitis, tongue coated, sensitivity of teeth, pruritus, swelling, swelling face, swelling of the tongue, skin tightness, syncope, palpitations, heart rate increased, tooth disorder, endodontic procedure, tooth extraction, wound debridement, impaired healing, osteonecrosis, skin tightness, throat tightness, alopecia, dry mouth, lip dry, drug ineffective, drug interaction, drug effect prolonged, drug toxicity (all 1 report each).

Another search in AERS performed by the Office of Drug Safety which included not only the term "articaine" but included a search of combination products containing articaine and epinephrine resulted in 158 cases. Other terms were found in the search: delayed recovery from anesthesia (7), nerve injury (6), nausea (5), tongue disorder (5), facial pain (5), asthenia (3), facial palsy (3), neuralgia (3), depression (3), dysphonia (3), chest discomfort (2), fatigue (2),

injection site edema (2), sinusitis (2), iatrogenic injury (2), injury (2), thermal burn (2), arthropathy (2), muscle tightness (2), neck pain (2), drooling (2), nervous system disorder (2), sensory disturbance (2), dyspnea (2), sinus disorder (2), hypertension (2), cardiac disorder, ear discomfort, ear disorder, eye pain, vision blurred, visual disturbance, aptyalism, colitis, dysphagia, gingival erosion, lip discoloration, edema of the mouth, oral discomfort, oral mucosal exfoliation, vomiting, chills, drug effect decreased, injection site hemorrhage, injection site necrosis, injection site nerve damage, injection site paresthesia, necrosis, edema, mucosal edema, tenderness, anaphylactic reaction, ear infection, infection, bite, contusion, corneal reflex decreased, heart rate abnormal, heart rate irregular, weight decreased, jaw disorder, muscle spasms, amnesia, balance disorder, coma, consciousness fluctuating, dysarthria, dyskinesia, facial nerve disorder, headache, hemiparesis, mastication disorder, memory impairment, movement disorder, muscle contractions involuntary, paralysis, somnolence, tongue biting, tongue paralysis, disorientation, eating disorder, emotional distress, major depression, panic attack, restlessness, screaming, staring, suicidal ideation, bronchospasm, hypoventilation, pharyngeal edema, pulmonary hypertension, alopecia, purpura, rash, urticaria, immobile, flushing (all 1 case each).

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/s/

Jane Filie
3/22/2006 08:35:21 PM
MEDICAL OFFICER

Arthur Simone
3/22/2006 08:39:41 PM
MEDICAL OFFICER
I have read Dr. Filie's review and concur with her conclusions and recommendations.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
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Memorandum

DATE: February 23, 2006

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
Stanka Kukich, M.D., Acting Director, DDDP

TO: Allison Meyer, Project Manager, DAARP

Cc: Florence Houn, M.D., Director, ODE III
Julie G. Beitz, M.D., Deputy Director, ODE III
Bronwyn Collier, ADRA, ODE3
M. J. Kozma-Fornaro, R.N., Supervisory PM, DDDP

SUBJECT: Consult to the Division of Anesthesia, Analgesia, and Rheumatology Products, for NDA 20-010, Septocaine® — (Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection)

HFD-540 Consult #808

Material Reviewed: The clinical volumes of NDA 20-010 – volumes 14-28.

Review:
Sponsor: Deproco, Inc.
Drug: Septocaine® — (Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection)
Indications: Infiltration or nerve block anesthesia for dentistry

Introduction and Regulatory Background

Septocaine® — (Articaine Hydrochloride 4% with epinephrine 1:200,000) is a local anesthetic of the amide type, combined with a vasoconstrictor. Articaine Hydrochloride 4% with epinephrine in the concentration of 1:100,000 was approved on April 3, 2000 as NDA 20-971 for "local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures." (Indications and Usage section of label) At this time, Deproco, Inc. seeks approval of Articaine 4% with 1:200,000 epinephrine and wishes to co-market it with the already-marketed Articaine 4% with epinephrine 1:100,000. The purpose of combining epinephrine with articaine is to increase the duration and profoundness of the anesthesia. Vasoconstrictors such as epinephrine oppose the vasodilatory actions of the local anesthetics; by constricting blood vessels, vasoconstrictors decrease blood flow to the site of administration. Increased amounts of the local anesthetic remain in and around the nerve for longer periods, thereby increasing the duration of action of most local anesthetics. (Stanley Malamed, Handbook of Local Anesthesia, 2004) By the same mechanism, a more profound anesthesia can be produced. The constriction of blood vessels should also result in reduced bleeding during surgical procedures. The sponsor believes that the pharmacologic response to vasoconstrictors is dose-related and wishes to produce Septocaine with both concentrations of vasoconstrictor in order to offer dentists a choice depending upon their needs.

Of the five other currently marketed US local anesthetic agents with dental indications, the majority are available only with a 1:200,000 concentration of epinephrine (Etidocaine, Bupivacaine, and Prilocaine). Lidocaine is available in a 1:100,000 and 1:50,000 concentration of epinephrine; and Mepivacaine is available only with levonordefrin as a vasoconstrictor. Mepivacaine and Prilocaine are also available without vasoconstrictor.

Literature supports reasons to market the same local anesthetic with two strengths of vasoconstrictor. In the case of a procedure that is of short duration, the advantage of a low concentration of epinephrine is that the anesthetic effect will diminish sooner, resulting in less time without sensation for the patient after completion of the procedure. The American Heart Association recommends local anesthesia without epinephrine where possible in patients with ischemic heart disease. If the duration is too short or the anesthesia is insufficiently profound without a vasoconstrictor, the lowest effective dose of vasoconstrictor should be used. A higher concentration of vasoconstrictor is generally used by dentists when a longer duration of action is required. One other use for higher concentration of vasoconstrictor is for procedures where bleeding control is required. This is particularly useful in procedures such as crown preparation, when bleeding at the gingival margins may impair 1) the ability of the dentist to clearly see the detail of the delicate procedure, and 2) the ability of hydrophobic impression materials to produce an undistorted imprint of the crown. Certain surgical procedures such as periodontal surgery often benefit from less bleeding in the area with better visualization of the site.

Local anesthetic agents for dental use are injected either adjacent to the nerve bundles for blocks or infiltrated around the roots of the teeth when possible. Due to the thickness of

the mandibular bone, infiltration has not been shown to be effective at reaching the nerves of individual teeth in the mandible – a mandibular block is required for sufficient anesthesia. To successfully administer a mandibular block, local anesthetic solution is deposited in close proximity to where the inferior alveolar nerve enters the mandibular foramen on the lingual aspect of the mandibular ramus. This nerve, a branch of the mandibular division of the trigeminal nerve, supplies the pulps (where sensory innervation originates) of all the teeth and the bone on one side of the mandible. The maxillary bone is thin enough for a local anesthetic agent to penetrate to the root of the tooth, where the branches of the maxillary nerve innervate an individual tooth. Soft tissue anesthesia is achieved by infiltration into the desired area.

