CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Statistical Review(s)

HFD170/Nolan

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Statistical Review and Evaluation

NDA 20-971
Drug name: Septanest®
Generic name: Articaine Hydrochloride
Applicant: Deproco Incorporation
Indication: infiltration and nerve block anesthesia in general dentistry
Documents reviewed: volumes 1.3, 1.4, 1.42-61, 1.64, received HFD-170 Mar. 30, 1998
Electronic data
User Fee Date: Jan. 30, 1999
Project manager: Kenneth Nolan
Medical reviewer: Harold Blatt, D.D.S.
Statistical reviewer: Chuanpu Hu, Ph.D.

Key words: clinical studies, equivalence

Introduction

Articaine hydrochloride (HCl) is an amide type of local anesthetic. It is indicated for infiltration anesthesia and nerve block anesthesia in clinical dentistry. The drug has been marketed under the name Septanest® in various countries for several years. This NDA contains one phase II efficacy study, three phase III safety/efficacy studies, and two "supportive" efficacy studies. The dose of 4% articaine HCl with 1:100,000 epinephrine was studied in the three phase III studies, and 4% articaine HCl with 1:200,000 epinephrine was studied in the phase II study. The three phase III studies (protocol 96001.02UK, 96001.02US, S96002.01) should be reviewed for the efficacy and safety of the drug, because only the phase III studies were designed with the objective of showing the effect of articaine.

Study Design

The three phase III studies were all multi-center, single dose, randomized, double blind, parallel group, active controlled. The control drug is lidocaine. At each site, patients were randomly assigned in a 2:1 ratio so that the number of patients receiving articaine was approximately twice of that of lidocaine. The number of sites and patients in each study were as follows.

Study No.	S96001.02 UK	S96001.02 US	S96002.01 (in U.S.)
No. of sites	8	13	9
Sample size (drug vs. control)	158:84	569:284	155:75

This NDA intended to show similarity in outcomes between articaine and lidocaine based on the efficacy and safety endpoints. The efficacy endpoints were patient and investigator assessed pain scores. The

safety endpoints were vital signs before and after administration, and adverse events. No formal statistical equivalence criteria were set.

Strata

At each site, subjects undergoing general dental procedures were randomized to stratum according to the investigator's assessment of the complexity of the procedure to be performed, based on the following criteria:

> Simple procedures: single extractions with no complications, routine operative procedures, single apical resections and single crown procedures;
>
> Complex procedures: multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations and other surgical procedures on the bone.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria were nearly identical in the three studies. On the whole, patients between 4 and 80 years of age who needed any of the simple or complex procedures described above were to be excluded only if they met any of the following criteria: were pregnant; had bony, fully impacted teeth or maxillofacial surgery; had any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions; had concomitant cardiac or neurologic disease; had a history of severe shock, paroxysmal tachycardia, frequent arrhythmia, severe untreated hypertension, or bronchial asthma; had evidence of soft tissue infection near the proposed injection site (localized periapical or periodontal infections were permitted); were taking monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs, or ergot-type oxytocic drugs; received chloroform, halothane, cyclopropane, trichloroethylene, or related anesthetics during the treatment visit; were expected to require nitrous oxide or any topical (topical anesthesia was allowed in the UK study because it is standard practice) or general anesthesia; or had taken aspirin, acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), or other analgesic agents within 24 hours prior to administration of study medication. In addition, because it was so difficult to recruit children into the study if they required blood to be drawn for clinical laboratory tests, children under 13 years of age were not required to have this performed in S96002.01. In addition, only in this study, was either a serum or a urine pregnancy test at screening allowed.

Dose:

Patients were to receive as much study drug as was deemed necessary to achieve adequate anesthesia, not to exceed 7 mg/kg.

Actual Exposure:

A total of 882 patients received Septanest® — (4% articaine HCl with 1:100,000 epinephrine) via

infiltration or nerve block, 675 patients underwent simple dental procedures and 207 patients underwent complex dental procedures. On average, patients undergoing simple procedures received 2.5 mL of Septanest® [redacted] and patients undergoing complex procedures received 4.2 mL. For comparison, a total of 443 patients received the comparator agent, 2% lidocaine HCl with 1:100,000 epinephrine, 338 patients underwent simple procedures and 104 patients underwent complex procedures. Patients in the lidocaine group received on average 2.6 mL for simple procedures and 4.5 mL for complex procedures.

