CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-010

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 22-010 (administratively split from sNDA 20-971)
Drug Name:	SEPTOCAINE® (Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:100,000 or 1:200,000 Injection)
Indication(s):	For infiltration or nerve block anesthesia for dentistry
Applicant:	Deproco, Inc.
Date(s):	Submitted: September 30, 2005 PDUFA: March 29, 2006
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	Thomas Permutt, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical Team:	Jane Filie, M.D.
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Keywords: Non-inferiority, McNemar's test, ANOVA

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study ART-02-01 with healthy subjects provided data showing an efficacy of 4% articaine with 1:200,000 epinephrine when administered for inferior alveolar nerve block anesthesia based on intent-to-treat (ITT) analysis. In terms of the profound anesthesia, 4% articaine with 1:200,000 epinephrine was shown as non-inferior to 4% articaine with 1:100,000 epinephrine and was shown as superior to 4% articaine without epinephrine. (See Tables 3 - 6 in the Appendix.)

Study ART-02-02 with healthy subjects provided data showing an efficacy of 4% articaine with 1:200,000 epinephrine when administered for maxillary infiltration anesthesia based on ITT analysis. In terms of the profound anesthesia, 4% articaine with 1:200,000 epinephrine was shown as non-inferior to 4% articaine with 1:100,000 epinephrine and was shown as superior to 4% articaine without epinephrine. (See Tables 7 - 10 in the Appendix.)

Study ART-02-03 with subjects with moderate to severe periodontal disease provided data showing an efficacy of 4% articaine with 1:200,000 epinephrine when administered for maxillary anesthesia based on ITT analysis. In terms of the visualization of surgical field, significantly less subjects with 4% articaine with 1:200,000 epinephrine had 'clear' visualization than those with 4% articaine with 1:100,000 epinephrine. (See Tables 11 - 15 in the Appendix.)

Overall, the submitted data provide statistically and clinically significant results supporting dental anesthesia of 4% articaine HCl with 1:200,000 epinephrine injection.

1.2 Brief Overview of Clinical Study

The sponsor submitted the results of three phase III efficacy studies ART-02-001, ART-02-002, and ART-02-003.

The design for the two studies ART-02-001 and ART-02-002 was identical and was a double-blind, randomized, active-controlled, multi-center, crossover trial to investigate the safety and anesthetic effect of 4% articaine HCl with 1:200,000 epinephrine injection in healthy subjects, when administered for inferior alveolar nerve block anesthesia for study ART-02-001, or when administered for maxillary infiltration anesthesia for study ART-02-002. Sixty-three subjects in each study were randomized to one of six possible sequences with three treatment periods: 4% articaine with 1:200,000 epinephrine, 4% articaine with 1:100,000 epinephrine, and 4% articaine without epinephrine.

The primary objective was to demonstrate the non-inferiority in anesthetic efficacy of the investigational formulation of 4% articaine with 1:200,000 epinephrine as compared to 4% articaine with 1:100,000 epinephrine.

The primary efficacy endpoint was the incidence of profound anesthesia (success rate). Secondary efficacy endpoints were the time to onset of anesthesia and the duration of profound anesthesia.

The design for the study ART-02-003 was a double-blind, randomized, active-controlled, multi-center, crossover trial to investigate the safety and hemostatic effect of 4% articaine HCl with 1:200,000 epinephrine injection in patients with moderate to severe periodontal disease, when administered for maxillary anesthesia. Forty-two subjects were randomized to one of two possible sequences with two treatment periods: 4% articaine with 1:200,000 epinephrine and 4% articaine with 1:100,000 epinephrine.

The primary objective was to assess the hemostatic efficacy of the investigational formulation of 4% articaine with 1:200,000 epinephrine as compared to 4% articaine with 1:100,000 epinephrine.

The primary efficacy endpoint was the surgeon's rating of visualization of the surgical field. Secondary efficacy endpoints were the surgeon's expectation and the quantity of blood loss.

1.3 Statistical Issues and Findings

Non-inferiority margin was not pre-specified in the protocols. In the study reports, however, the sponsor mentioned that they used 15% of difference used in the power calculation as non-inferiority margin. The 15% margin was considered by clinical reviewer as appropriate for non-inferiority claim.

The confidence interval used in non-inferiority testing was not matching with my confidence interval although the two gave the same conclusion. Neither protocol nor statistical analysis plan explained their method of CI calculation. I used a normal approximation in confidence interval estimation with correlated binary outcomes from the crossover design. (For details, see the section 10.1 of Categorical Data Analysis by Alan Agresti, Wiley 1990.)

