# CLINICAL REVIEW

| | |
|---|---|
| Application Type | 505(b)(2) |
| Application Number | 208032 |
| Priority or Standard | Standard |
| Submit Date | May 29, 2015 |
| Received Date | |
| PDUFA Goal Date | March 29, 2015 |
| Division / Office | Division of Anesthesia, Analgesia, and Addiction Products/ Office of Drug Evaluation II |
| Reviewer Name | Amelia Luckett, MD |
| Review Completion Date | June 28, 2016 |
| Established Name | Tetracaine HCl, 3% and oxymetazoline HCl, 0.05% |
| (Proposed) Trade Name | Kovanaze™ Nasal Spray |
| Therapeutic Class | Local anesthetic and vasoconstrictor |
| Applicant | St. Renatus |
| Formulation | Liquid to be administered as a spray |
| Dosing Regimen | 2 sprays (0.2 mL each) given 4 to 5 minutes apart in the nostril on the same side as the maxillary tooth on which the dental procedure will be performed. For adults, an additional spray (0.2 mL) may be given if adequate anesthesia has not been achieved 10 minutes after the 2nd spray |
| Indication | For regional anesthesia when performing a restorative procedure on teeth 4 through 13 and A through J |
| Intended Populations | (b) (4) |

# Table of Contents

# Table of Tables

# Table of Figures

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The Applicant requested [redacted (b) (4)]. I recommend that the product be approved for adult and pediatric patients [redacted (b) (4)] weighing 40 kg or more because the efficacy of Kovanaze was established in pediatric patients weighing 40 kg or more and adults.

## 1.2 Risk Benefit Assessment

Kovanaze is to be used for dental procedures in maxillary teeth 4 through 13 and A through J. The current standard of care for anesthesia for pain management during dental procedures is local anesthetic delivered by injection. Kovanaze is an important product because its use does not require needles and will be useful for patients who avoid dental care for fear of needles. Kovanaze also has the potential to protect dental providers from needle sticks.

To support approval of Kovanaze for the indication of regional anesthesia when performing a restorative procedure on teeth 4 through 13 and A through J, the Applicant, St. Renatus, submitted five Phase 1, four Phase 2, and four Phase 3 clinical trials. Kovanaze has demonstrated efficacy in three Phase 3 clinical trials. The Applicant also relied in part on the safety of oxymetazoline (final OTC Monograph in 21 CFR Part 341: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use) and tetracaine in Synera® (NDA 021623). Additionally, literature was provided in support of some aspects of the safety of Kovanaze.

Three Phase 3 trials, SR 3-01, SR 3-02 and SR 3-03 were intended to establish the efficacy of Kovanaze in adults. [redacted (b) (4)] " (Source: NDA 208032 page 6 of SR 3-01 Clinical Study Report)

The primary efficacy endpoint for SR 3-02 and SR 3-03 was completion of the Study Dental Procedure without local anesthetic injection rescue. While SR 3-02 and SR 3-03 had the same primary efficacy endpoint, SR 3-02 had a treatment group in which subjects received tetracaine only spray. In SR 3-02, Kovanaze demonstrated benefit compared to placebo and tetracaine spray in providing regional anesthesia when performing a restorative procedure on teeth 4 through 13. In SR 3-03, Kovanaze demonstrated benefit compared to placebo in providing regional anesthesia when performing a restorative procedure on teeth 4 through 13.



Reference ID: 3952361

One Phase 3 trial, SR 3-04, was intended to establish the efficacy of Kovanaze in patients aged 3 to 17-years-old. The primary efficacy endpoint for SR 3-04 was completion of the Study Dental Procedure without local anesthetic injection rescue. In this trial, subjects received a dose based on weight. One of the secondary efficacy endpoints for SR 3-04 was completion of the Study Dental Procedure without local anesthetic injection rescue by dose that subjects received (100 µL, 200 µL, or 400 µL). By this measure, Kovanaze demonstrated benefit compared to placebo for those weighing 40 kg or more in providing regional anesthesia when performing a restorative procedure on teeth 4 through 13 and A through J.

There were no deaths in any of the clinical trials submitted to support this NDA, and there were no serious adverse events (SAEs) in any subjects who received Kovanaze. Among the most common adverse events in subjects who received Kovanaze in the Integrated Safety Database are rhinorrhea, nasal congestion, nasal discomfort, increased lacrimation, headache, and sneezing. While the occurrence of these adverse events was frequent, only nasal congestion, nasal discomfort, and sneezing were ever assessed as being severe. More troublesome adverse events with Kovanaze, including epistaxis and dysphagia, are included as warnings in the product package insert.

In general, the risk-benefit profile of Kovanaze appears favorable for the indication of regional anesthesia when performing a restorative procedure on teeth 4 through 13 and A through J. Kovanaze has demonstrated efficacy in adults and pediatric patients weighing 40 kg or more for the proposed indication. Adverse events were mostly mild to moderate in severity. Common adverse events are included in the proposed package insert.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No safety issues identified in the review of this application require postmarket risk evaluation and mitigation strategies.

### 1.4 Recommendations for Postmarket Requirements and Commitments

No requirement for pediatric studies exists under the Pediatric Research Equity Act (PREA) because Kovanaze has already been evaluated in pediatric clinical trials.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Kovanaze Nasal Spray is delivered in a sprayer described as (b) (4) delivery system. It is designed for single use. Spray volume is 0.2 mL containing 6 mg tetracaine

HCl and 0.1 mg oxymetazoline HCl. Each sprayer is able to deliver 0.2 mL as a single spray (b) (4)

While Kovanaze was being developed, it was referred to as (b) (4) and (b) (4) Some tables and figures included in this review are the Applicant's. In these sources, Kovanaze is sometimes referred to as "(b) (4) or (b) (4)."

The proposed dosing is dependent on (b) (4) weight. Below is a table of the proposed dosing from St. Renatus's NDA submission.

| Age Group | Dose | Total Tetracaine HCl Content | Total Oxymetazoline HCl Content |
|---|---|---|---|
| Adults (≥ 18 years old) | 2 sprays (0.2 mL per spray) | 12 mg | 0.2 mg |
| | 1 additional spray (0.2 mL) if adequate anesthesia to initiate the dental procedure has not been achieved 10 minutes after the second spray | 6 mg | 0.1 mg |
| (b) (4) | | | |
| Children (b) (4) weighing ≥ 40 kg) | 2 sprays (0.2 mL per spray) | 12 mg | 0.2 mg |

(Source: NDA 208032 Applicant's table page 1 of Introduction to Summary)

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The indication in the proposed package insert states:

> Kovanaze™ is (b) (4) indicated for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J.

(Source: NDA 208032 applicant's proposed package insert revised 8/2015)

There are no other currently available nasal therapies with this indication. It appears that the current standard of care for regional anesthesia when performing a restorative procedure on teeth 4 through 13 and A through J is local anesthetic by injection for adults and pediatrics 3 to 17 years of age.

## 2.3 Availability of Proposed Active Ingredient in the United States

Oxymetazoline is available over-the-counter as a nasal decongestant. The oxymetazoline doses in Kovanaze may be comparable to those recommended for the over-the counter formulation. (For further information on this point, see section 2.4 of this review.)

Synera Topical Patch NDA 21623, FDA approved June 23, 2005 and Pliaglis Cream NDA 21717, FDA approved June 29, 2006 are both products containing tetracaine. Neither of these drugs has had labeling changes since their approval that would impact the safety of tetracaine in Kovanaze.

Therefore, the active ingredients in Kovanaze are currently available in the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs: Comparison of oxymetazoline dose in the Monograph with the amount of oxymetazoline in the proposed Kovanaze dose

The maximum amount of oxymetazoline in a single dose of Kovanaze is 0.3 mg. The maximum amount of oxymetazoline in a single dose, as recommended in the oxymetazoline Monograph, is unclear because the Monograph describes dosing in "sprays." To address this, on November 12, 2015, FDA sent an Information Request to St. Renatus in which the following was stated:

"On page 29 of 2.5 Clinical Overview of your NDA submission, it is written:

> "Given that the active ingredients of (b) (4) consist of tetracaine (an ester local anesthetic that has been on the market since 1936) and oxymetazoline (a topical decongestant that has also been available for decades in over-the-counter preparations), the safety profile associated with each of these compounds at the same dose levels used in the Sponsored clinical trials has been well-documented."

Provide documentation of the safety profile of 0.3 mg intranasal oxymetazoline referred to in the above passage."

On December 14, 2015, St. Renatus responded to the November 12, 2015 Information Request from FDA and provided evidence of the volume of oxymetazoline in a single spray. (b) (4) St. Renatus also cited a publication, Watanabe et al., 2003, in which each spray in a "conventional dose of 0.05% oxymetazoline nasal spray" is described as containing 0.1 mL. (Source: NDA 208032 page 3 of Response to FDA Information Request received December 14, 2015) (Watanabe et al. 2003)

21 CFR 341.80 Subpart C states that for the oxymetazoline 0.05% solution (500 mcg/mL), the dose for those over six years of age is two or three drops or sprays in each nostril not more often than every 10 to 12 hours. That means the maximum dose in a 10 hour period in the Monograph is six sprays of 500 mcg/mL.

According to two of the Applicant's sources (b) (4) and Watanabe et al., 2003 described above), the volume of one spray may be 0.1 mL. If each spray is 0.1 mL, then the maximum dose of oxymetazoline in a 10 hour period according to the Monograph is 0.3 mg. This is identical to the maximum amount of oxymetazoline in a single dose of Kovanaze. Therefore, the maximum amount of oxymetazoline in Kovanaze may be the maximum amount of oxymetazoline that can be given in a 10 hour period per the Monograph.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical trials with the product presently known as Kovanaze were performed under IND 70868.