In terms of prior requirements for the currently marketed local anesthetic agents with epinephrine, there is very little guidance as the approval dates for their NDA's were prior to the current FDA requirements. For example, Xylocaine was approved in 1948, Mepivacine in 1960, Priolocaine in 1965, Bupivacaine in 1972, and Etidocaine in 1975 (subsequently withdrawn by the sponsor, but not for safety reasons).

Regulatory Background
A meeting was held between the sponsor and the Division of Anesthetic, Critical Care and Addiction Drug Products (the precursor of the Division of Anesthesia, Analgesia, and Rheumatology Products) on July 18, 2002, with the objective "to reach agreement on what would be required for the Agency to grant approval to the sponsor's second formulation of Septocaine." (Meeting minutes, DFS) During this meeting, the agency requested one study with three arms: 1) articaine 4% with epinephrine 1:200,000 2) articaine 4% with epinephrine 1:100,000, and 3) articaine 4% alone. The agency requested "appropriate endpoints and adequate size to create a database which describes the new formulation well enough from which a label may be crafted." Dr. Cynthia McCormick, Division Director at that time, further pointed out that "the sponsor would still need to establish the efficacy of this formulation" Dr. Bob Rappaport (Deputy Division Director at that time) added "that the sponsor needed to characterize the new formulation and that if trials showed it to be the same as the other formulation, then the sponsor would need to demonstrate that the new formulation was at least as safe as the approved product."

Summary of NDA Submission
This NDA was submitted to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) on September 30, 2005. The Clinical portion consists of 14 volumes, which contain results of three clinical trials, ART-02-001, ART-02-002 and ART-02-003. Reports of biopharmaceutical studies were also submitted and relevant results will be referenced in this document. The focus of this consult is to assist DAARP in the review of the three trials for safety and efficacy.

Requested Information in the Current Consult:
In correspondence dated December 21, 2005, DAARP requested a consult from the Dental Team in the Division of Dermatology and Dental Products (DDDP) to review the

NDA from a dental perspective. The consult contains five questions in which comments are requested on trial design, choice of endpoints, results, and indications. In order to answer these questions fully, a summary of the three studies will be provided, which includes the objectives, study design, procedures, outcome variables and results. In the section of this review that follows, the questions will be answered individually, and will reference the study plan, outcome variables, and results.

Please note that it is not the intent of this consult to provide recommendations for regulatory action of this drug. DDDP is providing thorough answers to the questions posed in the consult in a way that reflects the expertise of a clinical reviewer who is familiar with dental drugs and procedures. This includes opinions on the clinical significance of treatment and actual use in clinical practice. However, since the indication of this drug is to reduce pain associated with a dental procedure, rather than to treat or prevent any dental disease, the regulatory decision will need to be in accordance with the policies of DAARP.

Clinical Trials

In this section of the consult, the three pivotal clinical trials will be summarized, beginning with an overview and containing elements of the trial that will help answer the consultative questions. Subsections include the inclusionary and exclusionary criteria, outcome variables, and results. Since Studies ART-02-001 and ART-02-002 are nearly identical, these two trials will be presented together. Study ART-02-003 is an entirely different study design, and it will be presented by itself.

Studies ART-02-001 and ART-02-002

Overview

ART-02-001 was designed as a double blind, randomized, cross-over multicenter clinical trial to evaluate the safety and efficacy of articaine with epinephrine 1:200,000 when used in the mandibular (lower) arch. Healthy male and female subjects between 18 and 65 years of age were assigned to one of 3 test products: 4% articaine HCl with 1:200,000 epinephrine, 4% articaine HCl with 1:100,000 epinephrine, or 4% articaine HCl with no epinephrine. A single dose of the study drug, which the sponsor defined as one dental cartridge, consisted of 1.7 mL of test product. The solution was injected submucosally at a location determined by using the standard anatomical landmarks of the mandible for inducing an inferior alveolar nerve block. The primary efficacy variable was incidence of profound anesthesia. Secondary efficacy variables were 1) time to onset of anesthesia, 2) duration of profound anesthesia and 3) change in blood pressure and heart rate. Endpoints for safety consisted of changes in vital signs, and adverse events incidence.

ART-02-002 was nearly identical in design to ART-02-001; the few differences were due to ART-02-002 evaluating the safety and efficacy of articaine with epinephrine 1:200,000 when used in the maxillary (upper) arch. This is reflected in the design of this trial in which 1.0 mL of test product was injected into the submucosa of maxillary teeth through the infiltration technique. Inclusion and exclusion criteria are identical between the two trials except for tooth selection and site of administration: instead of monitoring the mandibular cuspid tooth for anesthesia, the maxillary first premolar tooth was the

monitored tooth for anesthesia in this trial. In the case that the maxillary first premolar tooth was extracted for primary orthodontic treatment (a common orthodontic treatment), the second premolar was used for local infiltration delivery and monitoring. Except as noted above, the study plan and outcome measures were identical to ART-02-001, and for the remainder of this section, comments apply equally to both trials unless otherwise noted.

Inclusionary and Exclusionary Criteria
Only subjects between the ages of 18 and 65 were enrolled. Subjects with a history of cardiac disease or uncontrolled hypertension were excluded. Subjects were excluded who took medication that was sedating or would in other ways alter their pain perception. For mandibular teeth, subjects with a decayed or restored mandibular cuspid (the target tooth for measurement of anesthesia) were excluded as this would affect the validity of the measurement. For maxillary teeth, at least one premolar had to be free of caries and dental restorations.

The target tooth also needed to have normal sensation for the subject to be included in either trial. The sensation of the tooth was determined by stimulating the target tooth with a standard electric pulp tester (EPT). This commercially available device delivers a small current to the tooth, which can be adjusted to range from 0 – 80 (This scale has no units; it is a relative scale; the corresponding voltage for this range was not provided). Although highly variable between subjects, a vital tooth should respond to electrical current with the sensation of pain. A normal EPT reading for the target tooth was defined as a tooth responded to a score of 10-50 units, which was required for inclusion at baseline as well as at the time of each treatment visit. The site of tooth contact was the midpoint of the incisal third of the labial surface. The tooth being tested was isolated with cotton rolls and air dried prior to testing. Electrode contact was assured by applying fluoride gel toothpaste to the probe tip.