The sponsor dropped the subject #45 and #22 from the study ART-02-001 and the study ART-02-002, respectively, from their non-inferiority testing with the incidence of profound anesthesia because the subject did not complete the period with treatment A200. I conducted a sensitivity analysis including the subject treating the 'missing' period with A200 as failure of profound anesthesia.

Based on my review of the data, I obtained the following findings.

Study ART-02-001:

Data from Study ART-02-001 showed the non-inferiority of A200 to A100 in terms of incidence of profound anesthesia and both A200 and A100 were statistically significantly different from 4% articaine without epinephrine (Aw/o) by both sponsor and me. Time to onset and duration of profound anesthesia were not significantly different among A200, A100, and Aw/o. My sensitivity analyses including the subject #45 also showed the non-inferiority of A200 to A100.

Study ART-02-002:

Data from Study ART-02-002 showed the non-inferiority of A200 to A100 in terms of incidence of profound anesthesia and both A200 and A100 were statistically significantly different from 4% articaine without epinephrine (Aw/o) by both sponsor and me. Time to onset of profound anesthesia was not significantly different among A200, A100, and Aw/o. Onset of profound anesthesia was not significantly different between A200 and A100, but was significantly different between A200 and Aw/o or between A100 and Aw/o. My sensitivity analyses including the subject #45 also showed the non-inferiority of A200 to A100.

Study ART-02-003:

Data from Study ART-02-003 showed that A100 was superior to A200 in terms of visualization of surgical field, expectation of blood loss and quantity of blood loss.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

The following are quotes from the submission regarding drug class.

> Septocaine® is a sterile, aqueous solution for use in dental anesthesia. It contains two active ingredients: articane hydrochloride (HCl) and epinephrine bitartate.
> Articaine HCl is a local anesthetic of the amide type that has the reversible effect of blocking the transmission of action potentials along peripheral neurons. Its mechanism of action is to inhibit nerve conduction by diminishing the sodium ion flux initiating the action potential.
> Epinephrine, an adrenergic vasoconstrictor, is added to articaine HCl in amounts of either 1:100,000 or 1:200,000 in order to slow the absorption of articaine HCl from the site of injection into the systemic circulation and thus ensures the prolonged maintenance of an active tissue concentration of the anesthetic.

The following are quotes from the submission regarding regulatory history and interactions between the sponsor and FDA prior to NDA.

> Septocaine® — was included in the original application for NDA 20-971. Indeed, during the pre-IND meeting with the Reviewing Division on May 10, 1996 and a subsequent meeting on January 10, 1997, after explaining its proposed drug development plan to the Agency, Deproco and Agency representatives agreed that the NDA could cover both Articaine HCl 4% with Epinephrine 1:100,000 and Articaine HCl 4% with Epinephrine 1:200,000. During the January 1997 meeting, the Agency agreed that the proposed development plan (which, in addition to Phase 3 studies on Septocaine® —, included, at the Agency's request, a PK/efficacy study using Septocaine® —) would be adequate to approve both products. The Agency further agreed that it was not necessary to independently test Septocaine® — for safety. In reliance upon the Agency's guidance, Deproco implemented the agreed-upon drug development plan and, on March 30, 1998, submitted NDA 20-971 covering both formulations. In accordance with the PDUFA of 1992, the Sponsor paid the required application fee associated with this NDA upon submission of the application. The NDA was received by FDA on March 30, 1998, and accepted for filing by the Agency on May 29, 1998.
>
> In January 1999 and May 1999, the FDA issued to Deproco Approvable Letters, neither of which gave any indication that the Agency would not approve both products. Then, 2 1/2 weeks before the Agency's review goal date for Deproco's response to the second Approvable Letter, on a conference call, the Agency raised for the first time the possibility that it would approve Septocaine® —, but would not be able to approve Septocaine® — without additional data. Rather than delay approval of Septocaine® —, Deproco agreed to accept approval of Septocaine® — with the intention of resolving at a later date the Agency's desire for additional data on Septocaine® — Ultimately, on April 3, 2000, FDA approved Septocaine® —, while the second formulation that was the subject of the NDA, Septocaine® —, was not approved.
>
> During 2002 and 2003, Deproco participated in a meeting and on two conference calls with representatives of the Review Division to determine what additional information would be required by the Agency to secure approval of Septocaine® —. To satisfy the Agency's requests, Deproco agreed to conduct four additional Phase 3 clinical trials. These studies have now been completed and data from the studies are included in this supplemental application.

The review team decided to administratively split the formulation with epinephrine 1:200,000 from the sNDA 21-971 to form NDA 22-010.