**Table 1 Meetings between St. Renatus and FDA in regard to the product presently known as Kovanaze**

| Date | Meeting | Important clinical points |
|---|---|---|
| 6/06/2005 | Pre-IND, Type B | -Pharmacokinetic data should be obtained for the drug formulation used in pivotal trials.<br>-Clinical trials should be conducted with double the effective dose.<br>-A safety database should have at least 300 patients. |
| 3/03/2011 | EOP2, Type B | -Discussion of size and composition of safety database[1]<br>-Discussion of endpoints<br>(b) (4)<br>-SR states intent to carefully assess blood pressure in subjects with hypertension.<br>-Discussion of pediatric trials<br>-Human factors testing is necessary.<br>-SR should study the drug product versus only tetracaine in a Phase 3 trial to establish that added oxymetazoline has benefit. |
| 8/21/2014 | Pre-NDA, Type B | -Safety data from SR's Phase 3 clinical trials may be inadequate to support the safety of Kovanaze.<br>-FDA concerned about lack of vital sign assessments during dental procedures in Phase 3 trials.<br>-Indicate that methemoglobinemia was evaluated or provide rationale for not evaluating methemoglobinemia.<br>-Efficacy in (b) (4) will be a matter of review.<br>-FDA agrees with pooling safety data based on having a dental procedure.<br>-Adult and pediatric safety to be pooled separately.<br>-All adverse event data should be coded in MedDRA. |

[1] For further discussion of the adequacy of the safety database, see section 7.2 Adequacy of Safety Assessments of this review.

### 2.6 Other Relevant Background Information

This submission required a review extension- major amendment that extended the goal date by three months for a full review of the NDA. For further detail, see section 3.1 of this review.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

NDA 208032 was submitted in eCTD format. Over the course of the review of this NDA, clinically-related Information Requests were sent to St. Renatus in which the following subjects were included:

- November 2, 2015:
  - The number of adverse events reported from the CRF only compared to the number of adverse events in both the CRF and the Comment Logs
  - The number of subjects who received the maximum to-be-marketed dose of Kovanaze and in which clinical trials this occurred
  - Questions about the demographics dataset
- November 3, 2015:
  - Sources of adverse events in the NDA submission
- November 12, 2015:
  - Request for documentation of the safety profile of 0.3 mg intranasal oxymetazoline
  - Request for dataset that includes all adverse events regardless of causality
- December 22, 2015:
  - List of tables that FDA would like for the NDA submission
- December 30, 2015:
  - Reporting of adverse events
- January 7, 2016:
  - Request for table of incidence of treatment-emergent adverse events by Kovanaze batch
- February 4, 2016:
  - Request for (b) (4)
- February 11, 2016:
  - Clarification of potential conflicts of interest
- May 9, 2016:
  - Request for new adverse reactions table for package insert

During the course of NDA review, problems with the number of adverse events described in the Integrated Summary of Safety (ISS) and in the submitted data sets were noted. Specifically, the Integrated Safety Database only contained adverse events from the AE (adverse event) pages of the case report forms (CRFs) even though adverse events were also recorded on comment pages.

Below are tables that illustrate the difference in the number of adverse events that were coded from the case report forms (CRFs) compared with the number of adverse events coded from both the CRFs and the comment logs. These tables illustrate that the number of adverse events reported from the CRFs is frequently smaller than the number of adverse events reported from the CRFs and the comment logs.

**Table 2 Source of treatment-emergent adverse events for SR 3-01**

| | Kovanaze (N=10) | Tetracaine only (N=10) | Placebo (N=6) |
|---|---|---|---|
| Number of adverse events reported from CRF | 84 | 63 | 22 |
| Number of adverse events reported from CRF and comment log | 88 | 63 | 22 |

(Source: Reviewer generated table based on NDA 208032 Applicant's tables pages 109-110 of SR 3-01 Clinical Study Report)

**Table 3 Source of treatment-emergent adverse events for SR 3-02**

| | Kovanaze (N=44) | Tetracaine only (N=44) | Placebo (N=22) |
|---|---|---|---|
| Number of adverse events reported from CRF | 192 | 198 | 52 |
| Number of adverse events reported from CRF and comment log | 221 | 221 | 59 |

(Source: Reviewer generated table based on NDA 208032 Applicant's tables pages 188-189 of SR 3-02 Clinical Study Report)

**Table 4 Source of treatment-emergent adverse events for SR 3-03**

| | Kovanaze (N=100) | Placebo (N=50) |
|---|---|---|
| Number of adverse events reported from CRF | 314 | 100 |
| Number of adverse events reported from CRF and comment log | 538 | 136 |

(Source: Reviewer generated table based on NDA 208032 Applicant's tables pages 173-174 of SR 3-03 Clinical Study Report)

**Table 5 Source of treatment-emergent adverse events for SR 3-04**

| | Kovanaze (N=60) | Placebo (N=30) |
|---|---|---|
| Number of adverse events reported from CRF | 191 | 84 |
| Number of adverse events reported from CRF and comment log | 392 | 157 |

(Source: Reviewer generated table based on NDA 208032 Applicant's tables pages 229-230 of SR 3-04 Clinical Study Report)

St. Renatus was questioned about the discrepancy in the number of adverse events in the CRF compared to the number of adverse events reported from the CRF and the Comment Log. On November 2, 2015, an Information Request was sent from FDA in which the following was stated:

> There appears to be a large difference between the number of adverse events reported from the CRF only and the number of adverse events from the CRF and the Comment Logs. Explain why an adverse event would be placed in a Comment Log but not placed in the CRF only. Furthermore, you indicated in 2.5 Clinical Overview (page 16 of 35) that you concluded that the data from the CRFs captured the complete AE profile associated with these studies. Clarify how you addressed the possibility that utilizing only the data from the CRFs would result in an underestimation of the number of adverse events.

In a communication from St. Renatus on November 20, 2015, St. Renatus acknowledges that there is repetition of adverse events in the AE CRF pages present in the Comment Logs, but that reconciliation of adverse events did not occur. Excerpts from this communication are below.

> All adverse events (AEs) captured on the AE CRF pages were coded using the MedDRA coding dictionary [ver 15.0]. In addition, potential AEs from the Comment Log CRF pages were also MedDRA coded as a tool to be used by the Medical Reviewers for verifying that all events were properly captured on the AE CRF pages. Instead, due to an apparent miscommunication, the coded AEs from the Comment Log CRF pages were, in fact, incorporated within the AE database which was subsequently datalocked. This situation was not fully realized until after the studies were unblinded, and thus, the Medical Reviewers (who were unblinded to study drug assignments) were prevented from retrospectively removing or re-coding the AEs originating from the Comment Log CRFs. Therefore, an algorithm was developed for analyzing the Comment Log AEs which was discussed within each of the applicable Clinical Study Reports (CSRs). The final assessment was that the potential AEs from the Comment Logs did not appreciably alter the safety profile of the study drug, and therefore, those events were not included within the ISS tables. An in-depth discussion of the AE review and analysis process is included in Attachment A.

"Attachment A," to which St. Renatus refers in the above passage, is a 54 page document. Relevant excerpts from "Attachment A" (sent from St. Renatus via email on November 20, 2015) are below.

Attachment A page 1:

> During the medical review process conducted in parallel with the data management processes, questions were raised about the possibility of there being AEs embedded within the CRF comment sections that had originally been entered solely as text fields. The only studies that contained lengthy comments included SR 2-03 (the pediatric dose ranging) and the pivotal studies SR 3-01, SR 3-02, SR 3-03 and SR 3-04. Therefore, to assist with investigating the possibility of there being additional AEs not yet properly recorded, comments were reviewed by data analysts and any potential AEs were coded using the MedDRA dictionary. Medical Reviewers were to have reviewed these additional coded terms to assess whether or not these events should be added to the clinical database. Due to an apparent misunderstanding, all the additional MedDRA coded terms from the comments sections were, in fact, incorporated within the clinical databases as AEs prior to the completion of the formal reconciliation, and were subsequently "datalocked." This resulted in 2 discrete AE subsets captured in the database, one set originating from the CRF AE pages, and another set from the CRF comment logs… This unintentional situation was discovered after the study drug randomization codes were unblinded and the clinical study reports (CSRs) were in the process of being written… Once a comparison of the two discrete subsets contained within the safety database was made, it became readily apparent that a large number of AEs were duplicated in both subsets.

Attachment A page 3:

> …given the many deficiencies associated with the AE subset derived from the CRF Comment Log Pages, a decision was made to use the subset derived from the CRF AE Pages for the compilation of the ISS.

On November 12, 2015, an Information Request was sent to St. Renatus requesting a new MedDRA-coded dataset. In this Information Request, the following was stated:

> In your RESPONSE TO FDA INFORMATION REQUESTS (Received November 2, 2015 and November 3, 2015), you mention an "AE reconciliation process" and that "SR 2-01, SR 2- 04, SR 2-05, SR 2-06, and SR 2-07 did not have any AEs from the comment page." Assemble and provide a MedDRA-coded dataset that includes all adverse events, regardless of causality.

On December 14, 2015, in response to the above query, St Renatus submitted an updated Integrated Summary of Safety dataset that included adverse events from both the AE page of the CRF and any adverse events from the comment log.

As the above passages describe, the Integrated Summary of Safety datasets and tables initially submitted for the NDA contains a potential underestimation of adverse events associated with Kovanaze. The dataset submitted by St. Renatus on December 14, 2015 contains a potential overestimation of adverse events associated with Kovanaze.

On December 16, 2015, FDA held a teleconference with St. Renatus. On December 18, 2015, an email was sent by a St. Renatus representative indicating that adverse event reconciliation would occur and that a new data set would be submitted to the NDA. Below is an excerpt from this email.

> Thank you for coordinating our teleconference we had on Wednesday, December 16th. Below is an outline of our proposed timeline for addressing the adverse events that were discussed on the call.

- We are currently working to get all uncoded terms from the comment page coded by a blinded party. Once they are coded, based on our algorithm we will add relevant AEs from the comment page to the safety database for the ISS. We anticipate having this completed by the end of the year.
- With the updated safety database we will regenerate the ISS tables located in Module 5. We are anticipating to have this completed between January 8th and January 11th. We will email you these tables as soon as they are completed.
- After the tables have been regenerated, we expect to have the relevant clinical sections in Module 2 updated by January 25th. We will email you the updated redline sections as soon as they are ready and will then make an official submission to the NDA shortly thereafter. At this point we believe there will be changes in the pediatric numbers around non-serious events such as runny noses. The revision will have minimal impact on the adult data.
- During this time, we will also work on expanding the define file for the AE dataset contained in the ISS as well as ensuring you have a copy of the SR 2-01 dataset.

A revised data set with reconciled adverse event information was eventually submitted to the NDA on February 22, 2016. The submission received on February 22, 2016 was considered a major amendment and the review goal date was extended three months.

### 3.2 Compliance with Good Clinical Practices

A statement of Good Clinical Practice was located within the clinical study report of each trial submitted in support of this NDA.