Procedures
Three U.S. sites each enrolled 21 subjects per site to provide a total of 62 completed subjects for each of the two trials. The trials consisted of one 1-hour screening visit and three 4-5 hour treatment visits. Individuals were screened for eligibility criteria and if accepted, signed an informed consent, provided a medical history, had a brief physical exam including vital signs (blood pressure, pulse rate, respiratory rate, and body weight) and a urine pregnancy test for female subjects. A visit for the trial of the first of the three randomly assigned treatments was conducted within 8 days, and the two subject treatment sessions were scheduled at time intervals of at least one week and no greater than three weeks later.

At each treatment session, baseline vital signs were measured prior to injection. Following the administration of study formulations, the supine blood pressure and pulse rate were taken at five-minute intervals.

For mandibular applications, the inferior alveolar nerve block anesthesia was administered on the same side for all treatments. Injections were made using an

aspirating dental syringes and a 27 gauge long disposable needle. Injection volume was 1.7 mL (one cartridge) for all mandibular injections. Solutions were injected slowly with frequent aspirations over a one-minute time span. No topical anesthetics were applied prior to injection. For the maxillary injections, aspirating dental syringes were used with a 27 gauge short disposable needle. Injection volume was 1.0 mL and anesthesia was administered on the same side for all treatments. Evaluation for onset, duration and magnitude of anesthesia were conducted with the EPT, with outcomes recorded as is described in the next section.

Outcome Variables
Efficacy
Anesthetic efficacy was defined *a priori* as the incidence of profound anesthesia (success rate) following administration of anesthesia. The sponsor characterized adequate demonstration of efficacy as consisting of two parts: 1) being able to demonstrate that the Septocaine® — group was not inferior to the Septocaine® — group in efficacy and 2) to demonstrate superiority of both epinephrine concentrations to articaine with no vasoconstrictor. Superiority in magnitude, onset or duration of anesthesia resulting from Septocaine® — as compared to Septocaine® — was never an objective of this trial.

The incidence of profound anesthesia in each test group is the primary outcome variable. Onset time of the anesthesia and the duration of anesthesia are secondary outcomes. The efficacy and anesthetic characteristics of success, onset and duration were determined by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation using a standard commercially available EPT. The sponsor calibrated all EPT's prior to initiating the study and after study completion. For subjects receiving a mandibular block, the mandibular canine tooth on the anesthetized side of the mandible was the tooth monitored throughout the study session. For subjects receiving maxillary infiltration, the first premolar was monitored, unless it did not meet the inclusionary criteria, in which case the second premolar could be substituted if it met the inclusionary criteria.

The onset time for anesthesia was defined as the time in minutes from completion of the injection to the time when profound anesthesia, defined as EPT $\geq$ 80, was established. EPT was evaluated every 30 seconds after the injection until the threshold of 80 was reached. Three consecutive tests with a score of 80 were required to conclude that profound anesthesia had occurred. After the third 30-second EPT reading of 80 or above, the testing interval was extended to five minutes. Duration of anesthesia is the time from establishment of profound anesthesia to the initial loss of profound anesthesia. Loss of anesthesia was defined as three consecutive test results of below 80 at the five-minute intervals.

Another secondary outcome is heart rate and blood pressure change. The sponsor hypothesized that Septocaine® — would cause a lesser increase in BP and pulse after injection than Septocaine® — Changes in BP and pulse measurements at baseline, five minutes post injection and after completion of the test were calculated. In Study ART-

02-002, the changes in BP and pulse measurements were calculated for baseline, 10 minutes post injection and after completion of the test.

The investigator also asked the subjects to choose one of four categories to describe their sensory function at baseline and immediately following post-injection EPT testing. The choices were 1) no change or alteration in sensation, 2) slight feeling of numbness, 3) moderate but not complete feeling of numbness and 4) side of my mouth is completely numb. However, this was not listed as either a primary or secondary outcome variable, and its objective was listed as "providing a descriptive report of anesthetic characteristics."

Safety
The investigator recorded all adverse events that occurred. Subjects were specifically observed and/or asked about the following: 1) unexpected pain upon injection, 2) positive aspiration during injection, 3) discomfort at the injection site, 4) swelling at the sit of injection 5) rash or abnormal skin reaction 6) syncope and 7) other not specified. At 24 hours after the procedure, the subject was contacted via telephone and asked: "have you noticed any changes in your health since yesterday's testing session?" A positive response was followed by specific questions. Vital signs were assessed prior to injection, 10 minutes following injection and at the conclusion the session. Seven days following surgery, subjects returned for post-op visit; during that visit, subjects were specifically asked about swelling, headache, pain, infection, gingivitis, numbness or tingling, excessive bleeding, or poor healing.

At each treatment session, baseline vital signs were measured prior to injection. Following the administration of study formulations, the supine blood pressure and pulse rate were taken at five-minute intervals.

Results

Outcome variable results from Study ART-002-01 are as follows:

By Treatment	Total Number of Visits	Number of Visits with Success	% Success
4% articaine HCl without epinephrine	62	16	25.8*
4% articaine HCl with 1:100,000 epinephrine	63	30	47.6*
4% articaine HCl with 1:200,000 epinephrine	62	34	54.8*

* Septocaine® — is non-inferior to Septocaine® — both Septocaine® — and Septocaine® — are superior to Septocaine without vasoconstrictor

Treatment	Time to Onset						
	N	Mean	Median	Min	Max	Std	Range
4% articaine HCl without epinephrine	16	4.3	4.5	0.5	8.0	2.5	7.5
4% articaine HCl with 1:100,000 epinephrine	30	4.2	4.0	0.5	9.0	2.8	8.5
4% articaine HCl with 1:200,000 epinephrine	34	4.7	4.5	1.0	9.0	2.6	8.0

No significant difference in any comparison of the groups

Treatment	Duration						
	N	Mean	Median	Min	Max	Std	Range
4% articaine HCl without epinephrine	16	49.7	35.5	3.5	161.0	44.2	157.5
4% articaine HCl with 1:100,000 epinephrine	30	61.8	50.8	3.5	236.0	59.0	232.5
4% articaine HCl with 1:200,000 epinephrine	34	51.2	33.3	3.0	218.0	55.9	215.0

No significant difference in any comparison of the groups

Treatment	Change in Pulse Rate (5 min – preinjection)						
	N	Mean	Median	Min	Max	Std	Range
4% articaine HCl without epinephrine	62	-1.9*	-3.0	-20.0	28.0	7.8	48.0
4% articaine HCl with 1:100,000 epinephrine	62	3.3*	3.0	-21.0	25.0	8.9	46.0
4% articaine HCl with 1:200,000 epinephrine	62	2.5*	2.0	-13.0	22.0	7.1	35.0

*statistically significant difference of articaine without epinephrine compared to other two

Outcome variable results from Study ART-002-02

By Treatment	Total Number of Visits	Number of Visits with Success	% Success
4% articaine HCl without epinephrine	62	47	75.8*
4% articaine HCl with 1:100,000 epinephrine	63	60	95.2*
4% articaine HCl with 1:200,000 epinephrine	62	58	93.5*

