U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208-032
Supplement #:	Original
Drug Name:	Kovanaze (tetracaine HCl, 3% w/v, and oxymetazoline HCl, 0.05% w/v) intranasal spray
Indication(s):	Regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J.
Applicant:	St. Renatus, LLC
Date(s):	Received: 05/29/2015 PDUFA: 03/29/2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	James Travis, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Medical Officer: Amelia Luckett, M.D. Medical Team Leader: Rigoberto Roca, M.D.
Project Manager:	Mavis Darkwah

Keywords: NDA review, Subgroup Analyses

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

St. Renatus, LLC has submitted a New Drug Application (NDA) for Kovanaze (tetracaine HCl, 3% w/v, and oxymetazoline HCl, 0.05% w/v) intranasal spray and is seeking an indication of regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J.

This submission includes four multi-center, randomized, double-blind, parallel group clinical trials. The first two studies compared Kovanaze to both tetracaine alone and placebo in adult patients. The third study compared Kovanaze to placebo in adults. The final study compared Kovanaze to placebo in pediatric patients aged 3-17. The primary efficacy endpoint for all four studies was the proportion of patients who were able to complete the study dental procedure without the need for rescue by injection of local anesthetic.

The first adult study was stopped after randomizing only 26 of the planned 140 patients due to reasons related to the effectiveness of the product. The Applicant reports that they believe this was due to differences in the administration instructions provided to the investigators compared to the earlier phase 2 studies.

The other two adult studies both found a statistically significantly greater proportion of patients receiving Kovanaze were able to complete the study dental procedure without need for rescue than for either tetracaine alone or placebo. However, there was some evidence that the efficacy of Kovanaze for procedures on the 2nd pre-molar (teeth 4 & 13) was less than that observed for other teeth. Overall, procedures on these teeth were successfully completed without rescue 63% of the time compared to 96% for the other teeth studied. The Applicant stated that they believe that this was due to some anatomical differences that occur in approximately 30% of the population.

In the pediatric study the dosage administered depended on the patient's weight on the day of the dental procedure. See Table 11 for a summary of the dosages. Results showed that overall there were statistically significantly more successes in the Kovanaze group than the placebo group; (b) (4) (b) (4) The success rate for patients weighing greater than 40 kg was comparable to that seen in the adult studies for Kovanaze (94% vs 87% for adults) and significantly greater than the placebo success rate (40%).

Based on my review of this application, I recommend that this product be approved for the indication of regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J in patients weighing at least 40 kg. I also recommend that the prescribing information clearly informs prescribers that this product was not found to be as effective for procedures on the 2nd pre-molar (permanent teeth 4, and 13 and primary teeth A and J).

2 INTRODUCTION

2.1 Overview

Kovanaze (tetracaine HCl, 3% w/v, and oxymetazoline HCl, 0.05% w/v also referred to as (b) (4) and (b) (4)) is an intranasal spray that has been developed for regional anesthesia when performing a restorative procedure on permanent teeth 4-13 and primary teeth A-J. Tetracaine is an ester-anesthetic and oxymetazoline is a vasoconstrictor that was added to facilitate localized retention of tetracaine in the target area.

The development program for Kovanaze was conducted under IND 70,868 which was originally submitted in March 2005. The design of the Phase 3 trials was initially discussed at an End of Phase 2 meeting on March 3, 2011. In this meeting the Applicant asked for feedback on a number of statistical issues including the analyses of the primary and secondary endpoints and their sample size calculation. (b) (4)

The Applicant conducted four phase 3 studies comparing Kovanaze with Placebo which are summarized in Table 1. The first three studies, SR 3-01 – SR 3-03 were conducted in adults and study SR3-04 was conducted in pediatric patients aged 3-17. As this was a combination product the first two studies also compared Kovanaze with tetracaine alone. Oxymetazoline was not studied as a single entity product as it was not expected to provide any anesthetic effect. The primary efficacy endpoint for all four studies was a responder analysis where a responder was defined as a patient that completed the study dental procedure (SDP) without need for rescue by injection of local anesthetic.

Table 1: List of all Phase 3 studies conducted by the Applicant

Study #	Population	# of Patients	Ratio	Comparator(s)
SR3-01	Adult	140 Planned 26 Enrolled	2:2:1	Tetracaine alone & Placebo
SR3-02	Adult	110	2:2:1	Tetracaine alone & Placebo
SR3-03	Adult	150	2:1	Placebo
SR3-04	Pediatric (Age 3-17)	90	2:1	Placebo

Source: Reviewer

(b) (4)

(b) (4)

The protocol for the second adult study, SR3-02, was submitted to the Agency in September 2012 and was revised in October 2012. The administration instructions and training was modified to match those used successfully earlier in the development cycle. The study was initiated in October 2012 and was completed in February 2013. A total of 110 patients were enrolled at two sites within the United States. This study again included three treatment arms and the dosage was the same as the previous study.

The protocol for the third adult study, SR3-03, submitted in November 2012 and the study was initiated in February 2013 and completed in May 2013. A total of 150 patients were enrolled at three sites within the United States. This study included two important modifications from the previous studies. For this study only two treatment arms were included, Kovanaze and placebo and the third spray of the study drug was also made optional and only administered if the anesthesia was insufficient to complete the SDP after the first two sprays.

The final study, SR3-04, was conducted in pediatric patients and was initiated in April 2013 and was completed in August 2013. This study enrolled a total of 90 patients between the age of 3 and 17 at two sites within the United States. The dosage for this study was based on the weight of the patient on the day of the SDP and is shown in Table 2 as well as the doses used in the adult studies.

Table 2: Dosage Received

Study	Population	Number of Sprays	Spray Volume	Total Volume
SR3-01	Adults	3	0.2 mL	0.6 mL
SR3-02	Adults	3	0.2 mL	0.6 mL
SR3-03	Adults	2 (3rd Optional)	0.2 mL	0.4 mL (0.6 mL)
SR3-04	Age 3-5	1	0.1 mL	0.1 mL
SR3-04	Age 6-11	2	0.1 mL	0.2 mL
SR3-04	Age 12-17	2	0.2 mL	0.4 mL

Source: Reviewer

The Pre-NDA meeting for this product was held on August 21, 2014. One item discussed during this meeting was the efficacy findings from the pediatric study, SR3-04. The applicant was informed that efficacy of patients aged 12 to 17 years may be limited due to issues with the sample size and multiplicity. These results are discussed in Section 3.2.3.