Results of the inspections by the Office of Scientific Investigations (OSI) are present in the review by Jong Lee dated March 9, 2016.

### 3.3 Financial Disclosures

St. Renatus provided financial information for the principal investigators who conducted all 13 clinical trials and the Human Factors Validation study submitted for this NDA.

For further information, see section 9.7 of this review.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry, Manufacturing, and Controls

Review of Chemistry, Manufacturing, and Controls (CMC) information was conducted by Xiaobin Shen, Julia Pinto, and Ciby Abraham. For further information, see the CMC review of this submission. Clinical implications of variation in droplet size distribution and spray pattern parameter are addressed in sections 6.1.10.2 and 7.7.1 of this review.

## 4.2 Clinical Microbiology

Section 4.2 Clinical Microbiology is not applicable to this submission.

## 4.3 Preclinical Pharmacology/Toxicology

Review of Pharmacology Toxicology information was conducted by Alex Xu, Jay Chang, and Daniel Mellon. Clinical implications of the local toxicity of increased levels of P-butylaminobenzoic acid in Kovanaze are discussed in section 7.7.2 of this review.

This NDA has been filed as a 505(b)(2), relying, in part, on nonclinical data from toxicology studies performed by St. Renatus, the previous findings of safety of oxymetazoline (final OTC Monograph in 21 CFR Part 341: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use), the previous findings of safety of tetracaine (Synera NDA 021623), and published literature. For further information, see the Pharmacology Toxicology review of this submission.

## 4.4 Clinical Pharmacology

Review of Clinical Pharmacology information was conducted by David Lee and Yun Xu. St. Renatus conducted three clinical pharmacology/ pharmacokinetic studies in support of this NDA submission: SR 2-02, SR 2-06, and SR 2-07. Further detail of these studies is in section 9.5 of this review.

### 4.4.1 Mechanism of Action

Kovanaze contains tetracaine and oxymetazoline. Tetracaine is a local anesthetic. Oxymetazoline is an α-1 adrenergic agonist and partial α-2 adrenergic agonist that causes vasoconstriction.

Both the anterior superior alveolar nerve and middle superior alveolar nerve course through the nasal cavity before providing innervation to teeth. Kovanaze is intended to be sprayed on to the nasal mucosa, at which point it is absorbed. At that time, it appears to provide a nerve block of the anterior superior alveolar and middle superior alveolar branches of the infraorbital nerve. This produces regional anesthesia of teeth 4 through 13 and A through J.

### 4.4.2 Pharmacodynamics

Kovanaze provides anesthesia to maxillary teeth 4 through 13 and A through J.

### 4.4.3 Pharmacokinetics

Pharmacokinetic parameters were evaluated in SR 2-02, SR 2-06, and SR 2-07.

Absorption

Subjects in SR 2-06 received three sprays of Kovanaze to a total dose of 18 mg tetracaine/ 0.3 mg oxymetazoline. Time $T_0$ was the time of the last dose of Kovanaze nasal spray. The median $T_{max}$ of oxymetazoline was 5 minutes. The mean $C_{max}$ and mean $AUC_{0\text{-}inf}$ of oxymetazoline were 1.78 ng/mL and 4.24 h·ng/mL. According to the clinical study report, tetracaine was not detectable in enough samples to determine its pharmacokinetic parameters. P-butylaminobenzoic acid (PBBA) is the primary metabolite of tetracaine and is believed to have unspecified metabolic activity. The median $T_{max}$ of PBBA was 20 minutes. The mean $C_{max}$ and mean $AUC_{0\text{-}inf}$ of PBBA were 465 ng/mL and 973 h·ng/mL.

Elimination

As seen in Table 7 (below), the half-life ($t_{1/2}$) of oxymetazoline after Kovanaze in adults is 5.23 hours. The tetracaine in Kovanaze is rapidly cleared from plasma. $T_{1/2}$ of PBBA following Kovanaze is 2.6 hours.

Metabolism

In vitro, UGT1A9 converts oxymetazoline to a glucuronide conjugate. Esterases convert tetracaine into PBBA and deimethylaminoethanol.

Excretion

Clearance of both oxymetazoline and PBBA after Kovanaze is unknown, although it is thought that oxymetazoline may be renally excreted.

Below are tables of pharmacokinetic parameters from the trials in which pharmacokinetic parameters were studied: SR 2-02, SR 2-06, and SR 2-07.

**Table 6 Mean (SD) Oxymetazoline, Tetracaine, and PBBA Pharmacokinetic Parameters (Study SR 2-02)**

| Analyte | Dose (mg) | $C_{max}$ (ng/mL) | $t_{max}$[a] (min) | $t_{1/2}$ (h) | $AUC_{0-t}$ (ng·h/mL) | $AUC_{0-inf}$ (ng·h/mL) |
|---|---|---|---|---|---|---|
| Standard Dose | | | | | | |
| Oxymetazoline | 0.3 | 1.45[b] (0.473) | 15[b] (10-20) | 2.32[c] (0.86) | 1.16[b] (0.281) | 2.37[c] (0.705) |
| Tetracaine | 18 | 0.243[d] (0.113) | 55[d] (20-80) | ND | NR[e] | ND |
| PBBA | NA[f] | 492 (189) | 35 (5-120) | 1.00[g] (0.33) | 610 (243) | 861[g] (287) |
| High Dose | | | | | | |
| Oxymetazoline | 0.6 | 2.05 (0.748) | 25 (20-30) | 1.72[c] (0.46) | 1.95 (0.698) | 3.51[c] (1.07) |
| Tetracaine | 36 | 1.15[c] (2.45) | 100[c] (15-120) | ND | 0.160[d,h] (0.032) | ND |
| PBBA | NA[i] | 886 (289) | 45 (30-70) | 1.01[b] (0.32) | 1090 (444) | 1770[b] (1070) |

Source data: SR 2-02 CSR; Appendix 16.1.13; Tables 2, 3, and 4 in Appendix C of the Bioanalytical Report Doses are in mg of the HCl salt forms of oxymetazoline and tetracaine; n=12 unless otherwise indicated $AUC_{0-t}$ = Area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-inf}$ = Area under the plasma concentration-time curve from time 0 extrapolated to infinity; $C_{max}$ = maximum observed plasma concentration; NA = not applicable; ND = parameter could not be determined due to insufficient data; NR = not reported; PBBA = *p*-butylaminobenzoic acid; SD = standard deviation; $t_{1/2}$ = terminal half-life; $t_{max}$ = time of maximum concentration following the beginning of dosing.

a Values represent mean (SD) except for tmax, which is reported as median (range)

b n = 11

c n = 7

d n = 4

e Not reported; each subject had less than 3 samples with measurable tetracaine concentrations

f After subjects received 18 mg of tetracaine in a standard dose of (b) (4) at Visit 1

g n = 8

h Excludes 3 subjects who had less than 3 samples with measurable tetracaine concentrations

i After subjects received 36 mg of tetracaine in a high dose of (b) (4) at Visit 2

(Source: NDA 208032 Applicant's table page 10 of Summary of Clinical Pharmacology Studies)

**Table 7 Mean (SD) Oxymetazoline and PBBA Pharmacokinetic Parameters (Study SR 2-06)**

| Analyte | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{1/2}$ (h) | $AUC_{0-t}$ (h·ng/mL) | $AUC_{0-inf}$ (h·ng/mL) |
|---|---|---|---|---|---|
| Oxymetazoline | 1.78 (0.586) | 5.0 (5-10) | 5.23 (2.20) | 3.67 (1.79) | 4.24 (2.09) |
| PBBA | 465 (122) | 20 (15-40) | 2.60 (1.23) | 960 (509) | 973 (513) |

Source data: SR 2-06 CSR; Appendix 16.1.13, Table 3 in Appendix C of Bioanalytical Report
Values represent mean (SD) except for $t_{max}$, which is reported as median (range); n=24
$AUC_{0-t}$ = Area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-inf}$ = Area under the plasma concentration-time curve from time 0 extrapolated to infinity; $C_{max}$ = maximum observed plasma concentration; NA = not applicable; PBBA = *p*-butylaminobenzoic acid;
SD = standard deviation; $t_{1/2}$ = terminal half-life; $t_{max}$ = time of maximum concentration following the end of dosing.

(Source: NDA 208032 Applicant's table page 12 of Summary of Clinical Pharmacology Studies)

**Table 8 Mean (SD) Oxymetazoline and PBBA Pharmacokinetic Parameters (Study SR 2-07)**

| Group[a] | n | Analyte (Dose) | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{1/2}$ (h) | $AUC_{0-t}$ (h·ng/mL) | $AUC_{0-inf}$ (h·ng/mL) |
|---|---|---|---|---|---|---|---|
| 1 | 3 | Oxymetazoline (0.05 mg) | 0.367 (0.426) | 30 (0-180) | 1.57[b] | 0.630 (0.211) | 0.992[b] |
| | | PBBA (3.0 mg)[c] | 166 (70.5) | 30 (30-30) | 2.81 (0.384) | 515 (220) | 529 (222) |
| 2 | 9 | Oxymetazoline (0.1 mg) | 0.846 (0.454) | 10 (10-10) | 4.32[d] (2.24) | 1.88 (0.780) | 2.53[d] (1.08) |
| | | PBBA (6.0 mg)[c] | 345 (172) | 30 (10-30) | 2.18 (0.826) | 811 (606) | 826 (606) |
| 3 | 6 | Oxymetazoline (0.2 mg) | 1.20 (0.387) | 10 (10-10) | 3.49 (0.814) | 2.27 (0.390) | 2.64 (0.405) |
| | | PBBA (12.0 mg)[c] | 365 (29.9) | 20 (10-30) | 1.57 (0.283) | 647 (63.2) | 665 (85.7) |

Source data: SR 2-07 CSR; Appendix 16.1.13, Table/Appendix 2 and Table/Appendix 3 in Pharmacokinetic Analysis Report
Doses are in mg of the HCl salt forms of oxymetazoline and tetracaine; values represent Mean (SD) except for $t_{max}$, which is reported as Median (range)
[a] Group 1: 10 to < 20 kg (N=3); Group 2: 20 to < 40 kg (N=9); Group 3: ≥ 40 kg (N=6)
[b] n=1
[c] Dose of tetracaine
[d] n=7

$AUC_{0-t}$ = Area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-inf}$ = Area under the plasma concentration-time curve from time 0 extrapolated to infinity; $C_{max}$ = maximum observed plasma concentration; NA = not applicable; PBBA = *p*-butylaminobenzoic acid; SD = standard deviation; $t_{1/2}$ = terminal half-life; $t_{max}$ = time of maximum concentration following the end of dosing.