* Septocaine® — is non-inferior to Septocaine® —; both Septocaine® — and Septocaine® — are superior to Septocaine without vasoconstrictor

Treatment	Time to Onset						
	N	Mean	Median	Min	Max	Std	Range
4% articaine HCl without epinephrine	47	3.0	2.5	0.5	9.5	2.0	9.0
4% articaine HCl with 1:100,000 epinephrine	60	3.0	2.5	0.5	9.0	2.1	8.5
4% articaine HCl with 1:200,000 epinephrine	58	3.1	2.5	0.5	9.5	2.3	9.0

No significant difference in any comparison of the groups

Treatment	Duration						
	N	Mean	Median	Min	Max	Std	Range
4% articaine HCl without epinephrine	47	13.3*	12.5	2.0	38.0	6.8	36.0
4% articaine HCl with 1:100,000 epinephrine	60	45.0*	40.8	5.0	99.5	23.6	94.5
4% articaine HCl with 1:200,000 epinephrine	58	41.6*	37.5	3.5	103.0	21.1	99.5

*statistically significant difference of articaine without epinephrine compared to other two

Treatment	Change in Pulse Rate (10 min – preinjection)						
	N	Mean	Median	Min	Max	Std	Range
4% articaine HCl without epinephrine	62	-3.6*	-3.0	-21.0	22.0	8.5	43.0
4% articaine HCl with 1:100,000 epinephrine	63	-0.1*	1.0	-21.0	18.0	7.5	39.0
4% articaine HCl with 1:200,000 epinephrine	62	-1.4	-2.0	-25.0	19.0	8.4	44.0

*statistically significant difference of Septocaine without epinephrine compared to Septocaine® —

Safety Results

ART-02-001

AE	Treatment					
	4% articaine HCl without epinephrine		4% articaine HCl with 1:100,000 epinephrine		4% articaine HCl with 1:200,000 epinephrine	
	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment
Elevated blood pressure	1	1.6	0	0	1	1.6
Headache	2	3.2	1	1.6	3	4.8
Headache, soreness at injection site	0	0	0	0	1	1.6
Heartburn	2	3.2	0	0	0	0
Nausea	0	0	0	0	1	1.6
Numbness and tingling	0	0	1	1.6	0	0
Otitis media	0	0	0	0	1	1.6
Persistent pain	0	0	1	1.6	1	1.6
Positive aspiration	3	4.8	5	7.9	1	1.6
Soreness at injection site	3	4.8	4	6.3	3	4.8
Soreness at injection site, earache	0	0	1	1.6	0	0
Soreness of neck and shoulder, sensitive teeth	0	0	1	1.6	0	0
Subject had an electronic shock to the head – subject hit head on chandelier	0	0	1	1.6	0	0
Swelling, soreness at injection site	1	1.6	0	0	0	0
Trismus	1	1.6	1	1.6	0	0
Unexpected pain intensity upon injection	1	1.6	0	0	0	0

Note: None of the adverse events recorded were serious in nature, none were severe in intensity, and none resulted in subject discontinuation. The most common adverse events were headache, soreness at injection site and positive aspiration.

Safety Results of Study ART-02-002

Adverse Event	Treatment					
	4% articaine HCl without epinephrine		4% articaine HCl with 1:100,000 epinephrine		4% articaine HCl with 1:200,000 epinephrine	
	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment
Anemia	0	0	1	1.6	0	0
Elevated blood pressure	0	0	1	1.6	0	0
Headache	1	1.6	1	1.6	0	0
Headache, sinus pain	0	0	1	1.6	3	4.8
Itchy throat and persistent cough	0	0	1	1.6	0	0
Nausea	0	0	0	0	1	1.6
Numbness and tingling	0	0	0	0	1	1.6
Oral lesions	1	1.6	0	0	0	0
Positive aspiration	0	0	0	0	1	1.6
Sinus congestion	0	0	0	0	1	1.6
Soreness at injection site	1	1.6	1	1.6	1	1.6
Unexpected pain intensity upon injection	1	1.6	0	0	0	0

Note: None of the adverse events recorded were serious in nature, none were severe in intensity, and none resulted in subject discontinuation. The most common adverse events were headache, and soreness at injection site. Of note is that one subject in the Septocaine —/ group reported numbness or tingling of the mouth or face immediately following treatment Visit 1. All symptoms resolved within 5.5 hours.

ART-02-003

Overview

Trial ART-02-003 differs from ART-02-001 and ART-02-002 in that its objective is to demonstrate that the Septocaine® — is superior to Septocaine® — in its ability to improve visualization of the surgical field and limit surgical blood loss when used to induce anesthesia for periodontal surgery. In order to do this, the sponsor designed this double-blind, randomized, crossover study of 42 subjects at multiple study sites. Each subject required bilateral periodontal surgery to be included in the study; on one side, surgery was conducted with Septocaine® — and the other surgery with Septocaine® —/. Surgeons rated each surgery for the clearness of the surgical field with two different scales. Subjects' level of anesthesia was self-assessed, and their blood loss during the procedures was measured.

There was no group that received 4% articaine without epinephrine as was done in both ART-02-001 and ART-02-002 for two reasons. 1) It would be unethical to perform a periodontal surgical procedure without a vasoconstrictor, as excessive bleeding would likely result that may compromise the procedure's success and 2) the outcome is to prove superiority of Septocaine® — over Septocaine® — for bleeding control, rather than ART-02-001 and ART-02-002's objective of demonstrating that both were more

successful at providing adequate duration of anesthesia than Septocaine without vasoconstrictor.

Inclusionary and Exclusionary Criteria
Subjects were enrolled who required bilateral periodontal surgery of equal complexity. Only individuals age 21-65 were eligible for participation. To ensure a consistent level of surgical procedure, subjects were enrolled with gingival flap procedures and were matched on number of teeth involved and equal level of attachment loss. Subjects taking medication that interferes with blood coagulation or pain perception were excluded. Individuals with significant history of cardiac disease or uncontrolled hypertension were excluded.

Procedures
The trial consisted of a 1-hour screening visit and two 2-4 hour surgical visits, each followed by a telephone call 24-hours after surgery and a 7-day postoperative visit. The second surgery was performed 3 – 5 weeks after the first one. During the screening visit, potential subjects were screened for inclusion and exclusionary criteria. A medical history, physical examination, laboratory assessments and vital signs including blood pressure, pulse rate and respiratory rate were assessed. Subjects were randomly assigned to receive either Septocaine® — or Septocaine® — for the first surgical procedure. During the surgeries, subjects were injected with up to 4 carpules depending upon the needs of the subject. Topical anesthetic (——————————) was applied to the mucosa prior to all anesthetic injections. During the second surgical procedure, the other anesthetic was used, but otherwise, the procedures are repeated.