This review will focus on the two adult efficacy studies, SR3-02 and SR3-03 and the pediatric study SR3-04.

2.2 Data Sources

All data was provided electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):
\\CDSESUB1\evsprod\NDA208032\0000\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the submitted data was sufficient to reproduce the Applicant's efficacy analyses.

3.2 Evaluation of Efficacy

The efficacy will be discussed separately for studies SR3-02, SR3-03, and SR3-04 in sections 3.2.1, 3.2.2, and 3.3.3, respectively.

3.2.1 SR3-02

3.2.1.1 Study Design and Endpoints

Study SR3-02 was a phase 3, multicenter, double-blind, parallel-group clinical trial comparing the efficacy and safety of intranasally administered Kovanaze to tetracaine alone and to placebo for anesthetizing maxillary teeth in adults. The study was conducted from October 2012 to February 2013 at two sites in the United States and randomized 110 patients. These patients were male or female, 18 years of age or older, and in need for an operative restorative dental procedure requiring local anesthesia for a single vital maxillary tooth (other than a maxillary first, second, or third molar) with no evidence of pulpal pathology.

The primary objective for this study was to determine whether Kovanaze was safe and superior to tetracaine and placebo in providing local anesthesia sufficient to allow completion of an operative restorative dental procedure [the "Study Dental Procedure" or (SDP)] on a maxillary tooth (#4 to 13) in adults without need for intra-procedure rescue by injection of local anesthetic.

The Applicant also specified two secondary objectives: to determine if Kovanaze provides anesthesia of intraoral soft tissue and to evaluate the safety and tolerability of Kovanaze. The anesthesia of the soft tissue was assessed by exerting pressure using a mechanical probe on the incisive papilla and the greater palatine foramen ipsilateral to the SDP and reporting if there is a painful response.

On the day of the procedure the investigator was to complete the pre-study procedures which included a reassessment of eligibility, a baseline soft tissue anesthesia assessment (STAA), and baseline subjective numbness assessment (SNA). Eligible patients were randomized and administered 3 sprays of study drug. The time of the first spray was denoted as T=0 minutes. The 2nd and 3rd sprays were then to be administered at T=4 and T=8 minutes (± 1 minute) after the first spray. Fifteen minutes after the first spray was administered (T=15) the investigator performed the subjective numbness and soft-tissue anesthesia assessments and then initiated the SDP. If the anesthesia was insufficient then the investigator was to wait 5 minutes before

checking the pulpal anesthesia again. If the anesthesia was still insufficient then rescue anesthetic was to be injected.

Following the SDP the investigator was to perform the soft tissue, and subjective numbness assessments at T=30, 45, 60, 90 and 120 minutes. However, the investigator was instructed not to interrupt an ongoing SDP for these assessments.

3.2.1.2 Statistical Methodologies

With respect to the primary endpoint, completion of the SDP without rescue anesthesia, Kovanaze was required to demonstrate superiority to both tetracaine alone and placebo. These comparisons were tested using a 1-sided Fisher's exact test with a type I error rate of 2.5% rather than 5%. The Applicant stated that any patient who discontinued or withdrew from the study prior to completion of the dental procedure would be considered treatment failures.

The analysis population for this study was the Intention-to-Treat (ITT) population which was defined as all randomized patients who received at least one dose of study drug.

According to the Applicant the Soft Tissue Anesthesia Assessment (STAA) was a secondary endpoint and would be considered exploratory. Only summary statistics were to be presented and no adjustments were made for multiple comparisons and results would not be used to make definitive claims for efficacy.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 110 patients were randomized in a 2:2:1 ratio between Kovanaze, tetracaine alone and placebo at two sites in the United States. A summary of the patient disposition is presented in Table 3. All randomized subjects completed the study. The demographics for the subjects in this study are summarized in Table 4.

Table 3: Disposition of Patients – SR3-02

	(b) (4) (N = 44)	TET (N = 44)	PBO (N = 22)	Total (N = 110)
Screened	N/A	N/A	N/A	136
Randomized	44 (100.0%)	44 (100.0%)	22 (100.0%)	110 (100.0%)
Not Treated	0	0	0	0
Treated	44 (100.0%)	44 (100.0%)	22 (100.0%)	110 (100.0%)
Completed	44 (100.0%)	44 (100.0%)	22 (100.0%)	110 (100.0%)
Next Day: Clinical visit	42 (95.5%)	43 (97.7%)	21 (95.5%)	106 (96.4%)
Next Day: Phone visit (if needed)	2 (4.5%)	1 (2.3%)	1 (4.5%)	4 (3.6%)
Withdrawn	0	0	0	0

Abbreviations: (b) (4), Kovanaze; TET, Tetracaine; PBO, Placebo;
Source: Table 10.1 from Applicant's clinical study report