(Source: NDA 208032 Applicant's table page 14 of Summary of Clinical Pharmacology Studies)

For further information see the Clinical Pharmacology review of this NDA.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

Thirteen clinical trials were performed by St. Renatus in support of this NDA. Four hundred forty-four subjects received a dose of Kovanaze. Below is a table summarizing these trials. Trials SR 3-02, SR 3-03, and SR 3-04 are considered to be pivotal Phase 3 studies in support of this NDA. Trials SR 2-01, SR 2-03, SR 2-04, and SR 2-05 are considered to be Phase 2 studies submitted in support of this NDA.

**Table 9 Clinical Trials performed; NDA 208032**

| Study | Age | Population | Phase | Title |
|---|---|---|---|---|
| AP 1-01 | adult | Volunteer | 1 | A Phase 1 Single-Center Study of Various Dosages of a (b) (4) (Tetracaine Hydrochloride Solution for Nasal Administration) for Anesthetizing Maxillary Teeth in Healthy Subjects |
| AP 1-02 | adult | Volunteer | 1 | A Phase 1 Single-Center Dose-Ranging Study of (b) (4) with Oxymetazoline Hydrochloride for Anesthetizing Maxillary Teeth in Healthy Subjects |
| SR 2-01 | adult | Patient | 2 | A Phase II, Single-Center, Randomized, Double-Blind Active-Treatment-Controlled Parallel-Group Study of the Efficacy of (b) (4) Nasal Spray for Anesthetizing Maxillary Teeth in Healthy Dental Patients |
| SR 2-02 | adult | Volunteer | 1 | Phase I, Open-Label, Dose-Escalation, Safety and Pharmacokinetic Study of (b) (4) in Healthy Volunteers |
| SR 2-03 | pediatric | Patient | 2 | A Phase 2, Single-Center, Open-Label, Randomized, Parallel-Groups, Dose- Ranging Study to Assess the Efficacy and Safety of Intranasally Administered (b) (4) for Anesthetizing Maxillary Teeth in Pediatric Subjects |
| SR 2-04 | adult | Volunteer | 2 | A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 4-Period, Complete Crossover Comparison of the Dental Anesthetic Efficacy of Bilateral and Unilateral Application of (b) (4) (formerly (b) (4) in Healthy Volunteers |
| SR 2-05 | adult | Patient | 2 | A Two-part, Single Site, Open-label Investigation of Different Unilateral (b) (4) Dosing Regimens in Adult Dental Patients |
| SR 2-06 | adult | Volunteer | 1 | Single-center, Open-label, Single-dose Study of the Pharmacokinetics and Safety of Intranasally Administered (b) (4) in Healthy Volunteers |
| SR 2-07 | pediatric | volunteer | 1 | A Single-center Study Evaluating the Pharmacokinetics of Tetracaine, |

| Study | Age | Population | Phase | Title |
|---|---|---|---|---|
| | | | | Parabutylaminobenzoic Acid, and Oxymetazoline after Intranasal Administration of (b) (4) (tetracaine hydrochloride with oxymetazoline hydrochloride) to Healthy Pediatric Subjects |
| SR 3-01 | adult | patient | 3 | A Phase III, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Tetracaine Alone and to Placebo for Anesthetizing Maxillary Teeth in Adults |
| SR 3-02 | adult | patient | 3 | A Phase III, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Tetracaine Alone and to Placebo for Anesthetizing Maxillary Teeth in Adults |
| SR 3-03 | adult | patient | 3 | A Phase 3, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Placebo for Anesthetizing Maxillary Teeth in Adults |
| SR 3-04 | pediatric | patient | 3 | A Phase 3, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Placebo for Anesthetizing Maxillary Teeth in Pediatric Patients |

## 5.2 Review Strategy

The focus of this review is on the four Phase 3 clinical trials for evaluating the safety and efficacy of Kovanaze. The formulation used in Phase 3 trials is identical to the formulation for which approval is sought. Phase 2 clinical trials are viewed as supportive for the safety of Kovanaze.

## 5.3 Discussion of Individual Studies/Clinical Trials

In this section, emphasis is placed on pivotal Phase 3 clinical trials conducted under this NDA.

### 5.3.1 Phase 1 Clinical Trials

Five Phase 1 trials were conducted for this NDA:

- AP 1-01
- AP 1-02
- SR 2-02
- SR 2-06
- SR 2-07

Select Phase 1 clinical trials are summarized in section 9.5 of this review.

## 5.3.2 Phase 2 Clinical Trials

Four Phase 2 trials were conducted for this NDA:

- SR 2-01
- SR 2-03
- SR 2-04
- SR 2-05

Phase 2 clinical trials are summarized in section 9.6 of this review.

## 5.3.3 Phase 3 Clinical Trials

Four Phase 3 clinical trials were conducted for this NDA: SR 3-01, SR 3-02, SR 3-03, and SR 3-04. SR 3-01 was terminated early. SR 3-02 and SR 3-03 are considered to be pivotal studies in adults. SR 3-04 is considered to be a pivotal study in pediatrics.

### 5.3.3.1 Clinical Trial SR 3-01

(b) (4)

*5.3.3.1.1 Title:*

A Phase III, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Tetracaine Alone and to Placebo for Anesthetizing Maxillary Teeth in Adults

*5.3.3.1.2 Trial Design:*

This trial, conducted at one site in the United States, was to have been a randomized, double-blinded trial comparing intranasal Kovanaze, tetracaine, or placebo for anesthesia of maxillary teeth in adults. Below is a schedule of events for SR 3-01.

**Table 10 Schedule of Events (B) for SR 3-01**

| | |
|---|---|
| Screening<br>(Up to 14 days prior, including the day of the study) | Informed consent, HIPAA consent, review inclusion and exclusion criteria, demographic information, medical and surgical history, concomitant medications, vital signs (VS), dental history, intraoral examination, periapical and/or bite wing radiographs, diagnostic radiograph to assist in clinical evaluation of necessity for treatment, and Naris Examination (NE). |

| | |
|---|---|
| Pre-Study (Immediately prior to the start of the procedure) | Review Inclusion and Exclusion Criteria<br>Review concomitant medications<br>Urine pregnancy testing if female & of child-bearing potential<br>Record vital signs (VS)<br>Record body temperature<br>Subject Reported Safety Evaluation (SRSE)<br>Subjective Numbness Assessment (SNA)<br>Naris Examination (NE)<br>Alcohol Sniff Test (AST)<br>Soft Tissue Anesthesia Assessment (STAA) |
| 0 minutes | Administer first unilateral intranasal spray. |
| 4 minutes (± 1 minute ) | Administer second unilateral intranasal spray. |
| 8 minutes (± 1 minute ) | Administer third unilateral intranasal spray. |
| 10 minutes (+ 3 minutes) | VS. Record time of vital sign assessment. |
| 15 minutes (+ 3 minutes) | SNA, STAA<br>Start the Study Dental Procedure.<br>If pulpal anesthesia is insufficient, wait 5 minutes. |
| 20 minutes (+ 3 minutes) | If Study Dental Procedure is not started at $T_{15}$, administer SNA , then start Study Dental Procedure.<br>(If pulpal anesthesia is insufficient, administer rescue anesthetic injection. Record time(s) of rescue anesthetic injection(s) if any.) |
| **VS, SNA and STAA shall not be conducted until tooth preparation and restoration is complete. These questionnaires will be conducted at the first scheduled time following completion of tooth preparation and restoration and shall be repeated as scheduled above.** | |
| 30 minutes (± 3 minutes) | VS, SNA, STAA |
| 45 minutes (± 3 minutes) | VS, SNA, STAA |
| 60 minutes (± 3 minutes) | VS, SNA, STAA |
| 90 minutes (± 3 minutes) | VS, SNA, STAA |
| 120 minutes (± 3 minutes) | VS, SRSE, SNA, STAA, NE, AST |
| Next-day Follow-up Visit | VS, SRSE, SNA, STAA, NE, AST |

(Source: NDA 208032 Applicant's table page 8 of SR 3-01 protocol version 4.0)

Twenty-six subjects enrolled in SR 3-01 received one of three treatments divided into three unilateral nasal sprays:

- 0.6 mL of Kovanaze (18 mg tetracaine and 0.3 mg oxymetazoline)
- 0.6 mL tetracaine (18 mg tetracaine)
- 0.6 mL aqueous solution placebo

Batch 006775 was the source of Kovanaze in this clinical trial.

*5.3.3.1.3 Efficacy Endpoints:*

(verbatim from NDA 208032 page 5 of SR 3-01 protocol version number 4.0 June 7, 2012 page)

- Primary: Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no).

- Secondary: Intraoral soft-tissue anesthesia (yes/no) and the time to onset and duration of such soft-tissue anesthesia.


Efficacy assessments in SR 3-01 were not used in our determination of the efficacy of Kovanaze. The safety assessments from this trial are included in the ISS.

5.3.3.2 Clinical Trial SR 3-02

*5.3.3.2.1 Title:*

A Phase III, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Tetracaine Alone and to Placebo for Anesthetizing Maxillary Teeth in Adults

*5.3.3.2.2 Objectives:*

(verbatim from NDA 208032 page 3 of SR 3-02 protocol version 3.0)

**Primary:**

1. To determine whether [redacted] (b) (4) (3% tetracaine HCl/0.05% oxymetazoline HCl) is safe and superior to 3% tetracaine HCl alone in providing local anesthesia sufficient to allow completion of an operative restorative dental procedure (the "Study Dental Procedure") on a maxillary tooth (#4 to 13) in adults without need for intra-procedure rescue by injection of local anesthetic.
2. To determine whether [redacted] (b) (4) (3% tetracaine HCl/0.05% oxymetazoline HCl) is safe and superior to placebo in providing local anesthesia sufficient to allow completion of an operative restorative dental procedure (the "Study Dental Procedure") on a maxillary tooth (#4 to 13) in adults without need for intraprocedure rescue by injection of local anesthetic.