Efficacy Assessment:

Immediately following the dental procedure, the patients were asked to mark the level of pain experienced on a 10 cm Visual Analog Scale (VAS) with 0= (no pain) and 10=(worst pain imaginable). A similar VAS was used for the investigator evaluation. For children 4 through 12 years of age, a 10 cm VAS with "smiley faces" were used.

Safety Assessment:

Safety evaluations included vital signs obtained before and after administration of anesthetic (vital signs including supine and standing blood pressure, pulse and respiratory rate, 1 minute and 5 minutes post medication and at the end of the dental procedure), and assessment of adverse events during the treatment visit. In addition, adverse events were elicited during telephone follow-up at 24 hours and 7 days after the procedure.

Sponsor's Protocol-specified Statistical Analysis Plan

A summary of patient characteristics, including age, race, sex and weight, were to be presented by treatment group for all patients who received study drug. Patients were to be characterized by age in two groups: 4 to less than 13 years old and 13 years and older. Age and weight were to be summarized by treatment group using descriptive statistics including mean, median, standard deviation, and range. Counts and percents of race and sex were to be presented. Treatments were to be compared for balance in age group, sex, race, and strata using a Cochran-Mantel-Haenszel (CMH) test to adjust for center effects. Treatment comparison of weight were to be made with an analysis of variance (ANOVA) with treatment, center, strata, treatment-by-center and treatment by-strata interaction effects. If the assumptions of normality would not be met, appropriate normalizing transformations were to be used. No formal statistical equivalence criteria were set.

Treatment group comparisons of the patient and investigator VAS measurements were to be made with an ANOVA with treatment, center, strata, treatment-by-center interaction, and treatment-by-strata interaction effects. If the assumptions of normality are not met, appropriate normalizing transformations were to be used. No formal statistical equivalence criteria were set.

The two treatment groups were to be compared overall and within body system with respect to the incidence of adverse events reported during the study as well as treatment-related adverse events (defined as an adverse event that occurred during the study and was deemed to be probably, possibly, or of unknown relationship to study drug) using a Fisher's Exact test.

Vital signs including supine and standing blood pressure, pulse and respiratory rate were to be evaluated for changes from baseline to one minute post-therapy, five minutes post-therapy, and after the dental procedure. A summary of vital signs and change from baseline in vital signs were to be presented using descriptive statistics including mean, median, standard deviation, and range. An ANOVA were to be employed to test for treatment group differences in baseline vital signs and change from baseline vital signs at one minute post-therapy, five minutes post-therapy, and after the dental procedure. The ANOVA were to include treatment, *age group*, center, strata, treatment-by-center interaction, and treatment-by-strata interaction effects. Appropriate normalizing transformations might be used if the assumptions of normality would not be met. No formal statistical equivalence criteria were set.

Sample Size Determination:

The sample size was based on negotiations with the FDA. The FDA preferred larger sample size due to concerns on adequate representation of adverse events. The number of subjects on articaine in the largest study, protocol S96001.02.US, fell short of 1000, the number previously agreed upon. The applicant attributed this due to lack of study participants than expected.

Statistical Analysis

The analysis will address three topics the applicant analyzed: treatment balance of weight and other baseline characteristics, efficacy, and safety. Safety contains two types of endpoints: vital signs and adverse events. The protocol-specified analysis plan focused on statistical significance. However, statistical significance is not necessarily equivalent to significant clinical difference. In the case of efficacy, a small, clinically irrelevant difference could be statistically significant, merely because every patient has a pain score, resulting in a large number of data. The same holds for vital signs and some baseline characteristics such as weight. On the other hand, in the case of an adverse event, where the number of occurrence tends to be very small, failure to detect statistical significance does not guarantee no clinical difference in relative risk. That is, for most adverse events examined, the study is not powered to detect significance at a certain level. Therefore, different type of caution should be taken in interpreting the appropriateness of the analysis, depending on the type of endpoints.

Treatment Balance

The sponsor made a treatment comparison of weight with an ANOVA with treatment, center, and stratum effect. The analysis slightly deviated from the protocol in that the treatment-by-center and treatment-by-stratum interactions were removed due to non-significance. This deviation may be questionable, but should not matter for the following reason. The three tables presented by the applicant, attached in the appendix, show the differences of baseline characteristics in the three studies. The differences by treatment appeared to be sufficiently small that, even if statistical significance were found, they would not likely be clinically significant.