Table 4: Summary of Demographics – SR3-02

Variable Statistics	(b) (4) (N = 44)	TET (N = 44)	PBO (N = 22)	Total (N = 110)	*P*-value
Age at Dosing (years)					0.1277
n	44	44	22	110	
Mean (SD)	37.1 (14.73)	31.3 (12.01)	35.7 (14.64)	34.5 (13.82)	
Median	32.0	27.0	30.5	29.5	
Min, Max	18.73	18.64	19.65	18.73	
Gender [n (%)]					0.0113
Male	14 (31.8)	28 (63.6)	10 (45.5)	52 (47.3)	
Female	30 (68.2)	16 (36.4)	12 (54.5)	58 (52.7)	
Race [n (%)]					0.2671
White	35 (79.5)	36 (81.8)	13 (59.1)	84 (76.4)	
Black or African American	2 (4.5)	3 (6.8)	2 (9.1)	7 (6.4)	
Asian	1 (2.3)	2 (4.5)	4 (18.2)	7 (6.4)	
Native Hawaiian or Other Pacific Islander	2 (4.5)	0	1 (4.5)	3 (2.7)	
Other	4 (9.1)	3 (6.8%)	2 (9.1)	9 (8.2)	
Ethnicity [n (%)]					0.8762
Hispanic or Latino	3 (6.8)	2 (4.5)	1 (4.5)	6 (5.5)	
Not Hispanic or Latino	41 (93.2)	42 (95.5)	21 (95.5)	104 (94.5)	
Height (cm)					< 0.0001
n	44	44	22	110	
Mean (SD)	167.31 (8.380)	175.52 (8.880)	169.43 (9.186)	171.02 (9.450)	
Median	165.00	175.15	170.30	170.40	
Min, Max	150.5, 188.4	154.0, 198.0	154.0, 191.6	150.5, 198.0	
Weight (kg)					0.7178
n	44	44	22	110	
Mean (SD)	85.16 (23.333)	82.60 (21.063)	80.79 (19.214)	83.26 (21.536)	
Median	85.60	78.55	77.70	82.45	
Min, Max	40.9,138.4	55.5,173.6	52.9,132.7	40.9,173.6	

Abbreviations: (b) (4), Kovanaze; TET, Tetracaine; PBO, Placebo;
Source: Table 11.1 from Applicant's clinical study report

3.2.1.4 Results and Conclusions

The results of the primary efficacy analyses are shown in Table 5. The Applicant concluded that there were a statistically significantly greater proportion of treatment successes in the Kovanaze arm than either the tetracaine only arm or the placebo arm. I was able to confirm the Applicant's conclusions.

Table 5: Success Rates by Treatment Group – SR3-02

	Kovanaze (N=44)		Tetracaine (N=44)			Placebo (N=22)		
Anesthetic Outcome	**Count (%)**	**95% CI**	**Count (%)**	**95% CI**	**P-Value***	**Count (%)**	**95% CI**	**P-Value***
Success	37 (84.1%)	(69.9, 93.4%)	12 (27.3%)	(15.0, 42.8%)	<.0001	6 (27.3%)	(10.7, 50.2%)	<.0001
Failure	7 (15.9%)		32 (72.7%)			16 (72.7%)		

* One-Sided Fisher's Exact Test at 2.5% type-1 error
Source: Table 11.7 from Applicant's clinical study report

3.2.2 SR3-03

3.2.2.1 Study Design and Endpoints

Study SR3-03 was a multi-center, randomized, double-blind, parallel-group clinical trial comparing the efficacy and safety of Kovanaze to placebo for anesthetizing maxillary teeth in adults. This study was conducted from February 2013 to May 2013 at a total of three sites within the United States and randomized 150 subjects. There were two major changes in the conduct of this study from that of the previous study SR3-02. First, the tetracaine alone arm was removed and second, the third dose was made optional and the dosing schedule modified. The screening procedure and inclusion criteria were unchanged.

The primary objective for this study was to determine whether Kovanaze is safe and superior to placebo in providing local anesthesia sufficient to allow completion of an operative restorative dental procedure on a maxillary tooth (#4 to 13) in adults without need for intra-procedure rescue by injection of local anesthetic.

For this study the Applicant also specified two secondary objectives: To assess the safety and efficacy of Kovanaze versus placebo by age group (≤50 and >50 years) and to evaluate the safety and tolerability of Kovanaze.

On the day of the dental procedure, eligible patients will undergo a pre-Study assessment. These assessments no longer include the soft-tissue and subjective numbness assessments conducted in the previous study. Once the assessments are complete the subjects will be randomized in a 2:1 ratio to Kovanaze or placebo.

3.2.2.2 Statistical Methodologies

The proportion of patients completing the SDP without need for injection of rescue anesthesia, were compared between Kovanaze and placebo using a one-sided Fisher's Exact Test. Since the test is one-sided the type I error rate is set to 2.5%.

The analysis population for this study was the Intention-to-Treat (ITT) population which was defined as all randomized patients who received at least one dose of study drug.

To control the overall type I error for the secondary endpoint, success rate within age group (≤50 and >50 years of age), a step-down approach was utilized. Response rates within age would only be tested if the primary endpoint was significant. The Applicant specified that they would test this endpoint using a Cochran–Mantel–Haenszel (CMH) test. The Applicant also conducted a Breslow-Day test to evaluate the homogeneity of the odds ratio between the two age groups.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 150 patients were randomized into the study in a 2:1 between Kovanaze and placebo at three sites within the United States. The overall disposition in the study is shown in Table 6. A total of 148 subjects completed the study with one subject withdrawing from each arm of the study. The demographics of all randomized patients are summarized in Table 7

Table 6: Disposition of Patients – SR3-03

Disposition	(b) (4) (N = 100)	PBO (N = 50)	Total (N = 150)
Randomized	100 (100.0%)	50 (100.0%)	150 (100.0%)
Treated	100 (100.0%)	50 (100.0%)	150 (100.0%)
Completed	99 (99.0%)	49 (98.0%)	148 (98.7%)
Next Day: Phone visit	3 (3.0%)	3 (6.0%)	6 (4.0%)
Next Day: Clinical visit (if needed)	97 (97.0%)	47 (94.0%)	144 (96.0%)
Withdrawn	1 (1.0%)	1 (2.0%)	2 (1.3%)
Primary Reason for Withdrawal			
Adverse Event or Serious Adverse Event	0	0	0
Use of exclusionary medication or procedure	0	0	0
Protocol Violation	0	0	0
Lost to Follow-Up	1 (100.0%)	0	1 (50.0%)[a]
Patient Withdrew Consent	0	0	0
Investigator Decision to Withdraw Patient	0	0	0
Other	0	1 (100.0%)	1 (50.0%)[b]

Abbreviations: (b) (4), Kovanaze; PBO, Placebo;
Source: Table 10.1 from Applicant's clinical study report