2.1.2 Proposed Indication for SEPTOCAINE

Septocaine® is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.
Septocaine® — is preferred when it is desirable to limit exposure to cardiovascular stresses from the higher doses of epinephrine contained in Septocaine® —

Septocaine® — is preferred during operative or surgical procedures when hemostasis is necessary to improve visualization of the surgical field.

2.2 Data Sources

The original paper submission on September 29, 2005 can be found on the FDA, CDER document room.
The electronic SAS data submission on December 21, 2005 can be found on the FDA, CDER electronic document room (EDR).

Data set:

\\Cdsesub1\n22010\N_000\2005-12-21

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The design for the two studies ART-02-001 and ART-02-002 was identical and was a double-blind, randomized, active-controlled, multi-center, crossover trial to investigate the safety and anesthetic effect of 4% articaine HCl with 1:200,000 epinephrine injection in healthy subjects, when administered for inferior alveolar nerve block anesthesia for study ART-02-001, or when administered for maxillary infiltration anesthesia for study ART-02-002.

The design for the study ART-02-003 was a double-blind, randomized, active-controlled, multi-center, crossover trial to investigate the safety and hemostatic effect of 4% articaine HCl with 1:200,000 epinephrine injection in patients with moderate to severe periodontal disease, when administered for maxillary anesthesia.

Figure 1 in Appendix shows schematic of designs for Studies ART-02-001, ART-02-002, and ART-02-003.

Three investigators enrolled subjects from US sites and participated in the clinical trials ART-02-001, ART-02-002, and ART-02-003.

Sixty-three subjects in each of studies ART-02-001 and ART-02-002 were randomized to one of six possible sequences with three treatment periods: 4% articaine with 1:200,000 epinephrine, 4% articaine with 1:100,000 epinephrine, and 4% articaine without epinephrine. Two subsequent treatment periods were separated between 1 and 3 week.

Forty-two subjects in study ART-02-003 were randomized to one of two possible sequences with two treatment periods: 4% articaine with 1:200,000 epinephrine and 4% articaine with 1:100,000 epinephrine. Two subsequent treatment periods were separated between 3 and 5 week.

The primary objective of the two studies ART-02-001 and ART-02-002 was to demonstrate the non-inferiority in anesthetic efficacy of the investigational formulation of 4% articaine with 1:200,000 epinephrine as compared to 4% articaine with 1:100,000 epinephrine.

The primary efficacy endpoint was the incidence of profound anesthesia (success rate). Profound Anesthesia was considered achieved when three consecutive electrical pulp tests at 30 seconds intervals were greater than or equal to 80 (EPT$\geq$80). Secondary efficacy endpoints were the time to onset of anesthesia and the duration of profound anesthesia.

The primary objective of study ART-02-003 was to assess the hemostatic efficacy of the investigational formulation of 4% articaine with 1:200,000 epinephrine as compared to 4% articaine with 1:100,000 epinephrine.

The primary efficacy endpoint was the surgeon's rating of visualization of the surgical field. Secondary efficacy endpoints were the surgeon's expectation and the quantity of blood loss.

3.1.2 Patient Disposition and Demographics

As shown in Table 1 in Appendix, a total of 63 subjects were enrolled and randomized in the study ART-02-001. Sixty-two subjects completed the three treatment periods and one subject dropped out after one treatment period with A100.

As shown in the same table, a total of 63 subjects were enrolled and randomized in the study ART-02-002. Sixty-two subjects completed the three periods and one subject dropped out after one treatment period with A100.

As shown in the same table, a total of 42 subjects were enrolled and randomized in the study ART-02-003. Forty-two subjects completed the two periods.

Table 2 in Appendix shows patient demographics for Studies ART-02-001, ART-02-002, and ART-02-003, respectively. No comparison was done between treatment groups because of nature of the crossover design.

3.1.3 Statistical Methodologies

Studies ART-02-001 and -002:

McNemar's test was used for analyses of the incidence of the profound anesthesia and 95% confidence interval was calculated to test non-inferiority of A200 to A100. -15% was proposed as the non-inferiority margin. McNemar's test was also employed to test superiority of A200 and A100 over Aw/o.

ANOVA model with terms for treatment, period, sequence and site as fixed effects and subject nested in site*sequence as random effect was used to compare the time to onset and the duration of profound anesthesia among treatment groups adjusting for multiple comparisons with Tukey-Kramer method. In the analyses, the sponsor used the log-transformation for the time to onset variable and the square root-transformation for the duration variable due to departure from the normality assumption.