Efficacy

The efficacy endpoints are patients and investigator assessed pain scores on 0-to-10 scales with 0=(no pain) and 10=(worst pain imaginable). No formal statistical equivalence criteria were set. The sponsor used the Kruskal-Wallis test, which showed no significant treatment difference. Subgroup analyses by age were submitted. The pain scores by age and gender were tabulated, and claimed with no significant treatment difference in the efficacy summary. The applicant's analysis of efficacy changed somewhat from the protocol: the protocol specified an ANOVA, but the actual analysis used the Kruskal-Wallis test. The protocol stated that "If the assumptions of normality were not met, appropriate normalizing transformations were used." Because patients were expected to be well anesthetized, i.e., having scores mostly 0, the distribution of the scores can be anticipated to be upwardly skewed. Something similar to log-transformation might be expected (e.g., log(1+x)). It is difficult to view the Kruskal-Wallis test as a "normalizing transformation." It is therefore unclear why it was used by the applicant. In some cases, the applicant reported the result as statistically insignificant, and in other cases no result was reported.

On the other hand, the mean pain scores in all groups, by strata, age and gender, are sufficiently low, mostly ranging from 0.2 to 1.0. To some extent, this can be seen from the following three tables presented by the applicant, showing the pain scores by strata and age for each study. It thus suggests that even if an ANOVA had found significance, it probably would not be clinically significant.

96001.02UK, Summary of VAS Scores of Pain

	Pain Scores For All Treated Patients			
	Articaine		Lidocaine	
	Simple	Complex	Simple	Complex
All Patients				
N	114	43	60	24
Investigator Score (cm)				
Mean	0.3	0.4	0.2	0.4
Minimum	[redacted]			
Maximum				
Patient Score (cm)				
Mean	0.4	0.8	0.5	0.6
Minimum	[redacted]			
Maximum				
Patients 4 to <13 years				
N	2	1	1	1
Investigator Score (cm)				
Mean	0.0	0.0	0.0	2.2
Minimum	[redacted]			
Maximum				
Patient Score (cm)				
Mean	0.8	0.0	1.0	0.0
Minimum	[redacted]			
Maximum				
Patients ≥ 13 years				
N	113	42	59	23
Investigator Score (cm)				
Mean	0.3	0.4	0.2	0.4
Minimum	[redacted]			
Maximum				
Patient Score (cm)				
Mean	0.4	0.8	0.5	0.6
Minimum	[redacted]			
Maximum				

Extracted from Tables 7.1 and 7.2

96001.02US, Summary of VAS Scores of Pain

	Pain Scores For All Treated Patients			
	Articaine		Lidocaine	
	Simple	Complex	Simple	Complex
All Patients				
N	427	142	211	72
Investigator Score (cm)				
Mean	0.4	0.6	0.5	0.7
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.5	0.5	0.6	0.8
Minimum				
Maximum				
Patients 4 to <13 years				
N	1	0	1	0
Investigator Score (cm)	0.2	-	0.5	-
Patient Score (cm)	0.2	-	0.5	-
Patients≥ 13 years				
N	426	142	210	72
Investigator Score (cm)				
Mean	0.4	0.6	0.5	0.7
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.5	0.5	0.6	0.8
Minimum				
Maximum				

Extracted from Tables 7.1 and 7.2

96002.01, Summary of VAS Scores of Pain

	Pain Scores For All Treated Patients			
	Articaine		Lidocaine	
	Simple	Complex	Simple	Complex
All Patients				
N	133	22	67	8
Investigator Score (cm)				
Mean	0.2	0.4	0.3	0.8
Minimum	[redacted]			
Maximum				
Patient Score (cm)				
Mean	0.4	0.8	0.5	1.0
Minimum	[redacted]			
Maximum				
Patients 4 to <13 years				
N	40	6	16	1
Investigator Score (cm)				
Mean	0.4	0.8	0.3	3.4
Minimum	[redacted]			
Maximum				
Patient Score (cm)				
Mean	0.5	1.3	0.7	4.5
Minimum	[redacted]			
Maximum				
Patients ≥13 years				
N	93	16	51	7
Investigator Score (cm)				
Mean	0.2	0.3	0.3	0.4
Minimum	[redacted]			
Maximum				
Patient Score (cm)				
Mean	0.3	0.6	0.5	0.5
Minimum	[redacted]			
Maximum				

Extracted from Tables 7.1 and 7.2

Safety

There are two types of safety endpoints: vital signs and adverse events. These will be discussed separately.