Table 7: Summary of Demographics – SR3-03

Characteristic/ Statistic or Category	(b) (4)			PBO			Total (N = 150)
	All patients (N = 100)	Age ≤ 50 years (N = 69)	Age > 50 years (N = 31)	All patients (N = 50)	Age ≤ 50 years (N = 34)	Age > 50 years (N = 16)	
Age at Dosing (years)							
N	100	69	31	50	34	16	150
Mean (SD)	41.6 (13.98)	33.9 (8.48)	58.8 (6.09)	40.3 (15.23)	31.3 (8.22)	59.5 (5.57)	41.2 (14.37)
Median	40.5	32.0	57.0	36.0	29.5	58.5	39.0
Min, Max	18, 78	18, 50	51, 78	18, 71	18, 50	52, 71	18, 78
Gender, N (%)							
Male	43 (43.0%)	27 (39.1%)	16 (51.6%)	25 (50.0%)	16 (47.1%)	9 (56.3%)	68 (45.3%)
Female	57 (57.0%)	42 (60.9%)	15 (48.4%)	25 (50.0%)	18 (52.9%)	7 (43.8%)	82 (54.7%)
Race, N (%)[a]							
White	64 (64.0%)	44 (63.8%)	20 (64.5%)	30 (60.0%)	19 (55.9%)	11 (68.8%)	94 (62.7%)
Black or African American	16 (16.0%)	13 (18.8%)	3 (9.7%)	4 (8.0%)	4 (11.8%)	0	20 (13.3%)
Native Hawaiian or Other Pacific Islander	16 (16.0%)	8 (11.6%)	8 (25.8%)	14 (28.0%)	9 (26.5%)	5 (31.3%)	30 (20.0%)
Other	4 (4.0%)	4 (5.8%)	0	2 (4.0%)	2 (5.9%)	0	6 (4.0%)
Ethnicity, N (%)							
Hispanic or Latino	12 (12.0%)	11 (15.9%)	1 (3.2%)	7 (14.0%)	6 (17.6%)	1 (6.3%)	19 (12.7%)
Not Hispanic or Latino	88 (88.0%)	58 (84.1%)	30 (96.8%)	43 (86.0%)	28 (82.4%)	15 (93.8%)	131 (87.3%)
Height (cm)							
N	100	69	31	50	34	16	150
Mean (SD)	169.87 (10.356)	169.84 (10.009)	169.95 (11.263)	172.12 (10.222)	171.95 (10.363)	172.48 (10.238)	170.62 (10.332)
Median	170.10	170.10	167.00	171.65	171.65	172.10	170.10
Min, Max	144.8, 194.3	144.8, 191.8	150.6, 194.3	151.1, 190.5	152.4, 190.5	151.1, 188.0	144.8, 194.3
Weight (kg)							
N	100	69	31	50	34	16	150
Mean (SD)	81.09 (20.227)	80.99 (20.448)	81.31 (20.059)	85.44 (24.687)	85.46 (28.362)	85.40 (14.874)	82.54 (21.829)
Median	77.15	77.20	75.20	80.65	74.10	82.70	79.15
Min, Max	48.8, 142.0	48.8, 142.0	55.3, 132.8	52.2, 187.1	52.2, 187.1	59.4, 109.3	48.8, 187.1

Abbreviations: (b) (4), Kovanaze; PBO, Placebo;
Source: Table 11.1 from Applicant's clinical study report

3.2.2.4 Results and Conclusions

The results of the primary efficacy analysis are shown in Table 8. The Applicant concluded that there were a statistically significantly greater proportion of treatment successes in the Kovanaze arm than the placebo arm. I agree with the Applicant's overall conclusion for this study.

Table 8: Success Rates by Treatment Group – SR3-03

Anesthetic	Kovanaze (N=100)		Placebo (N=50)		
Outcome	Count (%)	95% CI	Count (%)	95% CI	P-Value*
Success	88 (88.0%)	(80.0, 93.6%)	14 (28.0%)	(16.2, 42.5%)	<.0001
Failure	12 (12.0%)		36 (72.0%)		

* One-Sided Fisher's Exact Test at 2.5% type-1 error
Source: Table 11.6 from Applicant's clinical study report

Since the third dose of study drug was optional and was only given to patients if the anesthesia was insufficient to initiate the SDP, I examined response rates based on the number of sprays received, 2 or 3. Results are shown in Table 9. Of the responders in the Kovanaze arm (88 patients), 16 or 18% required a third spray.

Table 9: Success Rates by Number of Sprays – SR3-03

	Anesthetic Success rate			
	Kovanaze (N=100)		Placebo (N=50)	
	N	Count (%)	N	Count (%)
Number of Sprays				
2	73	72 (98.6%)	17	14 (82.4%)
3	27	16 (59.3%)	33	0 (0.0%)

Source: Table 11.11 from Applicant's clinical study report

Since there was an overall significant difference in the response rates, the secondary endpoint, response rates within age groups, was examined. The results are shown in Table 10. The Applicant performed two hypothesis tests. The CMH test and the Breslow-Day test. The p-value for the Cochran-Mantel-Haenszel test was significant which means that there is evidence of a difference in success rates between the Kovanaze and placebo groups when stratified on age. The Breslow-Day test was not significant which means that we cannot conclude that there is a difference in the odds ratio between the two age groups.

Table 10: Success Rates by Age Group – SR3-03

	Anesthetic Success rate					
	Kovanaze (N=100)		Placebo (N=50)		CMH P-value	Breslow Day P-value
Stratification Factor	N	Count (%)	N	Count (%)		
Age [years]						
≤ 50	69	60 (87.0%)	34	7 (20.6%)	<.0001	0.4280
> 50	31	28 (90.3%)	16	7 (43.8%)		

Source: Table 11.7 from Applicant's clinical study report

3.2.3 SR3-04

3.2.3.1 Study Design and Endpoints

Study SR3-04 was a phase 3, multi-center, randomized, double-blind, parallel-groups clinical trial comparing the efficacy and safety of Kovanaze to placebo for anesthetizing maxillary teeth in pediatric patients.