Study ART-02-003:

[redacted] test was used for analyses of the surgeon's visualization of surgical field and expectation of blood loss after collapsing the original categorical variables into a binary variable.

ANOVA model with terms for treatment, period, sequence, side of mouth and site as fixed effects and subject nested in site*sequence as random effect was used to compare the quantity of blood loss between treatments and the square root-transformation for the duration variable due to departure from the normality assumption was done before the ANOVA.

3.1.4 Results and Conclusions

Tables 3 – 15 in Appendix present the statistical analyses done by the sponsor and me. Following are review results of the analyses.

Study ART-02-001:

Data from the study showed the non-inferiority of A200 to A100 and the superiority of both A200 and A100 over Aw/o in the incidence of the profound anesthesia.

The 95% confidence interval for the difference between A100 and A200 in the incidence of profound anesthesia was (-5.6%, 22.3%) and (-6.8%, 19.5%) by the sponsor and me, respectively. Because the lower limits were greater than -15%, the proposed margin, non-inferiority was shown. Both A200 and A100 were statistically significantly different from Aw/o ($p=.0196$ for A200 vs. Aw/o and $p<.0001$ for A100 vs. Aw/o by the sponsor; $p=.0133$ for A200 vs. Aw/o and $p<.0001$ for A100 vs. Aw/o by me).

There were no statistically significant differences among treatment groups in terms of the time-to-onset and the duration of profound anesthesia ($p \geq .2121$). (See Tables 3 – 6 in Appendix.)

Study ART-02-002:

Data from the study showed the non-inferiority of A200 to A100 and the superiority of both A200 and A100 over Aw/o in the incidence of profound anesthesia.

The 95% confidence interval for difference between A100 and A200 in the incidence of profound anesthesia was (-10.9%, 7.1%) and (-10.8%, 4.4%) by the sponsor and me, respectively. Because the lower limits were greater than -15%, the proposed margin, non-inferiority was shown. Both A200 and A100 were statistically significantly different from Aw/o ($p=.0013$ for A200 vs. Aw/o and $p=.0076$ for A100 vs. Aw/o by the sponsor; $p=.0008$ for A200 vs. Aw/o and $p=.0076$ for A100 vs. Aw/o by me).

There were no statistically significant differences among treatment groups in terms of the time-to-onset of profound anesthesia and between A200 and A100 in terms of the incidence of profound anesthesia ($p \geq .6503$). There were statistically significant differences between A100 and Aw/o or A200 and Aw/o in terms of the duration of profound anesthesia ($p < .0001$). (See Tables 7 – 10 in Appendix.)

Study ART-02-003:

Data from the study showed that A100 was superior to A200 in terms of the visualization of surgical field (A100=83.3%, A200=59.5%; $p=.0075$), the expectation of blood loss (A100=85.6%, A200=71.5%; $p=.0399$ by sponsor, $p=.0290$ by me), and the quantity of blood loss (A100=70.2 mL, A200=53.9 mL; $p=.0175$). (See Tables 11 – 15 in Appendix.)

3.2 Evaluation of Safety

Safety analyses were done by Clinical reviewer, Jane Filie, M.D.

No statistical problems or issues were found.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In subgroup analyses for Studies ART-02-001 and -002, there were no statistically significant interactions between treatment and site, age, sex, or race in the incidence of profound anesthesia. Although in study ART-02-001, there was a concern on quite variable and low overall success rates among the sites, the concern was alleviated because each subject played its own control in the crossover trial.

In subgroup analyses for Study ART-02-003, there were no statistically significant interactions between treatment and site, age, sex, or race for the visualization of surgical field.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

Non-inferiority margin was not pre-specified in the protocols. In the study reports, however, the sponsor mentioned that they used 15% of difference used in the power calculation as non-inferiority margin. The 15% margin was considered by clinical reviewer as appropriate for non-inferiority claim.

The confidence interval used in non-inferiority testing was not matching with my confidence interval although the two gave the same conclusion. Neither protocol nor statistical analysis plan explained their method of CI calculation. I used a normal approximation in confidence interval estimation with correlated binary outcomes from the crossover design.

The sponsor dropped the subject #45 and #22 from the study ART-02-001 and the study ART-02-002, respectively, from their non-inferiority testing with the incidence of profound anesthesia because the subject did not complete the period with treatment A200. I conducted a sensitivity analysis including the subject treating the 'missing' period with A200 as failure of profound anesthesia.