Vital Signs

The applicant's analysis slightly deviated from the protocol in that the interaction terms were dropped due to insignificance. The results by study are listed as follows.

96001.02UK:
Patients in the lidocaine group had significantly higher mean changes from baseline than the articaine group, in pulse rate at one minute post therapy ($p<0.001$) and in respiration rate post dental procedure ($p=0.027$). As can be seen from the next table, these differences are small and are considered by the medical reviewer as not clinically significant.

96001.02US:
At baseline (immediately prior to treatment), all mean vital signs were within normal range. Mean vital signs were similar for both treatment groups for blood pressure, pulse rate and temperature. There was a significant difference between the two treatment groups in mean respiration rate at baseline ($p=0.012$), but this is considered by the medical reviewer as not clinically significant.

96002.01:
Statistically significant differences between treatment groups were observed for supine systolic blood pressure for mean change from baseline to one minute ($p=0.039$) and five minutes ($p=0.019$) following administration of anesthetic and for respiration rate for mean change from baseline to five minutes following administration of anesthetic ($p=0.039$). These differences are considered by the medical reviewer as not clinically significant.

Again, the differences of the means among treatments seem sufficiently small to suggest that the statistical differences do not cause much concern. The following table illustrated the case of protocol 96001.02UK.

96001.02UK, Summary of Significant Changes from Baseline in Vital Signs

Parameter	Articaine			Lidocaine			
	Baseline	Visit	Change	Baseline	Visit	Change	P-value
Pulse (bpm)							
N	158			84			
Baseline							
Mean	79.4			78.2			
SEM	1.13			1.61			
One minute post-therapy							
Mean		79.8	0.4		82.3	4.1	<0.001
SEM		1.05	0.89		1.62	1.39	
Respirations (/minute)							
N	156			83			
Baseline							
Mean	18.9			18.7			
SEM	0.34			0.41			
Post-dental procedure							
Mean		18.7	-0.2		19.0	0.2	0.027
SEM		0.28	0.20		0.41	0.26	

Extracted from Table 8.1

Adverse Events

The applicant analyzed only the adverse events occurring at a rate of ≥5% for at least one treatment group and did not report this as a change from protocol. Other adverse events were only tabulated by race and gender. No statistically significant differences between treatment groups were seen in the frequency of adverse events overall or for any adverse event with an incidence of ≥5% with all three studies. It is, however, unclear why the applicant chose 5% as the boundary. Specifics by study are presented as follows.

96001.02UK:
It appears that the articaine group may have a higher risk of headache (12 in 158, vs. 3 in 84 in the lidocaine group). A summary of the most frequently reported adverse events is presented in the following table.

96001.02UK, Summary of Adverse Events Reported in At Least Two Patients in any Treatment Group

	Treatment Group	
	Articaine (N=158)	Lidocaine (N=84)
Adverse Events by Body System	Number (%) of Patients	
Number of Patients With at Least One Adverse Event	67 (42)	35 (42)
Body As A Whole		
Pain	53 (34)	27 (32)
Headache	12 (8)	3 (4)
Face edema	11 (7)	5 (6)
Infection	6 (4)	3 (4)
Accidental injury	2 (1)	0
Neck rigidity	0	2 (2)
Digestive System		
Gingivitis	8 (5)	3 (4)
Gum hemorrhage	2 (1)	1 (1)
Diarrhea	2 (1)	0
Nervous System		
Hypesthesia	3 (2)	2 (2)
Respiratory System		
Pharyngitis	3 (2)	2 (2)
Hemic and Lymphatic System		
Ecchymosis	2 (1)	1 (1)
Special Senses		
Ear Pain	2 (1)	1 (1)

Extracted from Table 9.1

In addition, twelve of 158 articaine patients (8%) and seven of 84 lidocaine patients (8%) experienced at least one adverse event considered related to the study drug by the investigator. There seems to be no reason to suspect any treatment differences in this group.

96001.02US:
The articaine group appears to have significantly higher risk of paresthesia (10 in 569, vs. 1 in 284 in the lidocaine group). Nausea might also be a concern (6 in 569 vs. 1 in 284). A summary of the most frequently reported adverse events is presented in the following table.