The primary objective for this study was to determine whether Kovanaze is effective for providing local anesthesia sufficient to allow completion of an operative restorative dental procedure (the "Study Dental Procedure [SDP]") on a maxillary permanent tooth (#4 to 13) or a maxillary primary tooth (A to J) in pediatric patients without need for intra-procedure rescue by injection of local anesthetic.

To be eligible for this study patients were required to be either male or female, age 3 to 17 years inclusive and in need of an operative restorative dental procedure requiring local anesthesia on a single maxillary primary tooth (#A to J) or permanent tooth (#4 to 13).

The Applicant specified that a total of 90 patients were to be randomized into the study at two sites within the United States to Kovanaze or placebo in a 2:1 ratio. The patients were divided into three different dosage groups based weight. A summary of the study drug dosing groups is provided in Table 11.

Table 11: Study Drug Dosing Groups – SR3-04

		Volume per	Number	Kovanaze Total Dose	
Patient Weight	Dose	Spray	of Sprays	Tetracaine HCl	Oxymetazoline HCl
10 to < 20 kg	0.1 mL	0.1 mL	1	3 mg	0.05 mg
20 to < 40 kg	0.2 mL	0.1 mL	2	6 mg	0.1 mg
40 kg or more	0.4 mL	0.2 mL	2	12 mg	0.2 mg

Source: Table 9.2 from Applicant's clinical study report

The primary efficacy endpoint for this study was completion of the SDP without need for rescue by injection of local anesthetic. The Applicant also defined two secondary endpoints:

Completion of the SDP without need for rescue by injection of local anesthetic by dose (0.1mL, 0.2 mL, or 0.4 mL) and by age group (3 to 5 years, 6 to 11 years, and 12 to 17 years, inclusive).

3.2.3.2 Statistical Methodologies

The Applicant again specified that the primary efficacy endpoint would be tested with a one-sided Fisher's exact test with a type I error rate of 2.5%.

The analysis population for this study was the Intention-to-Treat (ITT) population which was defined as all randomized patients who received at least one dose of study drug.

The Applicant specified that the secondary endpoints would be tested sequentially if the primary endpoint is significant in order to control the overall type I error for the study. The Applicant specified that both these endpoints would be tested using the CMH test stratified by dose group and age group respectively. The type I error for both these endpoints will be 5%.

The Applicant also performed several tests for the secondary endpoints which were not pre-specified or adjusted for multiplicity. These tests were the one-sided Fisher's exact tests for the individual age and weight subgroups and the Breslow-Day test of homogeneity of treatment effect across strata.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 90 patients were randomized into this study at two sites inside the United States. The disposition and demographics for all randomized patients in the trial are shown in Table 12 and Table 13, respectively.

Table 12: Disposition of Patients – SR3-04

Disposition	(b) (4) (N = 60)	PBO (N = 30)	Total (N = 90)
Enrolled and randomized	60 (100.0%)	30 (100.0%)	90 (100.0%)
Received study treatment	60 (100.0%)	30 (100.0%)	90 (100.0%)
Completed	59 (98.3%)	30 (100.0%)	89 (98.9%)
Withdrawn	1 (1.7%)*	0	1 (1.1%)
Primary Reason for Withdrawal			
Adverse Event or Serious Adverse Event	0	0	0
Use of exclusionary medication or procedure	0	0	0
Major Protocol Violation	0	0	0
Lost to Follow-Up	0	0	0
Patient Withdrew Consent*	1 (1.7%)	0	1 (1.7%)
Investigator Decision to Withdraw Patient	0	0	0
Other	0	0	0

Abbreviations: (b) (4), Kovanaze; PBO, Placebo;
Source: Table 10.1 from Applicant's clinical study report

Table 13: Summary of Demographics Study – SR3-04

Variable	(b) (4) (N = 60)	PBO (N = 30)	Total (N = 90)
Age at Dosing (years)			
Mean (SD)	8.3 (4.2)	8.1 (3.8)	8.2 (4.1)
Median	7.0	7.0	7.0
Min, Max	3, 17	3, 16	3, 17
Gender n (%)			
Male	32 (53.3%)	14 (46.7%)	46 (51.1%)
Female	28 (46.7%)	16 (53.3%)	44 (48.9%)
Race n (%)			
White	54 (90.0%)	26 (86.7%)	80 (88.9%)
Black or African American	3 (5.0%)	1 (3.3%)	4 (4.4%)
Asian	1 (1.7%)	0	1 (1.1%)
Native Hawaiian or Other Pacific Islander	0	1 (3.3%)	1 (1.1%)
American Indian	0	1 (3.3%)	1 (1.1%)
Alaska Native	0	0	0
Other	2 (3.3%)	1 (3.3%)	3 (3.3%)
Ethnicity n (%)			
Hispanic or Latino	28 (46.7%)	13 (43.3%)	41 (45.6%)
Not Hispanic or Latino	32 (53.3%)	17 (56.7%)	49 (54.4%)
Height (cm)			
Mean (SD)	132.2 (25.0)	131.1 (21.5)	131.8 (23.8)
Median	128.5	130.0	129.5
Min, Max	92.5, 190.5	97.0, 166.5	92.5, 190.5
Weight (kg)			
Mean (SD)	35.2 (20.0)	33.9 (15.9)	34.7 (18.6)
Median	26.9	27.8	26.9
Min, Max	14.5, 101.3	15.4, 66.1	14.5, 101.3

Abbreviations: (b) (4), Kovanaze; PBO, Placebo;
Source: Table 11.1 from Applicant's clinical study report

The dosage in this study was determined by the patient's weight on the day of the study procedure. Table 14 contains a summary of the patient distribution by age group and weight strata.

Table 14: Patient Distribution by Age and Weight Group – SR3-04

	Weight Group			
Age Group	**10 to <20 kg**	**20 to <40 kg**	**40 kg or more**	**Total**
3- 5 years	24	7	0	31
6-11 years	0	29	9	38
12-17 years	0	0	21	21
Total	24	36	30	90

Source: Reviewer

The distribution of patients by weight group and tooth age is shown in Table 15.