5.1.2 Collective Evidence

Put together, the data from the three studies - Study ART-02-01 and -02 for anesthetic efficacy and Study ART-02-003 for hemostatic efficacy - provided statistically significant evidence of efficacy of A200 as a dental anesthesia. The efficacy studies met our standards for dental anesthetic indication and agreement between the sponsor and FDA during regulatory interactions. In addition to the sponsor data, my sensitivity analysis with respect to analysis population corroborates the significant efficacy of A200.

5.2 Conclusions and Recommendations

Study ART-02-01 with healthy subjects provided data showing an efficacy of 4% articaine with 1:200,000 epinephrine when administered for inferior alveolar nerve block anesthesia based on intent-to-treat (ITT) analysis. In terms of the profound anesthesia,

4% articaine with 1:200,000 epinephrine was shown as non-inferior to 4% articaine with 1:100,000 epinephrine and was shown as superior to 4% articaine without epinephrine.

Study ART-02-02 with healthy subjects provided data showing an efficacy of 4% articaine with 1:200,000 epinephrine when administered for maxillary infiltration anesthesia based on ITT analysis. In terms of the profound anesthesia, 4% articaine with 1:200,000 epinephrine was shown as non-inferior to 4% articaine with 1:100,000 epinephrine and was shown as superior to 4% articaine without epinephrine.

Study ART-02-03 with subjects with moderate to severe periodontal disease provided data showing an efficacy of 4% articaine with 1:200,000 epinephrine when administered for maxillary anesthesia based on ITT analysis. In terms of the visualization of surgical field, significantly less subjects with 4% articaine with 1:200,000 epinephrine had 'clear' visualization than those with 4% articaine with 1:100,000 epinephrine.

Overall, the submitted data provide statistically and clinically significant results supporting dental anesthesia of 4% articaine HCl with 1:200,000 epinephrine injection.

5.3 Review of Clinical Studies of Proposed Label

Following is the text portion in the Clinical Study section from 'PROPOSED LABELING TEXT' regarding results from the three dental anesthesia studies:

[ ]

I found that they are consistent with what I found from the study reports.

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On Original

APPENDIX

Table 1. Patient Disposition by Treatment Sequence Group

Study ART-02-001:

	A200-A100-Aw/o	A200-Aw/o-A100	A100-A200-Aw/o	A100-Aw/o-A200	Aw/o-A200-A100	Aw/o-A100-A200	TOTAL
RANDOMIZED:	11	12	9	9	11	11	63
ITT:	11	12	9	9	11	11	63
COMPLETED, n (%):	11 (100.0)	12 (100.0)	9 (100.0)	8 (88.9)	11 (100.0)	11 (100.0)	62 (98.4)
DISCONTINUED, n (%):	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (1.6)
Protocol Violation	0	0	0	1	0	0	1

Study ART-02-002:

	A200-A100-Aw/o	A200-Aw/o-A100	A100-A200-Aw/o	A100-Aw/o-A200	Aw/o-A200-A100	Aw/o-A100-A200	TOTAL
RANDOMIZED:	9	12	11	12	9	10	63
ITT:	9	12	11	12	9	10	63
COMPLETED, n (%):	9 (100.0)	12 (100.0)	10 (90.9)	12 (100.0)	9 (100.0)	10 (100.0)	62 (98.4)
DISCONTINUED, n (%):	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Protocol Violation	0	0	1	0	0	0	1

Study ART-02-003:

	A200-A100	A200-A100	TOTAL
RANDOMIZED:	21	21	42
ITT:	21	21	42
COMPLETED, n (%):	21 (100.0)	21 (100.0)	42 (100.0)
DISCONTINUED, n (%):	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Violation	0	0	0

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Table 2. Patient Demographics (ITT Subjects)

Study ART-02-001:

	N (%)
Gender	
Male	36 (57.1)
Female	27 (42.9)
Race	
White	50 (79.4)
Black	5 (7.9)
Asian	5 (7.9)
Other	3 (4.8)
Age (years)	
Mean ± SD	30.4 ± 10.0
Range	19 - 57
Weight (lb)	
Mean ± SD	163.6 ± 39.6
Range	98.0 – 286.0

Study ART-02-002:

	N (%)
Gender	
Male	28 (44.4)
Female	35 (55.6)
Race	
White	40 (63.5)
Black	10 (15.9)
Asian	7 (11.1)
Other	6 (9.5)
Age (years)	
Mean ± SD	30.4 ± 8.4
Range	20 - 55
Weight (lb)	
Mean ± SD	164.4 ± 40.9
Range	104.0 – 277.0

Study ART-02-003:

	N (%)
Gender	
Male	26 (61.9)
Female	16 (38.1)
Race	
White	32 (76.2)
Black	7 (16.7)
Asian	2 (4.7)
Other	1 (2.4)
Age (years)	
Mean ± SD	46.3 ± 9.7
Range	22 - 65
Weight (lb)	
Mean ± SD	171.5 ± 36.8
Range	106.0 – 280.0

Table 3. Sponsor Analysis of Primary Efficacy Variable: Incidence of Profound Anesthesia (Study ART-02-001)

		ARTICAINE WITH 1:200,000 EPINEPHRINE		
ARTICAINE WITH 1:100,000 EPINEPHRINE		Success	Failure	Total
	Success	23	6	29
	Failure	11	22	33
	Total	34	28	62

McNemar's Test p=.2253
95% CI for $p_{A200} - p_{A100}$ = (-5.6%, 22.3%)
NI margin was specified as -15%.

Table 4. Reviewer Analysis of Primary Efficacy Variable including Subject #45: Incidence of Profound Anesthesia (Study ART-02-001)

	ARTICAINE WITH 1:200,000 EPINEPHRINE			
		Success	Failure	Total
ARTICAINE WITH 1:100,000 EPINEPHRINE	Success	23	7	30
	Failure	11	22	33
	Total	34	29	63

McNemar's Test p=.3458
95% CI for $p_{A200} - p_{A100}$ = (-6.8%, 19.5%)
NI margin was specified as -15%. CI is for $P_{A200} - P_{A100}$, based on normal approximation for correlated binary outcome variables.

Table 5. Sponsor Analysis of Efficacy Variables: Incidence, Onset, and Duration of Profound Anesthesia (Study ART-02-001)

	Articaine with 1:200,000 Epinephrine	**Articaine with 1:100,000 Epinephrine**	**Articaine without Epinephrine**
Success Rate P-value vs. Aw/o*	34/62 (54.8%) **.0196**	30/63 (47.6%) **<.0001**	16/62 (25.8%)
Time to Onset (min) Mean (SD) P-value vs. A100# P-value vs. A200#	 4.7 (2.6) .2930	 4.2 (2.8) .2930	 4.3 (2.5) .8920 .2121
Duration (min) Mean (SD) p-value vs. A100## p-value vs. A200##	 51.2 (55.9) .4461	 61.8 (59.0) .4461	 49.7 (44.2) .2943 .7711

*p-values from McNemar's test.
#p-values calculated from Mixed model: log(Y) = trt +site+seq+period+subj(site*seq).
##p-values calculated from Mixed model: sqrt(Y) = trt +site+seq+period+subj(site*seq).
Tukey-Kramer procedure was employed by the Sponsor to adjust for the multiple comparisons.

Table 6. Reviewer Analysis of Efficacy Variables including Subject #45: Incidence, Onset, and Duration of Profound Anesthesia (Study ART-02-001)

	Articaine with 1:200,000 Epinephrine	**Articaine with 1:100,000 Epinephrine**	**Articaine without Epinephrine**
Success Rate P-value vs. Aw/o*	34/63 (54.0%) **.0133**	30/63 (47.6%) **<.0001**	16/63 (25.4%)
Time to Onset (min) Mean (SD) P-value vs. A100# P-value vs. A200#	 4.7 (2.6) .2861	 4.2 (2.8) .2861	 4.3 (2.5) .8886 .2060
Duration (min) Mean (SD) p-value vs. A100## p-value vs. A200##	 51.2 (55.9) .4405	 61.8 (59.0) .4405	 49.7 (44.2) .2856 .7683

*p-values from McNemar's test.
#p-values calculated from Mixed model: log(Y) = trt +site+seq+period+subj(site*seq).
##p-values calculated from Mixed model: sqrt(Y) = trt +site+seq+period+subj(site*seq).
Tukey-Kramer procedure was employed by the Sponsor to adjust for the multiple comparisons.

Table 7. Sponsor Analysis of Primary Efficacy Variable: Incidence of Profound Anesthesia (Study ART-02-002)

	ARTICAINE WITH 1:200,000 EPINEPHRINE		
	Success	Failure	Total
ARTICAINE WITH 1:100,000 EPINEPHRINE			
Success	56	3	59
Failure	2	1	3
Total	58	4	62

McNemar's Test p=.6547
95% CI for $p_{A200} - p_{A100}$ = (-10.9%, 7.1%)
NI margin was specified as -15%.