Surgical blood loss was determined from the time of the initial incision to the time the final suture was placed. All free-flowing blood, saliva and irrigation solutions were collected into a separate canister attached to the portable vacuum system. The volume of all irrigation solutions used was recorded. All gauze was pre-weighed; gauze that was used during the procedure was collected in a sealed container immediately after removal from the mouth and weighed. The sponsor proposed that since the saliva collected should not vary with the amount of epinephrine used, the total difference in weight between the materials collected for each surgery should reflect any difference in blood collected.

Assessments
Efficacy Assessments
In addition to evaluating the amount of fluid collected as described above, the outcome was also evaluated with two separate surgeon's assessments and a patient self-assessment, as detailed below. The primary efficacy variable is the surgeon's rating of the ability to visualize the surgical site. The volume of blood collected and the other two scales are secondary endpoints.

Scale	The Visualization of Surgical Field Scale	The Expectation of Blood Loss Scale	Patient-assessed Level of Anesthesia
When measured	Conclusion of each of the surgical procedures	Conclusion of each of the surgical procedures	Immediately prior to injection, immediately prior to surgery, and following placement of the final

			suture
Question Posed	"How clear was your visualization of the surgical field?"	"Based on your past experience performing periodontal surgery, how well did the local anesthetic limit bleeding?"	Select one of the following categories to describe your anesthesia
Question Posed To:	Surgeon	Surgeon	Subject
Choice of Responses	1) Very unclear	1) Much worse than expected	1) Normal sensation
	2) Moderately unclear	2) Moderately worse than expected	2) Slight feeling of numbness
	3) Slightly unclear	3) Slightly worse than expected	3) Moderate but not complete feeling of numbness
	4) Neither clear nor unclear	4) Equal to expected	4) Side of my mouth is completely numb
	5) Slightly clear	5) Slightly better than expected	
	6) Moderately clear	6) Moderately better than expected	
	7) Very clear	7) Much better than expected	

Safety Assessments

The investigator recorded all adverse events that occurred. Subjects were specifically observed and/or asked about the following: 1) unexpected pain upon injection, 2) positive aspiration during injection, 3) discomfort at the injection site, 4) swelling at the sit of injection 5) rash or abnormal skin reaction 6) syncope and 7) other not specified. At 24 hours after the procedure, the subject was contacted via telephone and asked: "have you noticed any changes in your health since yesterday's testing session?" A positive response was followed by specific questions. Vital signs were assessed prior to injection, 10 minutes following injection and at the conclusion the session. Seven days following surgery, subjects returned for post-op visit; during that visit, subjects were specifically asked about swelling, headache, pain, infection, gingivitis, numbness or tingling, excessive bleeding, or poor healing.

Results
Study ART-02-003

Visualization of Surgical Field

By Treatment	4% articaine with 1:100,000 epinephrine		4% articaine with 1:200,000 epinephrine	
	Frequency	Percent	Frequency	Percent
Very unclear	0	0	1	2.4
Moderately unclear	0	0	4	9.5
Slightly unclear	6	14.3	6	14.3
Neither clear nor unclear	1	2.4	6	14.3
Slightly clear	7	16.7	5	11.9
Moderately clear	16	38.1	10	23.8
Very clear	12	28.6	10	23.8
Total in the clear categories*	35	83.3	25	59.5

*p value for the difference = 0.034

Quantity of Blood Loss

Treatment							
	N	Mean	Median	Min	Max	Std	Range
4% Articaine with 1:100,000	42	54.9	52.9	-8.6	165.3	36.0	173.9
4% Articaine with 1:200,000	42	70.2	60.2	5.0	305.7	53.0	300.7

P value for difference of means = 0.018

Summary of Expectation of Blood Loss

Expectation of Blood Loss	4% articaine with 1:100,000 epinephrine		4% articaine with 1:200,000 epinephrine	
	Frequency	Percent	Frequency	Percent
Much worse than expected	0	0	0	0
Moderately worse than expected	1	2.4	6	14.3
Slightly worse than expected	5	11.9	6	14.3
Equal to expected	9	21.4	12	28.6
Slightly better than expected	14	33.3	7	16.7
Moderately better than expected	10	23.8	7	16.7
Much better than expected	3	7.1	4	9.5
Total for equal to or better than expected*	36	85.6	30	71.5

*p value for difference is 0.034

Summary of Success

Treatment	Total Visits	Visits with Success	% Success
4% Articaine with 1:100,000 epinephrine	42	42	100
4% Articaine with 1:200,000 epinephrine	42	42	100

Safety results of Study ART-02-003

	Treatment			
Adverse Event	4% articaine HCl with 1:100,000 epinephrine		4% articaine HCl with 1:200,000 epinephrine	
	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment	Total Number of Adverse Events	% of Total Number of Exposures Within Treatment
Burning sensation above the injection site (underneath the right eye)	0	0	1	2.4
Cold sensitivity to tooth #13	1	2.4	0	0
Earache still present	1	2.4	0	0
Emisis (sic)	0	0	1	2.4
Facial swelling right side	1	2.4	1	2.4
Fractured toe	1	2.4	0	0
Intermittent pain	0	0	1	2.4
Loose tooth #13	1	2.4		
MO restored with dycal and amalgam tooth #31	0	0	1	2.4
Mild discomfort	1	2.4	1	2.4
Numbness/tingling in lip and corner of mouth post surgery	1	2.4	0	0
Pain	0	0	1	2.4
Pain – patient took ibuprofen	0	0	1	2.4
Persistent pain	1	2.4	0	0
Persistent pain (punch in face)	1	2.4	0	0
Post-op swelling and pain	0	0	1	2.4
Slight swelling	1	2.4	0	0
Soreness	0	0	1	2.4
Swelling	2	4.8	1	2.4
Swelling UL	1	2.4	0	0
Ulceration at corner of mouth angular cheilitis	0	0	1	2.4
Runny nose, cold symptoms	1	2.4	0	0

Specific Consult Questions and Responses:

1. *Are the study designs appropriate for ART-02-001, ART-02-002 and ART-02-003?*

Response:

ART-02-001 and ART-02-002

The designs of trials ART-02-001 and ART-02-002 are sufficient to determine whether subjects in the two groups receiving Septocaine with either of the vasoconstrictor concentrations have a better response to EPT compared to the no-vasoconstrictor group and whether the Septocaine® — is noninferior to Septocaine® ~ in efficacy. However, it is not clear how well these outcomes correlate to pain control during actual dental treatment. Prior to designing the EPT trials, the sponsor discussed how they would show efficacy of the Articaine with 1:200,000 epinephrine. The Agency agreed that as long as both Articaines (Septocaine® —and Septocaine® —) were demonstrated to be superior to the Articaine without vasoconstrictor and the Septocaine® — was noninferior to Septocaine® — ; it would be sufficient evidence of efficacy. The details were left to the sponsor's discretion. The sponsor most likely chose EPT to measure sensory response because it was a less burdensome assessment in a clinical trial than VAS measurements in combination with clinical procedures. EPT, however, is not necessarily going to predict how these products perform during a dental procedure and whether achieving a score of 80 with EPT is a good predictor of sufficient loss of sensation during routine dental procedures. This outcome will be discussed further in the response to Question #2 of this consult that follows.