Table 15: Patient Distribution by Weight Group and Tooth Age – SR3-04

Weight Group	Tooth Age		
	Primary	**Permanent**	**Total**
10 to <20 kg	24	0	24
20 - <40 kg	36	0	36
≥ 40 kg	6	24	30
Total	66	24	90

Source: Reviewer

3.2.3.4 Results and Conclusions

The results of the Applicant's primary efficacy analysis are shown in Table 16. (b) (4)

Table 16: Success Rates by Treatment Group – SR3-04

	Kovanaze (N=60)		Placebo (N=30)		
Anesthetic Outcome	**Count (%)**	**95% CI**	**Count (%)**	**95% CI**	**P-Value***
Success	46 (76.7%)	(64.0, 86.6%)	16 (53.3%)	(34.3, 71.7%)	0.0231
Failure	14 (23.3%)		14 (46.7%)		

* One-Sided Fisher's Exact Test at 2.5% type-1 error
Source: Table 11.9 from Applicant's clinical study report

The results of the analysis of efficacy by Weight/Dosage group are shown in Table 17. The pre-specified CMH test stratified by dosage/weight found that the difference between the success rates in the Kovanaze and placebo treatment arms were statistically different. The Applicant also analyzed the heterogeneity of the odds ratio between the dosage strata using the Breslow-Day test and the efficacy in the individual dosage strata using one-sided Fisher's exact tests.

The Breslow-Day test was not significant [redacted]. The Fisher's exact test was found to be significant only for patients weighing at least 40 kg.

Table 17: Success Rates Stratified by Weight/Dosage – SR3-04

Stratification Factor	Anesthetic Success rate				One-Sided Fisher's Exact Test P-Value	CMH P-value	Breslow Day P-value
	Kovanaze (N=60)		Placebo (N=30)				
	N	Count (%)	N	Count (%)			
Dosage Strata							
10 to <20 kg	16	[redacted]					
20 to <40 kg	24					0.0198	0.1669
≥ 40 kg	20	18 (90.0%)	10	4 (40.0%)	0.0072		

Source: Table 11.10 from Applicant's clinical study report

[redacted]

Table 18: Success Rates Stratified by Age Group – SR3-04

Stratification Factor	Anesthetic Success rate				One-Sided Fisher's Exact Test P-Value	CMH P-value	Breslow Day P-value
	Kovanaze (N=60)		Placebo (N=30)				
	N	Count (%)	N	Count (%)			
Age [years]							
3-5	21	[redacted]					
6-11	23						
12-17	16						

Source: Table 11.11 from Applicant's clinical study report

3.3 Evaluation of Safety

The reader is referred to the Medical Review by Dr. Amelia Luckett for an evaluation of the safety of Kovanaze.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor conducted analyses for several demographic subgroups in studies SR3-02, SR3-03, and SR3-04. Each subgroup was evaluated using two different tests which were 1) the CMH test to evaluate whether there was a significant difference between the two treatment groups when stratified on a demographic factor, and 2) the Breslow-Day test which evaluates whether the odds ratio for the two treatment groups was homogenous for the different demographic subgroups.

Subgroups evaluated were age group, ethnicity, gender, height, clinical site, weight, and tooth location (anterior [teeth 6-11 or C-H] or pre-molar [teeth 4-5, 12-13, A-B, and I-J]). The Applicant also analyzed the efficacy by tooth age (primary or permanent) for the pediatric study, SR3-04. I also analyzed the efficacy data by race. These results are presented by study in Section 4.1, 4.2, add 4.3.

Since all three studies demonstrated a lower success rate for SDP on premolar teeth versus anterior teeth, I examined success rate by tooth number further. Results are presented in Section 4.4.

4.1 Study SR3-02

The success rates for each of the demographic subgroups of interest and the p-values for the CMH test are shown in Table 19. The p-values for the Breslow-Day tests for each of the demographic strata are shown in Table 20. Since the odds ratio is only defined when there are two treatment arms the Applicant performed the Breslow-Day test separately for Kovanaze vs tetracaine alone and Kovanaze vs placebo.

Table 19: Analysis by Demographic Subgroup – SR3-02

		Anesthetic Success rate						
		Kovanaze (N=44)		Tetracaine (N=44)		Placebo (N=22)		CMH
Strata	Category	N	Count (%)	N	Count (%)	N	Count (%)	P-value
Age	≤ 50 Years	34	27 (79.4%)	39	8 (20.5%)	16	3 (18.8%)	<.0001
	> 50 Years	10	10 (100.0%)	5	4 (80.0%)	6	3 (50.0%)	
Ethnicity	Hispanic or Latino	3	2 (66.7%)	2	0 (0.0%)	1	0 (0.0%)	<.0001
	Not Hispanic or Latino	41	35 (85.4%)	42	12 (28.6%)	21	6 (28.6%)	
Gender	Female	30	24 (80.0%)	16	6 (37.5%)	12	3 (25.0%)	<.0001
	Male	14	13 (92.9%)	28	6 (21.4%)	10	3 (30.0%)	
Height	≤ 170cm	30	23 (76.7%)	11	4 (36.4%)	10	3 (30.0%)	<.0001
	> 170cm	14	14 (100.0%)	33	8 (24.2%)	12	3 (25.0%)	
Race	White	35	30 (85.7%)	36	10 (27.8%)	13	4 (30.8%)	<.0001
	Black or African American	2	1 (50.0%)	3	1 (33.3%)	2	1 (50.0%)	
	Asian	1	1 (100.0%)	2	1 (50.0%)	4	1 (25.0%)	
	Native Hawaiian or Other Pacific Islander	2	1 (50.0%)	0	——	1	0 (0.0%)	
	Other	4	4 (100.0%)	3	0 (0.0%)	2	0 (0.0%)	
Site	2	24	18 (75.0%)	24	3 (12.5%)	12	2 (16.7%)	<.0001
	4	20	19 (95.0%)	20	9 (45.0%)	10	4 (40.0%)	
Tooth Location	Anterior	17	17 (100.0%)	20	8 (40.0%)	10	1 (10.0%)	<.0001
	Premolar	27	20 (74.1%)	24	4 (16.7%)	12	5 (41.7%)	
Weight	≤ 80kg	16	12 (75.0%)	23	8 (34.8%)	13	2 (15.4%)	<.0001
	> 80kg	28	25 (89.3%)	21	4 (19.0%)	9	4 (44.4%)	

Source: Adapted from Table 11.14 from Applicant's clinical study report

The CMH tests were significant for all the demographic subgroups in Study SR3-02 indicating that there was a significant treatment effect for Kovanaze regardless of age, ethnicity, gender, height, race, site, tooth location, and weight.