**Secondary:**

1. To determine if [redacted] (b) (4) provides anesthesia of intraoral soft tissue.
2. To evaluate the safety and tolerability of [redacted] (b) (4)

*5.3.3.2.3 Trial Design:*

This trial, conducted at two sites in the United States, was to have been a randomized, double-blind superiority trial comparing intranasal Kovanaze to intranasal tetracaine and intranasal placebo for providing anesthesia to maxillary teeth.

Screening period:

The following were to have taken place up to 14 days before taking part in the trial:

- Informed consent
- Patient history
- Vital signs
- Oral and naris exam
- Periapical and/or bite wing radiographs as well as diagnostic radiograph

The following were to have taken place immediately before the dental procedure:

- Urine pregnancy test, if applicable
- Vital signs including: blood pressure, heart rate, temperature
- Randomization
- The following assessments:
    - Subject Reported Safety Evaluation (SRSE)
    - Subjective Numbness Assessment (SNA)
    - Naris Examination (NE)
    - Alcohol Sniff Test (AST)
    - Soft-Tissue Anesthesia Assessment (STAA)

Further description of these assessments is in Section 9.4 of this review.

Treatment period:

Subjects were administered three intranasal sprays of 0.2 mL of Kovanaze, tetracaine only, or placebo at four minute intervals on the ipsilateral side of the tooth to be treated.

Study drug was to have been administered in a very specific way: (verbatim from NDA 208032 page 89 of SR 3-02 protocol version 3.0)

Directions for administration of the treatment of 3 sprays of study drug are as follows:
1. Have the dental chair and subject sitting upright.
2. Sit on the same side as the Study Dental Procedure and face the subject. Dose from the front of the subject on the same side as the Study Dental Procedure.
3. Place the white tip of the sprayer inside the nostril up to the edge of the nasal valve.
4. Spray 1 – Approximately Horizontal: Position the sprayer slightly above horizontal. Direct the sprayer toward the middle of the nasal cavity.
5. Sprays 2 & 3 – 45 degrees: Position the sprayer approximately 45 degrees above the horizontal plane. Direct the sprayer toward the middle of the nasal cavity.
6. PUSH HARD AND FAST on the plunger rod. Expel the spray in approximately ½ second or less.
7. The goal of the 3 sprays is to achieve full coverage of the nasal cavity ipsilateral to the Study Dental Procedure.

As described in the table below, after 15 minutes, the dental procedure was to have begun. If the subject experienced pain when beginning the dental procedure 15 minutes after the first spray of Kovanaze, then the dental procedure was to have been delayed 5 minutes so that the dental procedure would have begun 20 minutes after the first spray of Kovanaze. If the dental procedure could not be completed due to inadequate anesthesia, the subject would have been given rescue medication and the study drug was to have been considered a treatment failure. For more detailed information on trial procedures, see the table below.

Post-treatment follow-up:

Subjects were to have been followed for 120 minutes after the first spray of Kovanaze and the next day.

For further detail, see the Overview of Procedures table for SR 3-02 below.

**Table 12 Overview of Procedures for SR 3-02**

| | |
|---|---|
| Screening<br>(Up to 14 days prior, including the day of the study) | Informed consent, HIPAA consent, demographic information, medical and surgical history, current medications, vital signs (VS), dental history, intraoral examination, periapical and/or bite wing radiographs, diagnostic radiograph to assist in clinical evaluation of necessity for treatment, Naris Examination (NE) , and review inclusion and exclusion criteria. |
| Pre-Study (Immediately prior to the start of the procedure) | Review inclusion and exclusion criteria<br>Review concomitant medications (con meds)<br>Urine pregnancy testing if female of child-bearing potential<br>Record vital signs (VS) SBP, DBP and HR<br>Record body temperature<br>Subject Reported Safety Evaluation (SRSE)<br>Subjective Numbness Assessment (SNA)<br>Naris Examination (NE)<br>Alcohol Sniff Test (AST)<br>Soft-Tissue Anesthesia Assessment (STAA)<br>Randomization |

| | |
|---|---|
| 0 minutes | Administer first unilateral intranasal spray. |
| 4 minutes (± 1 minute ) | Administer second unilateral intranasal spray. |
| 8 minutes (± 1 minute ) | Administer third unilateral intranasal spray. |
| 10 minutes (+ 3 minutes) | AE, VS. Record time of vital sign assessment. |
| 15 minutes (+ 3 minutes) | AE, SNA, STAA<br>Start the Study Dental Procedure.<br>If pulpal anesthesia is insufficient, wait 5 minutes. |
| 20 minutes (+ 3 minutes) | If Study Dental Procedure is not started at $T_{15}$, administer SNA , then start Study Dental Procedure.<br>(If pulpal anesthesia is insufficient, administer rescue anesthetic injection.<br>Record time(s) of rescue anesthetic injection(s) if any.) |
| **VS, SNA and STAA shall not be conducted until tooth preparation and restoration are complete. Administer at the first scheduled time following completion of tooth preparation and restoration and repeat as scheduled above.** | |
| 30 minutes (± 3 minutes) | AE, VS, SNA, STAA, con meds |
| 45 minutes (± 3 minutes) | AE, VS, SNA, STAA, con meds |
| 60 minutes (± 3 minutes) | AE, VS, SNA, STAA, con meds |
| 90 minutes (± 3 minutes) | AE, VS, SNA, STAA, con meds |
| 120 minutes (± 3 minutes) | AE, VS, SRSE, SNA, STAA, NE, AST, con meds |
| Next-day Follow-up Visit | AE, VS, SRSE, SNA, STAA, NE, AST, con meds |

(Source: NDA 208032 Applicant's table page 19 of SR 3-02 protocol version 3.0)

*5.3.3.2.4 Trial Population:*

(verbatim from NDA 208032 pages 3 and 4 of SR 3-02 protocol version 3.0)

**Inclusion Criteria:**

1. Male or female 18 years of age or older.
2. 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.
3. Normal lip, nose, eyelid, and cheek sensation.
4. Able to understand and sign the study informed consent document, communicate with the investigators, and understand and comply with the requirements of the protocol.
5. Patency of the naris ipsilateral to the tooth undergoing the Study Dental Procedure.
6. Resting heart rate (HR) between 55 and 100 beats per minute (bpm), inclusive.
7. Seated systolic blood pressure (SBP) between 95 and 140 mm Hg, inclusive and seated diastolic blood pressure (DBP) between 60 and 90 mm Hg, inclusive.

**Exclusion Criteria:**

1. Inadequately controlled hypertension (blood pressure greater than 140/90 mm Hg).
2. Inadequately controlled active thyroid disease of any type.
3. Frequent nose bleeds (≥ 5 per month).
4. Having received dental care requiring a local anesthetic within the last 24 hours.
5. History of allergy to or intolerance of tetracaine, benzyl alcohol, other ester local anesthetics, or paraaminobenzoic acid (as found in PABA-containing sunscreen).
6. History of allergy or hypersensitivity to articaine, oxymetazoline, epinephrine, or sulfite preservatives.
7. Use of a monoamine oxidase inhibitor within the 3 weeks preceding study entry.

8. Nursing, pregnant, suspected of being pregnant, or trying to become pregnant. (Females of child-bearing potential will be required to take a urine pregnancy test on the day of, but prior to, study drug administration to rule out pregnancy.)
9. Having received any investigational drug and/or participation in any clinical trial within 30 days prior to study participation.
10. Having used oxymetazoline or phenylephrine nasal spray, nasal irrigation, or other nasal or oral decongestant on the day of the study procedure.
11. History of congenital or idiopathic methemoglobinemia.

*5.3.3.2.5 Trial Medications and Treatment Groups:*

Trial Medications:
1. Kovanaze: 3 sprays= 0.6 mL= 18 mg tetracaine and 0.3 mg oxymetazoline
2. Tetracaine only (3% tetracaine): 3 sprays= 18 mg tetracaine
3. Placebo: Aqueous solution with all parts of Kovanaze except active ingredients

One hundred ten subjects were to have been randomized 2:2:1 to intranasal Kovanaze, tetracaine alone, or placebo.

Batch 006775 was the source of Kovanaze in this clinical trial.

*5.3.3.2.6 Rescue Medications:*

If the study drug that subjects receive does not provide adequate anesthesia, 4% articaine with epinephrine 1:200,000 is allowed as a rescue medication.

*5.3.3.2.7 Efficacy Assessments:*

The following efficacy assessments were to have been performed:

- Soft-Tissue Anesthesia Assessment (STAA)

See section 9.4 of this review for further detail of some of the efficacy assessments

*5.3.3.2.8 Efficacy Endpoints:*

(verbatim from NDA 208032 page 5 of SR 3-02 protocol version 3.0)

- Primary: Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no).
- Secondary: Intraoral soft-tissue anesthesia (yes/no) and the time to onset and duration of such soft-tissue anesthesia.

*5.3.3.2.9 Safety Assessments:*

The following safety assessments were to have been performed:

- Vital signs including blood pressure and heart rate
- Subject Reported Safety Evaluation (SRSE)
- Subjective Numbness Assessment (SNA)
- Naris Examination (NE)
- Alcohol Sniff Test (AST)
- Soft-Tissue Anesthesia Assessment (STAA)
- Adverse event capture

See section 9.4 of this review for further detail of some of the safety assessments

*5.3.3.2.10 Statistical Analysis for pivotal trials SR 3-01, SR 3-02, SR 3-03, and SR 3-04:*

The analysis populations were to have been:
1. The intent-to-treat population, defined as those who received ≥ 1 dose of trial drug.
2. The per-protocol population, defined as those subjects who followed the protocol.

Sample size calculation: This was a superiority trial. The Applicant's goal was to enroll 110 subjects with subjects randomized 2:2:1 to Kovanaze, tetracaine alone, and placebo respectively such that Kovanaze could be compared to tetracaine alone and Kovanaze could be compared to placebo. The statistical analysis did not include adjustment for multiplicity.

*5.3.3.2.11 Trial Results:*

Protocol Violations

One major protocol violation occurred during this trial. This violation occurred because, for one subject, tooth 11 was the tooth initially planned for treatment, but tooth 6 was treated instead. It is unlikely that this protocol violation will artificially bolster the efficacy of Kovanaze.