The selection of target teeth is appropriate. A mandibular cuspid (also referred to as a canine tooth) is far enough forward in the mouth for easy access and far enough away from the midline that the possibility of additional innervation from the mental nerve of the other side of the mouth is not a concern. The premolar (bicuspid) tooth as a choice for the maxillary arch is also appropriate, as this is a good tooth for access and visualization of the injection site.

The choice of 1.7 ml dosing in the mandibular trial and 1.0 ml dosing in the maxillary trial is rational. Norman Trieger (Pain Control, 1994) cites 1.0 ml as being sufficient for most mandibular blocks and 0.5 ml as being sufficient for infiltration. Malamed states that 1.5 ml is adequate for a mandibular block and 0.6 ml for infiltration. The current label for the approved Septocaine (Articaine 4% with epinephrine 1:100,000) provides a table under the Dosage and Administration section which recommends the wide range of between 0.5 and 2.5 ml for infiltration and 0.5 – 3.4 ml for nerve block. Its midpoint along with the other two citations corroborate that the injected amounts are adequate for these trials.

The selection of inclusionary and exclusionary criteria was reasonable – conditions for use of medication that causes drowsiness or alters pain perception would confound the study and be likely to produce invalid results. The sponsor allowed individuals into the trial who had a history of hypertension, as long as it was controlled, but did not allow subjects with uncontrolled hypertension. This is appropriate, as published guidelines

recommend against administration of a vasoconstrictor in a local anesthetic agent to those individuals. (Muzyka and Glick, JADA 1997) Similarly, a significant history of cardiac disease including severe or frequent arrhythmias is appropriate for exclusion as this is a contraindication for vasoconstrictor. Elimination of subjects with infection near the proposed injection site is also appropriate, as infection often prevents local anesthetic agents from being effective.

One limitation that may be problematic is the age restriction of 18 -65 for subject enrollment. With this, the sponsor has eliminated study of this product in either pediatric or geriatric populations. If approved, there is clearly going to be use of Articaine 4% with epinephrine 1:200,000 in both the pediatric and geriatric populations. Based upon dentists' perceptions of better safety with the 1:200,000 strength, it is predictable that these populations will be more likely to receive the articaine with the lower epinephrine concentration.

ART-02-003

There are many positive study design elements in ART-02-003, especially the actual use aspect when compared to ART-02-001 and ART-02-002. Both ART-02-001 and ART-02-002 used EPT as a surrogate for pain during dental procedures, leaving it inconclusive as to whether positive results will provide useful information for clinicians who are interested in the efficacy that they can expect in a clinical situation. ART-02-003, on the other hand, was an actual use study in which a periodontal surgeon performed procedures where better visualization of the field through control of bleeding is very important. In order to be enrolled, subjects required bilateral periodontal surgery; one procedure was randomly assigned to the Septocaine® — and the other to Septocaine® —. Because each subject served as his own control, the two bilateral surgeries per subject should have resulted in minimal differences in susceptibility to bleeding, length of procedure, or other factors.

The inclusionary and exclusionary criteria were nearly identical to those for the other two studies, and the same comments made for those studies apply here as well. In this study, criteria were added to exclude subjects who take any drugs which would affect bleeding, a wise precaution as well as a necessity to prevent confounded results.

Although periodontal surgery would be rarely performed on individuals under the age of 21, it is a common procedure in individuals over 65. Only subjects between the ages of 21 and 65 were enrolled; therefore, any difference in the impact of vasoconstrictor on blood loss in pediatric or geriatric individuals is unknown.

Potential problems with the design is that since the surgeon uses up to four carpules of test anesthetic agent, it is possible that the surgeon could be correcting for bleeding control by using additional local anesthetic to try to increase the volume of epinephrine to the area. Also, it is quite likely that by the second surgery, the surgeon could have guessed which anesthetic had which concentration of vasoconstrictor, compromising the blinding of the trial.

2. *Are the safety and efficacy endpoints adequate?*

Response:

Studies ART-02-001 and ART-02-002

Efficacy Endpoints:

The primary efficacy endpoint in both trials was the response to pulp testing, with adequate anesthesia characterized by an EPT score of 80 or for three consecutive readings, spaced 30 seconds apart. The EPT measures response to variable amounts of electrical current applied to the surface of the tooth. The sponsor chose "80" as the cutoff for successful anesthesia for these studies; however, there is no information provided about whether this score of 80 corresponds to sufficient depth of anesthesia for routine dental procedures.

In the original trials for the approved Septocaine (Articaine 4% with epinephrine 1:100,000), routine dental procedures were performed in subjects who received either the test product or an active control in a blinded fashion - VAS was used to gauge any discomfort during the procedure. Examples of simple procedures included single-tooth restorations (fillings) and single uncomplicated extractions; examples of complex procedures included multiple extractions, multiple crowns, and surgical procedures on the bone. The results of those clinical trials showed that on a 0 (no pain) to 10 (worse pain imaginable) VAS, the mean score in subjects having simple dental procedures was 0.3; subjects with complex procedures had a mean score of 0.5. Constructing language in the revised labeling that is meaningful to the clinician will be very difficult since the EPT results bear little resemblance to the results of the VAS.

The sponsor chose a measure of anesthesia intensity as the primary outcome variable even though increased duration of action is the more accepted reason for adding vasoconstrictor to local anesthetics. Vasoconstrictors cause a higher concentration of anesthesia to concentrate in the area before diffusing away which prolongs the effect of the anesthesia. By the same mechanism, vasoconstrictors may also increase the depth of anesthesia but this is not often cited as the reason for adding vasoconstrictor to local anesthetic agents. A question that would be more clinically meaningful to answer is whether Septocaine® — has a longer duration of anesthesia than Septocaine® —, and to characterize both anesthetic agents so dentists can make an informed choice based upon the results. However, to fulfill the Agency's request of demonstrating non-inferior efficacy of the Septocaine® — product, the sponsor chose instead to demonstrate non-inferiority of Septocaine — to Septocaine with EPT scores. The final design was made to accomplish that and was not adequately powered to adequately compare the two levels of vasoconstrictor for differences in either EPT response or in duration.