There were a total of two p-values from the Breslow-Day tests that were below the threshold of 0.05; the height strata for the comparison of Kovanaze vs tetracaine alone, and the tooth location strata for the comparison of Kovanaze vs placebo. My findings regarding the evaluation of efficacy by tooth location will be discussed further in Section 4.4.

Table 20: Breslow-Day P-Values by Demographic Subgroup and Comparator – SR3-02

	Breslow-Day P-Value	
Strata	**Tetracaine**	**Placebo**
Age	0.6833	0.4569
Ethnicity	0.6126	0.7144
Gender	0.1234	0.5296
Height	0.0345	0.0797
Race	0.3727	0.4427
Site	0.9407	0.6706
Tooth Location	0.2052	0.0060
Weight	0.0904	0.7266

Source: Adapted from Table 11.14 from Applicant's clinical study report

4.2 Study SR3-03

The results of the analyses by demographic subgroup for Study SR3-03 are shown in Table 21. The CMH tests found significant differences in the rates of treatment success for all demographic subgroups considered. All p-values for the Breslow-Day tests were found to be above 0.05.

Table 21: Analysis by Demographic Subgroup – SR3-03

		Anesthetic Success rate					
		Kovanaze (N=100)		Placebo (N=50)		CMH P-value	Breslow Day P-value
Strata	Category	N	Count (%)	N	Count (%)		
Ethnicity	Hispanic or Latino	12	11 (91.7%)	7	0 (0.0%)	<.0001	0.0957
	Not Hispanic or Latino	88	77 (87.5%)	43	14 (32.6%)		
Gender	Female	57	50 (87.7%)	25	5 (20.0%)	<.0001	0.4052
	Male	43	38 (88.4%)	25	9 (36.0%)		
Height	≤ 170cm	49	43 (87.8%)	22	6 (27.3%)	<.0001	0.9828
	> 170cm	51	45 (88.2%)	28	8 (28.6%)		
Race	White	64	59 (92.2%)	30	10 (33.3%)	<.0001	0.1639
	Black or African American	16	14 (87.5%)	4	0 (0.0%)		
	Native Hawaiian or Other Pacific Islander	16	11 (68.8%)	14	4 (28.6%)		
	Other	4	4 (100.0%)	2	0 (0.0%)		
Site	5	44	42 (95.5%)	22	5 (22.7%)	<.0001	0.0683
	6	32	25 (78.1%)	16	6 (37.5%)		
	7	24	21 (87.5%)	12	3 (25.0%)		
Tooth Location	Anterior	53	51 (96.2%)	26	8 (30.8%)	<.0001	0.1025
	Premolar	47	37 (78.7%)	24	6 (25.0%)		
Weight	≤ 80kg	53	46 (86.8%)	25	8 (32.0%)	<.0001	0.4683
	> 80kg	47	42 (89.4%)	25	6 (24.0%)		

Source: Adapted from Tables 11.8, 11.9, and 11.10 from Applicant's clinical study report

4.3 Study SR3-04

The results of the analyses by demographic subgroups for the pediatric study, SR 3-04, are shown in Table 22. The p-values for the CMH analyses were found to be significant for all demographic subgroups considered. The Breslow-Day p-value for the tooth age strata was the only one found to be below 0.05 for this study. This is not surprising since tooth age is highly correlated with the patient's age (see Table 15) and there was a large amount of variability in the success rates by age group (Table 18).

Table 22: Analysis by Demographic Subgroup – SR3-04

		Anesthetic Success rate					
		Kovanaze (N=60)		Placebo (N=30)		CMH P-value	Breslow Day P-value
Strata	Category	N	Count (%)	N	Count (%)		
Ethnicity	Hispanic or Latino	28	21 (75.0%)	13	9 (69.2%)	0.0270	0.1716
	Not Hispanic or Latino	32	25 (78.1%)	17	7 (41.2%)		
Gender	Female	28	23 (82.1%)	16	10 (62.5%)	0.0196	0.8294
	Male	32	23 (71.9%)	14	6 (42.9%)		
Race	White	54	42 (77.8%)	26	12 (46.2%)	0.0102	0.1637
	Black or African American	3	3 (100.0%)	1	1 (100.0%)		
	American Indian	0	——	1	1 (100.0%)		
	Asian	1	0 (0.0%)	0	——		
	Native Hawaiian or Other Pacific Islander	0	——	1	1 (100.0%)		
	Other	2	1 (50.0%)	1	1 (100.0%)		
Site	3	32	24 (75.0%)	16	6 (37.5%)	0.0242	0.2161
	5	28	22 (78.6%)	14	10 (71.4%)		
Tooth Age	Permanent	16	15 (93.8%)	8	3 (37.5%)	0.0253	0.0350
	Primary	44	31 (70.5%)	22	13 (59.1%)		
Tooth Location	Anterior	18	17 (94.4%)	7	5 (71.4%)	0.0337	0.4645
	Premolar	42	29 (69.0%)	23	11 (47.8%)		

Source: Adapted from Tables 11.12, 13, and 15 from Applicant's clinical study report

4.4 Efficacy by Tooth Number

In all three studies the Applicant consistently found a lower success rate for patients receiving Kovanaze for a SDP on their premolar teeth than for patients receiving a SDP on their anterior teeth. The Applicant provided a summary of treatment success by tooth number for all patients enrolled in the two adult studies. This summary is shown in Table 23 with the addition of the success rates for patients who received tetracaine alone in Study SR3-02. The success rate for patients receiving a procedure on their 2nd premolar (teeth 4 and 13) was 63% compared to an overall success rate of 96% for patients receiving a procedure on either their 1st premolar (teeth 5 and 12) or any other anterior teeth (teeth 6-11). According to the Applicant this is possibly due to anatomical differences that occur in approximately 30% of the population.