Table 8. Reviewer Analysis of Primary Efficacy Variable including Subject #22: Incidence of Profound Anesthesia (Study ART-02-002)

		ARTICAINE WITH 1:200,000 EPINEPHRINE		
		Success	Failure	Total
ARTICAINE WITH 1:100,000 EPINEPHRINE	Success	56	4	60
	Failure	2	1	3
	Total	58	5	63

McNemar's Test p=.4142
95% CI for $p_{A200} - p_{A100}$ = (-10.8%, 4.4%)
NI margin was specified as -15%. CI is for $P_{A200} - P_{A100}$, based on normal approximation for correlated binary outcome variables.

Table 9. Sponsor Analysis of Efficacy Variables: Incidence, Onset, and Duration of Profound Anesthesia (Study ART-02-002)

	Articaine with 1:200,000 Epinephrine	**Articaine with 1:100,000 Epinephrine**	**Articaine without Epinephrine**
Success Rate P-value vs. Aw/o*	58/62 (93.5%) **.0013**	60/63 (95.2%) **.0076**	47/62 (75.8%)
Time to Onset (min) Mean (SD) p-value vs. A100# p-value vs. A200#	 3.1 (2.3) .8597	 3.0 (2.1) .8597	 3.0 (2.0) .8268 .9945
Duration (min) Mean (SD) p-value vs. A100## p-value vs. A200##	 41.6 (21.1) .6503	 45.0 (23.6) .6503	 13.3 (6.8) **<.0001** **<.0001**

*p-values from McNemar's test.
#p-values calculated from Mixed model: log(Y) = trt +site+seq+period+subj(site*seq).
##p-values calculated from Mixed model: sqrt(Y) = trt +site+seq+period+subj(site*seq).
Tukey-Kramer procedure was employed by the Sponsor to adjust for the multiple comparisons.

Table 10. Reviewer Analysis of Efficacy Variables including Subject #22: Incidence, Onset, and Duration of Profound Anesthesia (Study ART-02-002)

	Articaine with 1:200,000 Epinephrine	**Articaine with 1:100,000 Epinephrine**	**Articaine without Epinephrine**
Success Rate P-value vs. Aw/o*	58/63 (93.1%) **.0008**	60/63 (95.2%) **.0076**	47/63 (74.6%)
Time to Onset (min) Mean (SD) P-value vs. A100# P-value vs. A200#	 3.1 (2.3) .8596	 3.0 (2.1) .8596	 3.0 (2.0) .8263 .9945
Duration (min) Mean (SD) p-value vs. A100## p-value vs. A200##	 41.6 (21.1) .6499	 45.0 (23.6) .6499	 13.3 (6.8) **<.0001** **<.0001**

*p-values from McNemar's test.
#p-values calculated from Mixed model: log(Y) = trt +site+seq+period+subj(site*seq).
##p-values calculated from Mixed model: sqrt(Y) = trt +site+seq+period+subj(site*seq).
Tukey-Kramer procedure was employed by the Sponsor to adjust for the multiple comparisons.

Table 11. Frequency Tables of Efficacy Variables: Visualization of the Surgical Field, Expectation of Blood Loss (Study ART-02-003)

	ARTICAINE WITH 1:200,000 EPINEPHRINE (N=42)	**ARTICAINE WITH 1:100,000 EPINEPHRINE (N=42)**
Visualization of the Surgical Field		
Very unclear	1 (2.4%)	0 (0.0%)
Moderately unclear	4 (9.5%)	0 (0.0%)
Slightly unclear	6 (14.3%)	6 (14.3%)
Neither clear nor unclear	6 (14.3%)	1 (2.4%)
Slightly clear	5 (11.9%)	7 (16.7%)
Moderately clear	10 (23.8%)	16 (38.1%)
Very clear	10 (23.8%)	12 (28.6%)
Expectation of Blood Loss		
Much worse than expected	0 (0.0%)	0 (0.0%)
Moderately worse than expected	6 (14.3%)	1 (2.4%)
Slightly worse than expected	6 (14.3%)	5 (11.9%)
Equal to expected	12 (28.6%)	9 (21.4%)
Slightly better than expected	7 (16.7%)	14 (33.3%)
Moderately better than expected	7 (16.7%)	10 (23.8%)
Much better than expected	4 (9.5%)	3 (7.1%)

Table 12. Analysis of Primary Efficacy Variable after Dichotomization: Visualization of the Surgical Field (Study ART-02-003)

	ARTICAINE WITH 1:200,000 EPINEPHRINE			
ARTICAINE WITH 1:100,000 EPINEPHRINE		Clear Visualization	Unclear Visualization	Total
	Clear Visualization	23	12	35
	Unclear Visualization	2	5	7
	Total	25	17	42

McNemar's Test p=**.0075**
Clear Visualization: 'slightly clear', 'moderately clear', or 'very clear'
Unclear Visualization: 'very unclear', 'moderately unclear', 'slightly unclear', or 'neither clear nor unclear'