The current label for Septocaine (articaine 4% with epinephrine 1:100,000) describes its pharmacodynamics with information about the onset of anesthesia (between 1 to 6 minutes of injection) and the duration as "Complete anesthesia lasts approximately 1 hour." Because the EPT does not seem to correlate well to the level of anesthesia required for dental procedures, the information about onset and duration may be

misleading to extrapolate to actual effectiveness during dental procedures. Therefore, by using the EPT, there is little useful information that can be relayed to practitioners on the label.

There are three secondary efficacy measurements – onset time of anesthesia, duration of anesthesia, and pulse/blood pressure changes. The first two are reasonable additional endpoints; as was discussed earlier in this section, duration of anesthesia is clinically relevant information. Onset time of anesthesia is useful to explore, but based upon what is known about the action of vasoconstrictors, there is no expectation of a difference between any of the three groups. Pulse and blood pressure changes are probably better characterized as safety endpoints, but the sponsor listed them as efficacy measures. This is a valuable outcome to examine, as one of the important reasons cited in the literature for avoiding vasoconstrictor is elevated blood pressure or a compromised cardiac condition. The amount of epinephrine injection as part of a local anesthesia that contains 1:100,000 concentration for a typical dental procedure is equivalent to endogenous epinephrine generated during strenuous exercise (Dionne, Management of Pain and Anxiety in the Dental Office, 2002). Therefore, as per the current American Heart Association recommendations, medically compromised individuals should use one of the locals without epinephrine, unless the dental procedure cannot be comfortably completed without the vasoconstrictor. A useful question to answer therefore would be whether Septocaine® — produces significantly less increase in BP and pulse than Septocaine® —; however, the study was not designed or powered to accomplish this.

Safety

Since vasoconstrictors result in lower anesthetic blood levels (Malamed), one concern with lower concentrations of epinephrine in vasoconstrictor is that it could potentially lower the maximum safe dosage of the Septocaine® — compared to Septocaine® —. Towards this end, Study ART-03-001, a pharmacokinetics study of 13 subjects, was specifically conducted to measure and compare peak plasma concentrations of Septocaine® — and Septocaine® — following injections up to the maximum recommended dosage (11.9 ml). The results of that study led the biopharmaceutics reviewer to conclude that although the Septocaine® — did show higher concentrations of articaine in the plasma than the Septocaine® —, the difference was not clinically important.

Another general comment about safety is that literature has remarked upon a concern with Septocaine's ability to create paresthesia, particularly in the mandibular nerve after performing a mandibular block injection. Malamed and Dionne propose that nerve irritation is greater in local anesthetic agents with higher concentrations (e.g., 4% articaine vs. 2% lidocaine). For example, Malamed cites a 20-year study performed in Canada which collected data on all of the local anesthetics used in dentistry in Ontario. This includes 2% lidocaine, 2% etidocaine, 2% mepivacaine, 4% prilocaine, and 4% articaine. The highest incidence of paresthesia occurred after the administration of 4% articaine and 4% prilocaine. Based upon the local anesthetic use figures in Ontario, the area of study, the incidences of these events was much higher than expected only in these two local agents. Additional evidence is that prilocaine is available in 3% and 4%

concentrations in European countries. In these countries, the incidence of paresthesia is significantly greater in the 4% solutions than in the 3% solutions. In the sponsor's pivotal trials, examiners collected data after injections and followed up for one week. Although one week is adequate time to determine if persistent paresthesia had developed, the number of subjects enrolled was insufficient to gather sufficient data about this fairly rare outcome. Monitoring of post-marketing events from Septocaine® — if approved may provide further information. In addition, DAARP has consulted with the Office of Postmarketing Surveillance to evaluate MEDWatch and other safety data from the currently marketed Articaine 4% with epinephrine 1:100,000.

In addition to assessing adverse events during the trials, the sponsor also contacted subjects via telephone 24 hours after the trial completion. During this interview, they asked an open-ended question about changes in health, and specify follow-up questions to any positive response. All events were characterized by date and time of onset and resolution, duration of the event, assessment of relation to the study drug, the dose administered, the outcome of the event, the intensity of the event, the seriousness of the event, any treatment required, and results of any diagnostic procedures required. There was a follow up to any subject experience an adverse event until a clinically satisfactory resolution was achieved. Any abnormalities uncovered during the physical examination or vital signs assessments were recorded as well. For the scope of the trials, these safety measurements appear adequate.

Study ART-02-003
Efficacy
The choice of endpoints for efficacy are logical, particularly the primary outcome variable, the "Visualization of Surgical Field" scale. In this scale, investigators were asked to mark their perception of the visualization of the surgical field in one of seven categories, ranging from very unclear to very clear. The middle category was "neither clear nor unclear"; the three better categories were classified as "slightly clear", "moderately clear" and "very clear"; the three worse categories were "slightly unclear", "moderately unclear" and "very unclear." The results were then collapsed into a binary outcome, with responses in the "slightly clear", "moderately clear", or "very clear" categories being considered "clear", and all of the other categories collapsed into "not clear." Although the sponsor did not state how or if this scale has been validated prior to its use in this trial, it nonetheless should be capable of providing useful information to evaluate visualization, the most clinically relevant aspect of reducing bleeding during surgery.

The secondary efficacy endpoints included the Expectation of Blood Loss scale, Patient-Assessed Level of Anesthesia, and objective measurements of blood loss. None of these secondary outcomes are as strong of an endpoint as the primary one for several reasons. In the Expectation of Blood Loss scale, the examiners were required to rely on their memory of prior surgeries, which can produce recall bias. For that reason, DDDP generally prefers static measures, i.e., how an outcome looks at that moment over dynamic measures such as "compared to prior experiences, how does this rate?" This may partially explain why the results showed higher expectations being met for both

groups. The sponsor's method for calculation of blood loss may have relied upon some erroneous assumptions which significantly overestimated the amounts, as will be discussed further in the answer to the next question of this consult. Published articles that examine blood loss during dental procedures have relied on the cyanmethemogloban comparison technique for a more accurate measure of blood loss. The third secondary endpoint, patient-assessed level of anesthesia, is a useful measurement, and is similar to the primary outcome in the pivotal trials for the NDA for Articaine 4% with epinephrine 1:100,000. Instead of using a VAS for a continuous result, the assessment used in ART-02-003 relied on categories.