Table 23: Success Rates by Tooth Number for all Adult Dental Patients

Tooth No.	Kovanaze Successes	Tetracaine Successes	Placebo Successes
8 & 9	28/29 (96.6%)	6/10 (60.0%)	4/14 (28.6%)
7 & 10	25/26 (96.2%)	2/5 (40.0%)	4/16 (25.0%)
6 & 11	15/15 (100.0%)	0/5 (0.0%)	1/6 (16.7%)
5 & 12	31/33 (93.9%)	3/10 (30.0%)	8/22 (36.4%)
4 & 13	26/41 (63.4%)	1/14 (7.1%)	3/14 (21.4%)

Source: Reviewer

The first adult study, SR3-02, gave all patients a total of three sprays of either Kovanaze or placebo. However, in study SR-03 the third spray was optional and only administered if the anesthesia was determined to be insufficient. Table 24 shows the percentage of patients in the study that required the third spray by treatment group and by tooth location in study SR-03. Overall, patients receiving the SDP on one of their premolar teeth required a third spray much more frequently those who received the procedure on one of their anterior teeth.

Table 24: Number of Sprays Required by Tooth Location – SR3-03

Tooth Location	Kovanaze N (% Successes)			Placebo N (% Successes)		
	N	2 Sprays	3 Sprays	N	2 Sprays	3 Sprays
Anterior	53	45 (100.0%)	8 (75.0%)	26	10 (80.0%)	16 (0.0%)
Premolar	47	28 (96.4%)	19 (52.6%)	24	7 (85.7%)	17 (0.0%)

Source: Reviewer

Finally, we will evaluate the effect of the 2nd pre-molar in the pediatric population. The proportion of patients who received the SDP on their 2nd pre-molar is shown by dosage group in Table 25. The percentage of subjects who received the procedure on their 2nd pre-molar is much larger for the 20 – <40 kg weight group than for any other population studied which may partially explain the lower success rate for that group.

Table 25: Target Tooth by Weight/Dosage Strata

Tooth Location	Weight 10 – <20 kg	Weight 20 – <40 kg	Weight ≥40 kg	Adults
2nd Premolar (A, J, 4, 13)	9/24	18/36	12/30	41/144
Other	15/24	18/36	18/30	103/144

Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This Application included the results of four phase 3 efficacy studies. (b) (4) .

Even though there were no statistical issues with the primary analyses for the subsequent studies and efficacy was established, (b) (4)

5.2 Collective Evidence

The efficacy of Kovanaze was evaluated in total of four studies, three in adults and one in pediatric patients. (b) (4) One issue I noted was that the success rates in both studies appear to be much lower (63% for 2nd pre-molar vs 96% otherwise) for patients receiving the SDP on a 2nd pre-molar than for any of the other teeth. The Applicant hypothesizes that this could be due to differences in the innervation for these teeth that occur in approximately 30% of the population. Regardless, there was a significant treatment effect noted for Kovanaze for all teeth in adult patients.

While overall the difference in success rates was statistically significant for the pediatric study, the results from the analyses by age and weight subgroups were not as clear. (b) (4) The success rates for the patients who weighed 40 kg and above were similar to those seen in the adult patients (90% vs 87% for adults) and statistically significant.

5.3 Conclusions and Recommendations

Based on my review of the two studies submitted to support efficacy, there is evidence of efficacy for Kovanaze in the indication of regional anesthesia when performing a restorative procedure on teeth 4-13. However, the success rate for patients receiving the procedure on their 2nd pre-molars (teeth 4 & 13) was much lower than the overall success rate.

(b) (4) The success rate in patients weighing greater than 40 kg was statistically significantly greater for patients receiving Kovanaze than placebo and so approval is recommended for subjects weighing greater than 40 kg.

5.4 Labeling Recommendations (as applicable)

I recommend the following changes to the prescribing information:

1. [redacted] (b) (4).
2. The Dosage and Administration section should clearly inform prescribers that this product was less effective for procedures on the 2nd pre-molar (permanent teeth 4, and 13 and primary teeth A and J).
3. The description of the [redacted] (b) (4) duration of effect should be removed from the clinical studies section.
4. Consider including a description of the failed study in the clinical studies section.

6 APPENDICES

Table A1: Patient Distribution across Study Site by Dosage Cohort and Age Group – SR3-04

Cohort	K305 (N = 60)	PBO (N = 30)
Site Number 3 (n = 48)	32 (53.3%)	16 (53.3%)
Site Number 5 (n = 42)	28 (46.7%)	14 (46.7%)
By Site and Dosage Cohort		
Site Number 3		
10 to < 20 kg	12 (20.0%)	6 (20.0%)
20 to < 40 kg	16 (26.7%)	8 (26.7%)
40 kg or more	4 (6.7%)	2 (6.7%)
Site Number 5		
10 to < 20 kg	4 (6.7%)	2 (6.7%)
20 to < 40 kg	8 (13.3%)	4 (13.3%)
40 kg or more	16 (26.7%)	8 (26.7%)
By Site and Age Group		
Site Number 3		
3 to 5 years	17 (28.3%)	7 (23.3%)
6 to 11 years	11 (18.3%)	8 (26.7%)
12 to 17 years	4 (6.7%)	1 (3.3%)
Site Number 5		
3 to 5 years	4 (6.7%)	3 (10.0%)
6 to 11 years	12 (20.0%)	7 (23.3%)
12 to 17 years	12 (20.0%)	4 (13.3%)

Source: Table 11.3 from Applicant's Study Report

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

/s/

JAMES E TRAVIS
02/22/2016

DAVID M PETULLO
02/22/2016
I concur.