Enrollment/Subject Disposition

One hundred thirty-six subjects were screened, of which 110 subjects were randomized and 110 subjects completed the trial. Forty-four subjects were randomized to receive Kovanaze. Forty-four subjects were randomized to receive tetracaine alone, and 22 subjects were randomized to receive placebo. A table of subjects in SR 3-02 is below:

**Table 13 SR 3-02 Disposition of Patients- N (%) (All Screened Patients)**

| | (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 |

Source data: Table 14.1.1.5; Listing 16.2.1
TET: Tetracaine alone; PBO: Placebo; N/A; Not applicable
(Source: NDA 208032 Applicant's table page 50 of SR 3-02 Clinical Study Report)

Extent of Exposure

Forty-four subjects received Kovanaze (18 mg tetracaine and 0.3 mg oxymetazoline). Forty-four subjects received tetracaine alone, and 22 subjects received placebo. All randomized subjects received trial drug and were included in the safety and efficacy analysis. In this study, the modified Intent-to-treat population (mITT) was defined as all randomized subjects who received one spray of study drug (n=110).

Demographics

Subject characteristics across the Kovanaze, tetracaine only, and placebo treatment groups were unequal. More females than males were in the Kovanaze treatment group and more males than females were in the tetracaine only treatment group. Below is a table summarizing the demographic characteristics of subjects in SR 3-02.

**Table 14 Summary of Demography (mITT Population) (SR 3-02)**

| 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 | |

| Variable Statistics | (b) (4) (N = 44) | TET (N = 44) | PBO (N = 22) | Total (N = 110) | *P*-value |
|---|---|---|---|---|---|
| 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 | |

Source data: Table 14.1.2.1
TET: Tetracaine alone; PBO: Placebo
*P*-values are calculated from a chi-square test for categorical variables and an ANOVA model with effect for treatment for continuous variables.
(Source: NDA 208032 Applicant's table page 55 of SR 3-02 Clinical Study Report; header row added by reviewer)

For information on the analysis of efficacy, see section 6.0 of this review.

5.3.3.3 Clinical Trial SR 3-03

*5.3.3.3.1 Title:*

A Phase 3, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered (b) (4) to Placebo for Anesthetizing Maxillary Teeth in Adults

*5.3.3.3.2 Objective:*

(verbatim from NDA 208032 page 6 of SR 3-03 protocol version 2.0)

**Primary:**
To determine whether (b) (4) (3% tetracaine HCl/0.05% oxymetazoline HCl) is safe and superior to placebo in providing local anesthesia sufficient to allow completion of an operative restorative dental procedure (the "Study Dental Procedure") on a maxillary tooth (#4 to 13) in adults without need for intra-procedure rescue by injection of local anesthetic.
**Secondary:**
1. To assess the safety and efficacy of (b) (4) versus placebo by age group (≤50 and >50 years) .
2. To evaluate the safety and tolerability of (b) (4)

*5.3.3.3.3 Trial Design:*

This trial, conducted at three sites in the United States, was to have been a randomized, double-blind trial comparing intranasal Kovanaze to placebo for providing anesthesia to maxillary teeth.

Screening period:

The following were to have taken place up to 14 days before taking part in the trial:

- Informed consent
- Patient history
- Vital signs
- Oral and naris examination

- Periapical and/ or bitewing radiographs, as well as diagnostic radiograph

The following were to have taken place immediately before the dental procedure:

- Urine pregnancy test, if applicable
- Vital signs, including: blood pressure, heart rate, temperature
- Randomization
- The following assessments:
    - Subject-Reported Safety Evaluation
    - Naris Examination
    - Alcohol Sniff Test

Further description of these assessments is in section 9.4 of this review.

Treatment period

Subjects were administered two intranasal sprays of 0.2 mL of Kovanaze or placebo 4 minutes apart on the ipsilateral side of the tooth to be treated. As described in the table below, after 15 minutes, the dental procedure was to have begun. If anesthesia at that time was not sufficient, a third ipsilateral intranasal spray is to have been administered. If a third ipsilateral spray is given, the dental procedure is to have begun 10 minutes later, 25 minutes after the first spray of trial drug. At this time, if anesthesia was not sufficient, rescue medication was to have been given.

Post-treatment follow-up

Subjects were to have been followed for 120 minutes after the first spray of Kovanaze and the next day.

For further detail, see the Overview of Procedures table for SR 3-03 below.

**Table 15 Overview of Procedures for SR 3-03**

| | |
|---|---|
| Screening<br>(Up to 14 days prior, including the day of the study) | Informed consent, HIPAA consent, demographic information, medical and surgical history, current medications, dental history, intraoral examination, periapical and/or bitewing radiographs, diagnostic radiograph to assist in clinical evaluation of necessity for treatment, Naris Examination (NE) , vital signs (VS), and review of inclusion and exclusion criteria. |
| Pre-Study (Immediately prior to the administration of study drug) | Urine pregnancy testing if female of child-bearing potential<br>Record VS (SBP, DBP, HR)<br>Record body temperature<br>Review of inclusion and exclusion criteria<br>Review concomitant medications (con meds)<br>NE<br>Subject-Reported Safety Evaluation (SRSE)<br>Alcohol Sniff Test (AST)<br>Randomization |
| 0 minutes | Administer first intranasal spray on the same side as the treatment tooth. |

| | |
|---|---|
| 4 minutes (± 1 minute ) | Administer second intranasal spray on the same side as the treatment tooth. |
| 10 minutes (+ 3 minutes) | AE, VS. Record time of VS assessment. |
| 15 minutes (+ 3 minutes) | AE<br>Start the Study Dental Procedure.<br>If anesthesia is insufficient, administer a third intranasal spray of the study drug on the same side as the treatment tooth and wait 10 minutes to $T_{25}$. |
| 25 minutes (+ 3 minutes) | AE<br>Start the Study Dental Procedure.<br>If pulpal anesthesia is insufficient at T25 or at any time before restoration is complete, administer rescue anesthetic injection. Record time(s) of rescue anesthetic injection(s) if any. |
| **Do not begin post-procedure assessments until tooth preparation and restoration are complete. Make the assessments at the first scheduled time following completion of tooth preparation and restoration, and continue as scheduled.** | |
| 30 minutes (± 3 minutes) | AE, VS, con meds |
| 45 minutes (± 3 minutes) | AE, VS, con meds |
| 60 minutes (± 3 minutes) | AE, VS, con meds |
| 90 minutes (± 3 minutes) | AE, VS, con meds |
| 120 minutes (± 3 minutes) | AE, VS, SRSE, NE, AST, con meds |
| Next-Day Follow-Up Visit | AE, VS, SRSE, NE, AST, con meds |

(Source: NDA 208032 Applicant's table page 27 of SR 3-03 protocol version 2.0)

*5.3.3.3.4 Trial Population:*

(verbatim from NDA 208032 pages 2 and 3 of SR 3-03 protocol version 2.0)

**Inclusion Criteria:**

1. Male or female 18 years of age or older.
2. Need for an operative restorative dental procedure requiring local anesthesia for a single vital maxillary tooth (anterior or premolar tooth #4 to #13) with no evidence of pulpal pathology.
3. Normal lip, nose, eyelid, and cheek sensation.
4. Able to understand and sign the study informed consent document, communicate with the Investigators, and understand and comply with the requirements of the protocol.
5. Patency of the naris ipsilateral to the tooth undergoing the Study Dental Procedure (the treatment tooth).
6. Resting heart rate (HR) between 55 and 100 beats per minute (bpm), inclusive.
7. Seated systolic blood pressure (SBP) between 95 and 150 mm Hg, inclusive, and seated diastolic blood pressure (DBP) between 60 and 100 mm Hg, inclusive.

**Exclusion Criteria:**

1. Inadequately controlled hypertension (blood pressure greater than 150/100 mm Hg).
2. Inadequately controlled active thyroid disease of any type.
3. Frequent nose bleeds (≥ 5 per month).
4. Having received dental care requiring a local anesthetic within the 24 hours preceding study entry.
5. History of allergy to or intolerance of tetracaine, benzyl alcohol, other ester local anesthetics, or para-aminobenzoic acid (as found in PABA-containing sunscreen).

6. History of allergy or hypersensitivity to articaine, oxymetazoline, epinephrine, or sulfite preservatives.
7. Use of a monoamine oxidase inhibitor within the 3 weeks preceding study entry.
8. Nursing, pregnant, suspected of being pregnant, or trying to become pregnant. (Females of child-bearing potential will be required to take a urine pregnancy test on the day of, but prior to, study drug administration to rule out pregnancy.)
9. Having received any investigational drug and/or participation in any clinical trial within the 30 days prior to study participation.
10. History of congenital or idiopathic methemoglobinemia.

*5.3.3.3.5 Trial Medications and Treatment Groups:*

Trial Medications:
1. Kovanaze: 2 or 3 sprays= 0.4 or 0.6 mL= 12 mg tetracaine and 0.2 mg oxymetazoline or 18 mg tetracaine and 0.3 mg oxymetazoline
2. Placebo: Aqueous solution with all parts of Kovanaze except active ingredients

One hundred fifty subjects were to have been randomized 2:1 to intranasal Kovanaze or placebo.

Batch 200093 was the source of Kovanaze in this clinical trial.

*5.3.3.3.6 Rescue Medications:*

If the trial drug that subjects received did not provide adequate anesthesia, 4% articaine with epinephrine 1:200,000 was to have been allowed as a rescue medication.

*5.3.3.3.7 Efficacy Assessments:*

Success of the trial drug was to have been determined by completion of the Study Dental Procedure without rescue medication.

*5.3.3.3.8 Efficacy Endpoints:*

(verbatim from NDA 208032 page 4 of SR 3-03 protocol version 2.0)

- Primary: Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no).
- Secondary: Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by age group (≤50 and >50 years).

*5.3.3.3.9 Safety Assessments:*

The following safety assessments were to have been performed:

- Vital signs including blood pressure and heart rate
- Subject-Reported Safety Evaluation (SRSE)
- Naris Examination (NE)
- Alcohol Sniff Test (AST)
- Adverse event capture

See section 9.4 of this review for further detail of some of the safety assessments.

*5.3.3.3.10 Statistical Analysis:*

Sample size calculation: The applicant's goal was to treat 150 subjects randomized 2:1 to Kovanaze and placebo such that proportion of successes among those receiving Kovanaze could be compared to the proportion of successes among subjects receiving placebo.