96001.02US. Summary of Adverse Events Reported in At Least Two Patients in any Treatment Group

	Treatment Group	
	Articaine (N=569)	Lidocaine (N=284)
Adverse Events by Body System	Number (%) of Patients	
Number of Patients With at Least One Adverse Event	110 (19)	52 (18)
Body As A Whole		
Pain	58 (10)	26 (9)
Headache	15 (3)	11 (4)
Injection site pain	5 (<1)	1 (<1)
Infection	3 (<1)	0
Face edema	2 (<1)	1 (<1)
Abdominal pain	2 (<1)	0
Back pain	2 (<1)	0
Neck pain	2 (<1)	0
Chills	0	2 (<1)
Digestive System		
Nausea	6 (1)	1 (<1)
Gingivitis	5 (<1)	2 (<1)
Stomatitis	3 (<1)	2 (<1)
Vomiting	2 (<1)	1 (<1)
Diarrhea	2 (<1)	0
Musculoskeletal System		
Arthralgia	2 (<1)	1 (<1)
Myalgia	2 (<1)	1 (<1)
Nervous System		
Paresthesia	10 (2)	1 (<1)
Hypesthesia	4 (<1)	3 (1)
Dizziness	1 (<1)	2 (<1)
Respiratory System		
Rhinitis	3 (<1)	1 (<1)
Skin and appendages		
Rash	0	3 (1)

Extracted from Table 9.1

In addition, twenty-one of 569 (4%) articaine patients and seven of 284 (2%) lidocaine patients reported at least one adverse event considered by the investigator to be related to study drug. Once again, the articaine group appears to have much higher risk of paresthesia (8 in 569, vs. 1 in 284 in the lidocaine group). A summary of the treatment-related adverse events is presented in the following table.

96001.02US, Summary of All Adverse Events Considered Related to Study Drug: by Body System

	Treatment Group	
	Articaine (N=569)	Lidocaine (N=284)
	Number (%) of Patients	
Number of Patients With at Least One Adverse Event	21 (4)	7 (2)
Body As A Whole		
Headache	2 (<1)	2 (<1)
Abdominal pain	1 (<1)	0
Infection	1 (<1)	0
Injection site pain	1 (<1)	0
Pain	1 (<1)	0
Asthenia	0	1 (<1)
Chest pain	0	1 (<1)
Chills	0	1 (<1)
Cardiovascular System		
Tachycardia	1 (<1)	0
Digestive System		
Constipation	1 (<1)	0
Diarrhea	1 (<1)	0
Dyspepsia	1 (<1)	0
Mouth ulceration	1 (<1)	0
Stomatitis	1 (<1)	0
Metabolic and Nutritional System		
Thirst	1 (<1)	0
Musculoskeletal System		
Arthralgia	0	1 (<1)
Nervous System		
Paresthesia	8 (1)	1 (<1)
Hypesthesia	3 (<1)	0
Dizziness	1 (<1)	2 (<1)
Dry mouth	1 (<1)	0
Increased salivation	1 (<1)	0
Skin and Appendages		
Pruritus	1 (<1)	1 (<1)
Rash	0	2 (<1)
Sweating	0	1 (<1)
Special Senses		
Taste perversion	1 (<1)	0

Extracted from Table 10.1

96001.02:

The number of patients experienced at least one adverse event were quite higher in the articaine group (9% vs. 3% in the lidocaine group). However, for any particular adverse events, the number of occurrences is too small to reach a definitive conclusion. A summary of the adverse events reported by 1% of patients in any treatment group is presented in the following table.

Summary of Adverse Events Reported by 1% of Patients in Any Treatment Group

	Treatment Group	
	Articaine (N=155)	Lidocaine (N=75)
Adverse Events by Body System	Number (%) of Patients	
Number of Patients With at Least One Adverse Event	14 (9)	2 (3)
Body As A Whole		
Headache	4 (3)	1 (1)
Pain	3 (2)	1 (1)
Injection site pain	1 (<1)	1 (1)
Digestive System		
Vomiting	0	1 (1)
Musculoskeletal System		
Osteomyelitis	2 (1)	0
Respiratory System		
Rhinitis	1 (<1)	1 (1)

Extracted from Table 9.1

In addition, four of 155 articaine patients (3%) and two of 75 lidocaine patients (3%) experienced at least one adverse event considered treatment-related. The treatment differences appeared to be small.