Safety
The safety data collected in ART-02-003 was very similar to that collected in ART-02-001 and ART-02-002. Because this trial involved periodontal surgery, laboratory evaluations were completed at baseline for hematology and normal values were required for inclusion into the trial. In addition to assessing adverse events during the trials, the sponsor also contacted subjects via telephone 24 hours after the trial completion. During this interview, they asked an open-ended question about any changes in health, and specific follow-up questions to a positive response. All events were characterized by date and time on onset and resolution, duration of the event, assessment of relation to the study drug, the dose administered, the outcome of the event, the intensity of the event, the seriousness of the event, any treatment required, and results of any diagnostic procedures required. There was follow up to any subject experiencing an adverse event until a clinically satisfactory resolution was achieved. In this trial, subjects returned to the clinic after 7 days for suture removal and surgical evaluation. At that time, postoperative recovery and wound healing were assessed and specific adverse reactions were again elicited. These safety measurements appear adequate for this trial.

3. *In your opinion, is there a plausible explanation for the variability in response to the treatments by the same patient as well as the variability in responses among the centers?*

Response:
Study ART-02-001 and ART-02-002
The results are somewhat unexpected in two main areas: the much lower success rate than expected in the mandibular (ART-02-001) study and the wide variation by study site. The hypothesis tested in both trials was whether there would be a statistically significant difference between articaine without vasoconstrictor and articaine with vasoconstrictor in subjects responding to the EPT. Although both studies were successful in demonstrating non-inferiority of Septocaine® — to Septocaine® — , the results in the mandibular trial show a lower than expected percentage of subjects who demonstrated successful anesthesia in both the Septocaine® — and Septocaine® — groups. The percentage of overall success from all sites using Septocaine® without vasoconstrictor is 25.8 and the percentage of overall success from all sites using Septocaine® — is 47.6. The percentage of overall success from all sites using the already approved Septocaine® — has only a 54.8% success rate. Literature shows that the percentage of success for a mandibular block should be much higher, including a citation from Allen (Dental

Anesthesia and Analgesia (Local and General), 1984) of 65 – 85% and one from Malamed of "80-85% or higher."

The sponsor proposed operator variability in EPT usage or injection technique as an explanation for the difference between sites. When examining all treatments combined, the Forsythe site had a success score of 19.7%, University of Pennsylvania had 39.7% and University of Pittsburgh had 68.3%. Perhaps a more plausible explanation for why all of the centers scored lower than historically expected is that the *a priori* definition of success - a score of 80 or above from the EPT - was too demanding a level. It is plausible that this was a more profound level of anesthesia that can be achieved in many individuals with only one carpule of Septocaine as delivered through the mandibular block. Although subjects may not have achieved 80 on the scale, it is unknown if they may have achieved sufficient level of anesthesia for commencing routine dental procedures. Although EPT is accepted as one measure of tooth vitality, it has never been correlated with specific depth of local anesthesia.

In terms of why Forsyth Center is so much lower than the other two sites, there are two choices: 1) The clinicians who injected the local anesthetic into the site were not able to correctly execute the injection or 2) the EPT was malfunctioning or not calibrated properly. It is hard to believe that a clinician who is selected for this study is not capable of properly injecting a mandibular block. To address whether the EPT is inaccurate or unreliable, the sponsor reports calibrating the EPT within each center, but not between centers. If the EPT's were all calibrated to a standard that would not have varied between centers, then differences in EPT calibration would not explain the results.

Another outcome that is unusual in the mandibular trial is the duration results. The Septocaine® — group has a nearly identical duration to the Septocaine® without vasoconstrictor group, but the Septocaine® — group has a much greater duration than either of the other two. If these results are valid, this lack of improved duration with the 1:200,000 is inconsistent with the magnitude of effect shown with the primary outcome. Specifically, if the difference between Septocaine® — and Septocaine® without vasoconstrictor was too small to show any effect on duration, it is surprising that the EPT comparison shows a statistically significant difference.

In the maxillary study, the results were much more as expected. The success rate was 95% in the Septocaine® — group, 94% in the Septocaine® — group and 76% in the Septocaine® without vasoconstrictor group. This is consistent with the figure of greater than 95% that is cited as a success rate with maxillary infiltration (Malamed). Once again, the Forsyth center had the worst overall outcome at 86%, compared to University of Pennsylvania's 90% and University of Pittsburgh's 89%, suggesting that training of examiners, calibration of equipment or execution of the protocol may have been deficient at the Forsyth center.

As would be predicted, the duration was significantly greater in Septocaine® — and Septocaine® — than in the Septocaine® without vasoconstrictor group. Also consistent

with literature, the results show a magnitude of duration which is greater in the maxillary infiltration than was shown in the mandibular block. (Dionne, page 90)

Another possible explanation for unexpected results in some of the secondary endpoints is that there are a very large number of comparisons within the secondary endpoints without any correction for multiple endpoints. With the sheer number of comparisons, some unexpected events are likely to occur by chance.

ART-02-003
The outcomes in Trial ART-02-003 are fairly consistent, and all support the conclusion that there is a better visualization of the surgical field with the Septocaine® — group compared to the Septocaine® — group. However, there are several minor inconsistencies in both the primary and secondary outcomes.

The Visualization of Surgical Field results demonstrate a statistically significant different between the Septocaine® — and Septocaine® — groups, with 85% of the surgeries being rated in the slightly clear, moderately clear or very clear categories in the Septocaine® — group and 60% of the surgeries being rated in the slightly clear, moderately clear or very clear categories in the Septocaine® — group. One discrepancy is in the Forsyth Center, in which every surgery in both groups was rated in one of the clear categories. There was no further statistical breakdown of the results to examine whether there is a difference between treatment groups in the numbers in the "slightly clear", "moderately clear" and "very clear." If the trend of better clarity is apparent in the Septocaine® — group, it would be consistent with the other centers and one could conclude that the surgeon was overly optimistic about the clarity of the field in all subjects. However, once again, the Forsyth center has unusual results which raise questions about examiner training and performance. Although surgeons have differing abilities, it is unlikely that the amount of bleeding would be significantly different between surgeons for similar procedures.

The results of the Investigators Scale show that the Septocaine® — group had a mean score of 85.7%, whereas the Septocaine® — group had a mean score of 71.4%. This supports the superior bleeding control with Septocaine® —, but also means that even the lower scoring Septocaine® — group exceeded the investigator's expectations of blood loss from prior surgeries. Since all of the local anesthetics currently marketed with vasoconstrictor have a minimum concentration of 1:200,000, and are also available in 1:100,000 and 1:50,000 concentrations, it is a surprising result. It may show that the placebo effect works as well in investigators as in subjects, or it may show that the scale is not particularly valid. Nonetheless, it is supportive that the trend is in the proper direction.

The quantity of blood lost as measured is also a secondary endpoint, and being objective, should be less susceptible to any kind of bias. However, the results show a mean of 70 ml of blood lost in the Septocaine® — group and 55 ml of blood lost in the Septocaine® — group, which is higher than expected from similar surgeries. For example, in a study by Braganza et al (The effect of non-steroidal anti-inflammatory drugs on bleeding