*5.3.3.3.11 Trial Results:*

Protocol Violations

Two major protocol violations occurred during this trial. The first violation, occurring in the Kovanaze treatment group, was the trial medication being administered into the wrong nostril in one subject. In spite of this dosing error, the subject did not require rescue anesthesia for performance of the dental procedure. The second violation, occurring in the placebo treatment group, was informed consent obtained after initiation of trial procedures in one subject. It is unlikely that these protocol violations will artificially bolster the efficacy of Kovanaze.

Enrollment/Subject Disposition

One hundred sixty-six subjects were screened, of which 150 subjects were randomized and treated. One hundred subjects were randomized to receive Kovanaze. Fifty subjects were randomized to receive placebo. One hundred forty-eight subjects completed the trial. Two subjects discontinued the trial: Subject 06-094 in the Kovanaze treatment group was lost to follow-up. Subject 07-164 in the placebo treatment group discontinued the trial for insufficient response to placebo. A table of subjects in SR 3-03 is below.

**Table 16 Disposition of Patients (mITT) in SR 3-03**

| 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] |

Source data: Table 14.1.1.5; Listing 16.2.1
[a] Patient 06-094
[b] Patient 07-164
PBO: placebo
Note: The "other" patient in the bottom row of the table above is patient 07-164, who had an insufficient response to placebo.
(Source: NDA 208032 Applicant's table page 52 of SR 3-03 Clinical Study Report; header row added by reviewer)

Extent of Exposure

One hundred subjects received Kovanaze, of which 27 subjects received 3 sprays of Kovanaze (tetracaine 18 mg/ oxymetazoline 0.3 mg) and 73 subjects received 2 sprays of Kovanaze (tetracaine 12 mg/ oxymetazoline 0.2 mg). Fifty subjects received placebo.

Demographics

Subject characteristics across the Kovanaze and placebo treatment groups were similar. Below is a table summarizing the demographic characteristics of subjects in SR 3-03.

**Table 17 Summary of Demography (mITT)**

| 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%) |

| Characteristic/ Statistic or Category | [redacted] | | | 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) | |
| 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 |

Source data: Table 14.1.2.1; Table 14.1.2.1a; Listing 16.2.4.1
[a] No patients of Asian, American Indian or Alaskan native race were enrolled. Other = Malagasy (1), Latino (1), Middle Eastern (1), White/Native Hawaiian Or Other Pacific Islander (1)
PBO: placebo; SD: standard deviation
(Source: NDA 208032 Applicant's table page 59 of SR 3-03 Clinical Study Report; header row added by reviewer)

For information on the analysis of efficacy, see section 6.0 of this review.

5.3.3.4 Clinical Trial SR 3-04

*5.3.3.4.1 Title:*

A Phase 3, Multi-Center, Randomized, Double-Blind, Parallel-Groups Clinical Trial Comparing the Efficacy and Safety of Intranasally Administered [redacted] to Placebo for Anesthetizing Maxillary Teeth in Pediatric Patients

*5.3.3.4.2 Objective:*

(verbatim from NDA 208032 page 2 of SR 3-04 protocol version 1.0)

**Primary:**

**1. Effectiveness**

To determine whether [redacted] (3% tetracaine HCl/0.05% oxymetazoline HCl) is effective for providing local anesthesia sufficient to allow completion of an operative restorative dental procedure (the "Study Dental Procedure") 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.

**2. Safety**

To determine whether [redacted] (3% tetracaine HCl/0.05% oxymetazoline HCl) is safe for providing local anesthesia sufficient to allow completion of an operative restorative dental procedure (the "Study Dental Procedure") 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

**Secondary:**
1. To evaluate the efficacy of [redacted]
2. To evaluate the safety of [redacted]
3. To evaluate the tolerability of [redacted]

*5.3.3.4.3 Trial Design:*

This trial, conducted at two sites in the United States, was to have been a randomized, double-blind trial comparing intranasal Kovanaze to intranasal placebo for providing anesthesia to the maxillary teeth of pediatric patients.

Screening period

This was to have taken place up to 14 days before taking part in the trial. Additional items were to have been completed immediately before study drug administration. The screening period is described in the Overview of Procedures table below. Naris Examination (NE) is described in Section 9.4.3 of this review.

Treatment period

Kovanaze dosing was to have been determined by the weight of the subject. This dosing is described in the table below:

**Table 18 Kovanaze dosing for trial SR 3-04**

| Subject Weight | Treatment Group: [redacted] or Placebo | Volume per Spray | Number of Sprays | [redacted] Total Dose | |
|---|---|---|---|---|---|
| | | | | Tetracaine HCl | Oxymetazoline HCl (Oxymetazoline Equivalent) |
| 10 kg to <20 kg | 100 µL | 100 µL | 1 | 3 mg | 0.05 mg (0.044 mg) |
| 20 kg to <40 kg | 200 µL | 100 µL | 2 | 6 mg | 0.1 mg (0.088 mg) |
| 40 kg or more | 400 µL | 200 µL | 2 | 12 mg | 0.2 mg (0.175 mg) |

(Source: NDA 208032 Applicant's table page 25 of SR 3-04 protocol version 1.0)

Subjects were to have been randomized to Kovanaze or placebo nasal spray by randomization of the kits of study drug. Subjects were to have been administered Kovanaze or placebo spray based on weight according to the table described in the Overview of Procedures table below.

Study drug was to have been administered in a very specific way: (verbatim from NDA 208032 page 40 of SR 3-04 protocol version 1.0)

Directions for administration of the treatment of 1 or 2 sprays of study drug are as follows:
1. Have the dental chair and subject sitting upright.
2. Sit on the same side as the Study Dental Procedure and face the subject. Dose from the front of the subject on the same side as the Study Dental Procedure.
3. Place the white tip of the sprayer inside the nostril up to the edge of the nasal valve.
4. All groups: Spray 1 – Approximately Horizontal: Position the sprayer tip slightly above horizontal. Direct the sprayer toward the middle of the nasal cavity.
5. 200 µL and 400 µL Groups: Spray 2 – 45 degrees: Position the sprayer tip approximately 45 degrees above the horizontal plane. Direct the sprayer toward the middle of the nasal cavity.
6. PUSH HARD AND FAST on the plunger rod. Expel the spray in approximately ½ second or less.

Post-treatment follow-up

Subjects were to have been followed for 120 minutes after the first spray of Kovanaze or placebo and the next day.

For further detail, see the Overview of Procedures (SR 3-04) table below.

**Table 19 Overview of Procedures (SR 3-04)**

<table>
<tr><td>Screening<br>(Up to 14 days prior, including the day of the study)<br><br>Note: Phone screening and Informed Consent/Assent may be carried out prior to the Screening Visit but not before IRB Approval and SIV Training</td><td colspan="3">Informed consent; (subject assent if required)<br>HIPAA consent<br>Demographic information Medical and surgical history Concomitant medications (con meds) Dental history<br>Intraoral examination<br>Periapical and/or bitewing radiographs to assist in clinical evaluation of necessity for treatment (if required for the completion of the dental procedure)<br>Naris Examination (NE) on the same side as the Study Treatment Tooth<br>Vital signs (VS)<br>Review of inclusion and exclusion criteria</td></tr>
<tr><td rowspan="2">Pre-Study (Immediately prior to the administration of study drug)</td><td colspan="3">Urine pregnancy testing if female of child-bearing potential<br>Record body temperature<br>Randomization</td></tr>
<tr><td colspan="3">If screening and pre-study are not on the same day, the following must be performed again at pre-study:<br>Review of inclusion and exclusion criteria<br>Review concomitant medications (con meds)<br>Record VS (SBP, DBP, HR)<br>NE on the same side as Study Treatment Tooth<br>Intraoral examination</td></tr>
<tr><td colspan="2">100 µL dose group (1 spray)</td><td colspan="2">200 µL or 400 µL dose groups (2 sprays)</td></tr>
<tr><td>0 minutes</td><td>Administer intranasal spray on the same side as the Study Treatment Tooth.</td><td>0 minutes</td><td>Administer first intranasal spray on the same side as the Study Treatment Tooth.</td></tr>
<tr><td></td><td></td><td>4 minutes<br>(± 1 minutes)</td><td>Administer second intranasal spray on the same side as the Study Treatment Tooth.</td></tr>
</table>

| | | | |
|---|---|---|---|
| **10 minutes**(- 3 minutes) (range 7-10 mins) | AE, VS. Record time of VS assessment. | **10 minutes** (- 3 minutes) (range 7-10 mins) | AE, VS. Record time of VS assessment. |
| **10 minutes** (+ 3 minutes) (range 10-13 mins) | Start the Study Dental Procedure. If pulpal anesthesia is insufficient, wait 5 minutes. | **15 minutes** (+ 3 minutes) (range 15-18 mins) | Start the Study Dental Procedure. If pulpal anesthesia is insufficient, wait 5 minutes. |
| **15 minutes** (+ 3 minutes) (range 15-18 mins) | If Study Dental Procedure was not started at $T_{10}$, start Study Dental Procedure. | **20 minutes** (+ 3 minutes) (range 20-23 mins) | If Study Dental Procedure was not started at $T_{15}$, start Study Dental Procedure. |
| If anesthesia is insufficient, administer rescue anesthetic injection. Record time(s) of rescue anesthetic injection(s) if any, and record the event as an AE (i.e., pain on drilling) and list the rescue medication as a ConMed in source documents. | | | |
| **120 minutes** (± 3 minutes) | AE, VS, NE, con meds | | |
| **Next-Day Follow-Up Visit** | AE, VS, NE, con meds | | |

(Source: NDA 208032 Applicant's table page 27 of SR 3-04 protocol version 1.0)

5.3.3.4.4 Trial Population:

(inclusion and exclusion criteria verbatim from NDA 208032 pages 38 and 39 of SR 3-04 protocol version 1.0)

## Inclusion Criteria

1. Male or female 3-17 years of age inclusive.
2. Need for an operative restorative dental procedure and requiring local anesthesia on a single vital maxillary primary tooth (#A to J) or permanent tooth (#4 to13), with no evidence of pulpal pathology.
3. Normal lip, nose, eyelid, and cheek sensation.
4. Accompanied and/or represented by a parent or guardian able to comprehend and sign the informed consent document.
5. Subject able to understand and provide assent to an age-appropriate subject assent form (as defined by local practice or regulation).
6. Patient or parent/guardian able to communicate with the investigator and comply with the requirements of the protocol.
7. Patency of the naris on the same side as the tooth undergoing the Study Dental Procedure (the Study Treatment Tooth).