Analysis Using Odds Ratio

As previously mentioned, no statistical significance does not necessarily imply no clinical difference in the case of adverse events, where the study is not powered to detect significance at a certain level. Therefore, this reviewer calculated the odds ratios and their 90% confidence intervals (computed from asymptotic standard error of log(odds ratio)), for adverse events reported by 1% or more of patients in either treatment group, combining all three studies:

Adverse event	# of occurrence with 882 articaine patients	# of occurrence with 443 lidocaine patients	Odds ratio of articaine/lidocaine	Asymptotic 90% C.I.
Face edema	13	6	1.09	(0.50, 2.40)
Headache	31	15	1.04	(0.62, 1.75)
Infection	10	3	1.68	(0.61, 4.66)
Pain	114	54	1.07	(0.80, 1.43)
Gingivitis	13	5	1.31	(0.57, 3.03)
Hypesthesia	7	5	0.70	(0.28, 1.77)
Paresthesia	11	2	2.78	(0.88, 8.81)

Therefore, the risk of paresthesia is numerically higher in the articaine group than the lidocaine group. There also seems to be a suggestion that the risks of infection and gingivitis are somewhat higher. For

other adverse events, the risks appear to be comparable in the two treatment groups, although the numbers of events are too small to indicate statistical significance.

In addition, it might not be statistically desirable to combine the three studies, because one study may have different factors than another. However, because of the small numbers of events, the increased variability associated with separating the studies would result in more difficulties in drawing conclusions. Consequently, the risk that articaine may cause higher incidence of adverse events could be even higher than what the above analysis suggests.

Among adverse events occurred at rate <1%, nausea appeared also to have a treatment difference in the larger study, 96001.02US. The occurrence was 6 in 569 in the articaine group vs. 1 in 284 in the lidocaine group. The corresponding odds ratio is 3.03, with 90% confidence interval (0.68, 13.47). Nausea was not reported in the other two studies. A possible interpretation for this may be that 6 in 569 is roughly a 1% event, but the sizes of articaine group each of the two smaller studies were 155 and 158, not large enough to detect a 1% event. The odds ratio calculated in the combined population, as 6 in 882 in the articaine group vs. 1 in 443 in the lidocaine group, is almost identical: 3.02 with 90% confidence interval (0.68, 13.45). For other adverse events, it is difficult to draw conclusions because of low numbers of occurrence.

Conclusion

In three active-controlled studies, articaine appeared to be similar in efficacy to lidocaine, although without confirmatory evidence due to the lack of prespecified statistical criteria. On the vital signs of safety indications, articaine was also shown to be comparable to lidocaine. Regarding the adverse events, there is evidence that the risks of *paresthesia* and *nausea* are higher with articaine than with lidocaine. There are also suggestions that the risks of *infection* and *gingivitis* might be somewhat higher with articaine. For other adverse events, there are no reasons to indicate that risks of the two treatments are different, although the event numbers are too small to conclude statistical equivalence. Therefore, there lacks the certainty that the risk profiles will be similar.

Labeling Recommendation

In the "ADVERSE REACTIONS" section, after the second sentence ending with "...
', add:

Appendix: Treatment Balance

96001.02UK. Summary of Patient Demographics and Baseline Characteristics

Variable	Articaine (N=158)	Lidocaine (N=84)	P-Value
	Number (%) of Patients		
Sex Male Female	 78 (49) 80 (51)	 33 (39) 51 (61)	NS[a]
Age (years) 4 to <13 years ≥13 years Mean ± SEM Range	 3 (2) 155 (98) 33.7 ± 1.19 4-77	 2 (2) 82 (98) 34.0 ± 1.56 9-74	NS[a]
Weight (kg) Mean ± SEM Range	 71.3 ±1.13 16-105	 67.9 ± 1.62 23-118	NS[b]
Race White Black Asian Other	 143 (91) 6 (4) 8 (5) 1 (1)	 80 (95) 3 (4) 1 (1) 0	NS[a]
Stratification Simple Procedure Complex Procedure	 115 (73) 43 (27)	 60 (71) 24 (29)	NS[a]
Supine systolic blood pressure (mmHg) Mean ± SEM Range	 121.2 ± 1.60	 120.0 ± 2.31	NS[b]
Supine diastolic blood pressure (mmHg) Mean ± SEM Range	 73.2 ± 1.07	 72.2 ± 1.30	NS[b]
Pulse rate (bpm) Mean ± SEM Range	 79.4 ± 1.13	 78.2 ± 1.61	NS[b]
Respirations (/minute) Mean ± SEM Range	 18.9 ± 0.33	 18.7 ± 0.41	NS[b]
Temperature (°C) Mean ± SEM Range	 36.5 ± 0.04	 36.5 ± 0.05	ND