Table 13. Sponsor Analysis of Secondary Efficacy Variable after Dichotomization: Expectation of Blood Loss (Study ART-02-003)

	ARTICAINE WITH 1:200,000 EPINEPHRINE			
ARTICAINE WITH 1:100,000 EPINEPHRINE		Above Expectation	Below Expectation	Total
	Above Expectation	29	7	36
	Below Expectation	1	5	6
	Total	30	12	42

McNemar's Test p=**.0339**
Above Expectation: 'much better', 'moderately better', or 'slightly better than expected'
Below Expectation: 'equal to expected', 'slightly worse', 'moderately worse', or 'much worse than expected'

Table 14. Reviewer Analysis of Secondary Efficacy Variable after Dichotomization: Expectation of Blood Loss (Study ART-02-003)

	ARTICAINE WITH 1:200,000 EPINEPHRINE			
ARTICAINE WITH 1:100,000 EPINEPHRINE		Above Expectation	Below Expectation	Total
	Above Expectation	14	13	27
	Below Expectation	4	11	15
	Total	18	24	42

McNemar's Test p=**.0290**
Above Expectation: 'much better', 'moderately better', or 'slightly better than expected'
Below Expectation: 'equal to expected', 'slightly worse', 'moderately worse', or 'much worse than expected'

Table 15. Analysis of Secondary Efficacy Variable: Quantity of Blood Loss (Study ART-02-003)

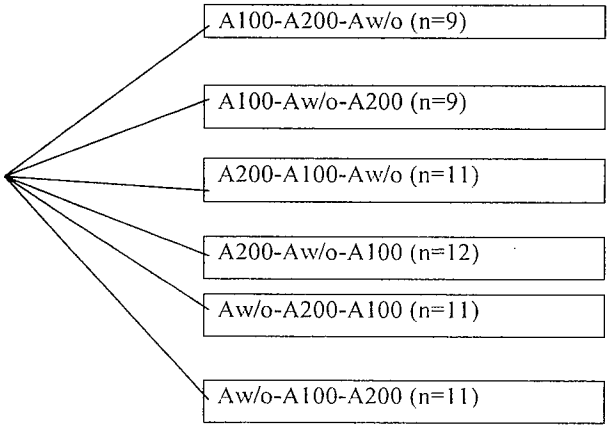
	ARTICAINE WITH 1:200,000 EPINEPHRINE (N=42)	**ARTICAINE WITH 1:100,000 EPINEPHRINE (N=42)**
Quantity of Blood Loss (mL)		
N	42	42
Mean (SD)	70.2 (53.0)	54.9 (36.0)
Min, Max	5.0, 305.7	-8.6, 165.3
p-value*	**.0175**	

*p-value calculated from Mixed model: sqrt(Y) = trt+site+mouthside+seq+period+subj(site*seq).

Figure 1. Schematic of Study Design

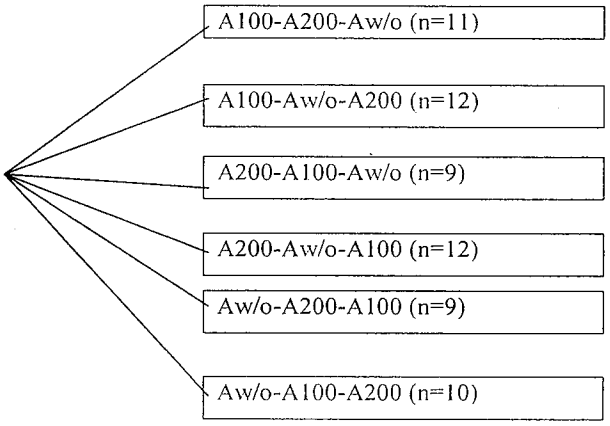
Study ART-02-001:

(N=63)
Randomized 1:1:1:1:1:1
Treatment duration
4-5 hours per period



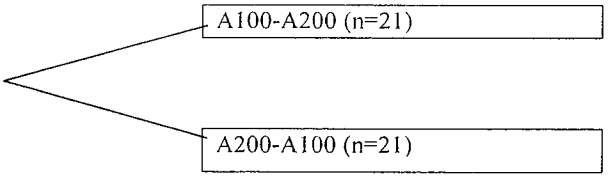
Study ART-02-002:

(N=63)
Randomized 1:1:1:1:1:1
Treatment duration
4-5 hours per period



Study ART-02-003:

(N=42) Randomized 1:1
Treatment duration
2-4 hours per period



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