Extracted from Table 2
NS No statistical significance (p>0.05)
ND Not determined
a Cochran-Mantel-Haenszel test
b ANOVA

96001.02US, Summary of Patient Demographics and Baseline Characteristics

Variable	Articaine (N=569)	Lidocaine (N=284)	P-Value
	Number (%) of Patients		
Sex Male Female	 256 (45) 313 (55)	 121 (43) 163 (57)	NS[a]
Age (years) 4 to <13 years ≥13 years Mean ± SEM Range	 1 (<1) 568 (>99) 38.9 ± 0.60 10-79	 1 (<1) 283 (>99) 38.7 ± 0.87 12-77	NS[a]
Weight (kg)[c] Mean ± SEM Range	 75.4 ± 0.72 42.7-139.5	 74.1 ± 1.00 43.2-150.9	NS[b]
Race White Black Asian Hispanic Other	 429 (75) 54 (9) 28 (5) 42 (7) 16 (3)	 214 (75) 28 (10) 20 (7) 15 (5) 7 (2)	NS[a]
Stratification Simple Procedure Complex Procedure	 427 (75) 142 (25)	 211 (74) 73 (26)	NS[a]
Supine systolic blood pressure (mmHg) Mean ± SEM Range	122.4 ± 0.67	122.2 ± 0.90	NS[b]
Supine diastolic blood pressure (mmHg) Mean ± SEM Range	74.7 ± 0.42	74.5 ± 0.59	NS[b]
Pulse rate (bpm) Mean ± SEM Range	71.8 ± 0.51	72.7 ± 0.67	NS[b]
Respirations (/minute)[d] Mean ± SEM Range	16.8 ± 0.14	16.6 ± 0.19	0.012[b]
Temperature (°C) Mean ± SEM Range	36.6 ± 0.02	36.6 ± 0.03	ND

Extracted from Table 2
NS No statistical significance (p>0.05)
ND Not determined
a Cochran-Mantel-Haenszel test
b ANOVA
c N=568 (articaine); N=281 (lidocaine)
d N=567 (articaine); N=284 (lidocaine)

96002.01, Summary of Patient Demographics and Baseline Characteristics

Variable	Articaine (N=155)	Lidocaine (N=75)	P-Value
	Number (%) of Patients		
Sex Male Female	 84 (54) 71 (46)	 30 (40) 45 (60)	0.037[a]
Age (years) 4 to <13 years ≥13 years Mean ± SEM Range	 46 (30) 109 (70) 29.1 ± 1.43 4-79	 17 (23) 58 (77) 31.0 ± 2.01 5-71	NS[a]
Weight (kg)[c] Mean ± SEM Range	 62.1 ± 1.83 18.2-145.5	 62.1 ± 2.61 15.9-122.7	NS[b]
Race White Black Asian Hispanic Other	 75 (48) 14 (9) 8 (5) 52 (34) 6 (4)	 36 (48) 3 (4) 6 (8) 27 (36) 3 (4)	NS[a]
Stratification Simple Procedure Complex Procedure	 133 (86) 22 (14)	 67 (89) 8 (11)	NS[a]
Supine systolic blood pressure (mmHg) Mean ± SEM Range	115.6 ± 1.31	115.1 ± 1.88	0.004[b]
Supine diastolic blood pressure (mmHg) Mean ± SEM Range	74.2 ± 0.96	75.0 ± 1.35	NS[b]
Standing systolic blood pressure (mmHg) Mean ± SEM Range	119.1 ± 1.33	117.3 ± 1.71	0.009[b]
Standing diastolic blood pressure (mmHg) Mean ± SEM Range	76.2 ± 0.89	77.9 ± 1.35	NS[b]
Pulse rate (bpm) Mean ± SEM Range	76.6 ± 0.88	75.8 ± 1.55	NS[b]
Respirations (/minute) Mean ± SEM Range	17.0 ± 0.26	16.9 ± 0.36	NS[b]
Temperature (°C)[d] Mean ± SEM Range	36.6 ± 0.04	36.6 ± 0.05	ND

Extracted from Tables 2 and 8.1.
NS No statistical significance (p>0.05)
ND Not determined
a Cochran-Mantel-Haenszel test
b ANOVA
c N=153 (articaine); N=73 (lidocaine)
d N=154 (articaine); N=75 (lidocaine)

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