## Exclusion Criteria

1. Having received dental care requiring a local anesthetic within the 24 hours preceding study entry.
2. History of allergy to or intolerance of tetracaine, benzyl alcohol, other ester local anesthetics, or para-aminobenzoic acid (as found in PABA-containing sunscreen).
3. History of allergy or hypersensitivity to lidocaine, oxymetazoline, epinephrine, or sulfite preservatives.
4. Use of a monoamine oxidase inhibitor within the 3 weeks preceding study entry.
5. Nursing, pregnant, suspected of being pregnant, or trying to become pregnant. (Females of child-bearing potential will be required to undergo urine testing on the day of, but prior to, study drug administration to rule out pregnancy.)
6. Inadequately controlled thyroid disease of any type.
7. Having received any investigational drug (including (b) (4) and/or participation in any clinical trial within 30 days of study participation.

8. Frequent nose bleeds (≥ 5 per month).
9. History of congenital or idiopathic methemoglobinemia.
10. Presence of an upper respiratory infection and/or fever defined as body temperature ≥100.4° (38°C) on the day of and prior to study drug administration.

*5.3.3.4.5 Trial Medications and Treatment Groups:*

Trial Medications:
1. Kovanaze: This formulation of Kovanaze is the to-be-marketed formulation that contains 3 mg tetracaine and 0.05 mg oxymetazoline in 0.1 mL (100 µL) of Kovanaze.

2. Placebo nasal spray: Aqueous solution with all parts of Kovanaze except active ingredients

Ninety subjects were to have been randomized 2:1 to intranasal Kovanaze or intranasal placebo.

*5.3.3.4.6 Rescue Medications:*

If the study drug that subjects receive does not provide adequate anesthesia, 2% lidocaine HCl with 1:100,000 epinephrine was to be allowed as a rescue medication.

*5.3.3.4.7 Efficacy Assessments:*

Success with Kovanaze is completion of the planned procedure without rescue medication.

*5.3.3.4.8 Efficacy Endpoints:*

(verbatim from NDA 208032 page 24 of SR 3-04 protocol version 1.0)

> The primary efficacy endpoint for this study is completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no).
>
> There are two secondary efficacy endpoints for the study.
>
> - Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by dose (100 µL, 200 µL or 400 µL).
> - Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by age group (3-5, 6-11, and 12-17 years old, inclusive).

*5.3.3.4.9 Safety Assessments:*

The following safety assessments were to have been performed:

- Intraoral examination
- Urine pregnancy test, if applicable
- Temperature
- Vital signs including blood pressure and heart rate
- Naris Examination (NE)
- Adverse event capture

See section 9.4 of this review for further detail of the Naris Examination.

*5.3.3.4.10 Statistical Analysis:*

The analysis populations were to have been:
1. The intent-to-treat population, defined as those who received ≥ 1 dose of trial drug.
2. The per-protocol population, defined as those who followed the protocol.

*5.3.3.4.11 Trial Results:*

Protocol Violations

No major protocol violations occurred during this trial.

Enrollment/Subject Disposition

Ninety subjects were randomized, of which 89 subjects completed the trial. 60 subjects were randomized to receive Kovanaze and 30 subjects were randomized to receive placebo. A table of subjects in SR 3-04 is below:

**Table 20 Disposition of Patients (mITT) (SR 3-04)**

| 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 |

Source data: Table 14.1.1.5 and Listing 16.2.1.
* Patient 5-123 withdrew consent after receiving one spray of (b) (4) No SDP was carried out for this patient.
Values provided as n (%).
(Source: NDA 208032 Applicant's table page 42 of SR 3-04 Clinical Study Report)

Extent of Exposure

Sixty subjects received varying doses of Kovanaze. Thirty subjects received placebo. In this study, the modified Intent-to-treat population (mITT) was defined as all subjects who received one spray of study drug. The table below displays study drug exposure in this trial:

**Table 21 Study Drug Administration by Dosage Cohort and Age Group (Safety) (SR 3-04)**

| Variable | (b) (4) (N = 60) | | | | PBO (N = 30) | |
|---|---|---|---|---|---|---|
| | N (%) | Treatment Volume (mL) | Tetracaine HCl (mg) | Oxymetazoline HCl (mg) | N (%) | Treatment Volume (mL) |
| **Dosage Cohort** | | | | | | |
| 10 to < 20 kg | 16 (26.7%) | 0.100 (0.0) | 3.0 (0.0) | 0.05 (0.00) | 8 (26.7%) | 0.100 (0.0) |
| 20 to < 40 kg* | 24 (40.0%) | 0.196 (0.02) | 5.9 (0.6) | 0.10 (0.01) | 12 (40.0%) | 0.200 (0.0) |
| 40 kg or more | 20 (33.3%) | 0.400 (0.0) | 12.0 (0.0) | 0.20 (0.0) | 10 (33.3%) | 0.400 (0.0) |
| **Age Group** | | | | | | |
| 3 to 5 years | 21 (35.0%) | 0.124 (0.04) | 3.7 (1.3) | 0.06 (0.02) | 10 (33.3%) | 0.120 (0.04) |
| 6 to 11 years* | 23 (38.3%) | 0.230 (0.08) | 6.9 (2.5) | 0.12 (0.04) | 15 (50.0%) | 0.266 (0.10) |
| 12 to 17 years | 16 (26.7%) | 0.400 (0.0) | 12.0 (0.0) | 0.20 (0.00) | 5 (16.7%) | 0.400 (0.0) |

Source: Table 14.1.9.2.2 through Table 14.1.9.2.7 and Listing 16.2.5.1
*Includes Patient 5-123, patient withdrew consent after 1 spray of (b) (4)
Data provided as n (%) and mean (SD). mg = milligrams, mL = milliliters.
(Source: NDA 208032 Applicant's table page 65 of SR 3-04 Clinical Study Report)

Demographics

Subject characteristics across the Kovanaze and placebo treatment groups were similar. Below is a table summarizing the demographic characteristics of subjects in SR 3-04.

**Table 22 Summary of Demography (mITT) (SR 3-04)**

| 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%) |

| Variable | (b) (4) (N = 60) | PBO (N = 30) | Total (N = 90) |
|---|---|---|---|
| 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 |

Source data: Table 14.1.2.1 and Listing 16.2.4.1.
(Source: NDA 208032 Applicant's table page 45 of SR 3-04 Clinical Study Report; header row added by reviewer)

For information on the analysis of efficacy, see section 6.0 of this review.

# 6 Review of Efficacy

## ***Efficacy Summary***

For the adult population, Kovanaze appears to be efficacious for providing anesthesia to maxillary teeth 4 through 13. Kovanaze appears to be most efficacious in adults for teeth that are more anterior (i.e., teeth 5 through 12).

For pediatric patients, Kovanaze appears to be efficacious in those weighing ≥ 40 kg

(b) (4)

Because those weighing ≥ 40 kg received a dose of two sprays of 0.2 mL, this should be the recommended dosing in that weight group. Two sprays of 0.2 mL of Kovanaze is the same as the starting adult dose. In order to evaluate the risk: benefit profile for this dose in pediatrics, adverse events in all adult and pediatric patients who received Kovanaze in Phase 3 trials were compared with adverse events occurring in pediatric patients weighing 40 kg or more in SR 3-04 who received Kovanaze. The adverse event profiles were similar in those two groups of patients.

Below is a summary table of anesthetic success rates with Kovanaze by dosage cohort.

**Table 23 Success Rates by Dosage Cohort (mITT) (SR 3-04)**

| **Successful Anesthetic Response by Dosage Strata** N (%) | **Volume/Spray x Spray no.** | **(b) (4) (N = 60)** | **PBO (N = 30)** | **One-Sided Fischer's Exact Test P-Value** | **Stratified CMH P-Value**** |
|---|---|---|---|---|---|
| 10 to < 20 kg (n = 24) | [redacted] | | | | 0.020 |
| 20 to < 40 kg (n = 36)* | | | | | |
| 40 kg or more (n = 30) | 0.2 mL x 2 | 18/20 (90.0%) | 4/10 (40.0%) | 0.0072 | |

Source data: Table 14.2.2 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across dosage strata p = 0.17.
(Source: NDA 208032 Applicant's table page 56 of SR 3-04 Clinical Study Report)

## 6.1 Indication

St. Renatus seeks approval of Kovanaze for regional anesthesia when performing a restorative procedure on teeth 4 through 13 and A through J in adults and children (b) (4) .

### 6.1.1 Methods

Phase 3 trials SR 3-02, SR 3-03, and SR 3-04 were all performed with the formulation of Kovanaze that is identical to the one for which this NDA has been submitted and for which approval is sought. SR 3-02, SR 3-03, and SR 3-04 are meant to support the efficacy of Kovanaze. These clinical trials were performed under IND 70868.

Below is a table that summarizes endpoints for trials submitted for this NDA. Trials SR 3-02, SR 3-03, and SR 3-04 are considered pivotal trials. SR 3-02 and SR 3-03 took place in adult dental patients. SR 3-04 took place in pediatric dental patients.

**Table 24 Summary of Endpoints and Statistical Methods**

| **Endpoints** | **Study Number** | **Statistical Methods** |
|---|---|---|
| Success based on the Global Profound Pulpal Anesthesia (GPPA) | SR 2-04 | McNemar's exact test |

| Endpoints | Study Number | Statistical Methods |
|---|---|---|
| Incidence of Profound Pulpal Anesthesia (PPA) for Electric Pulp Test (EPT) tested teeth | SR 2-04 | Descriptive statistics |
| For all individually EPT-tested teeth achieving PPA, time to onset and duration of PPA for unilateral and bilateral drug administration | SR 2-04 | Descriptive statistics |
| Correlation between positive responses in a questionnaire of Subjective Numbness Assessment (SNA) and incidence of global EPT scores of 80 | SR 2-04 | Descriptive statistics |
| Success based on the completion of standard dental procedure (SDP) without need for rescue by injection of local anesthetic | SR 2-05 | Descriptive statistics |
| Success based on the completion of SDP without need for rescue by injection of local anesthetic | SR 3-02[1]<br>SR 3-03[1]<br>SR 3-04[1] | Fisher's exact test |
| Incidence, onset and duration of soft-tissue anesthesia by (b) (4) as measured by the soft tissue anesthesia assessment (STAA) | SR 3-02[1] | Descriptive statistics |
| Success based on the completion of SDP without need for rescue by injection of local anesthetic by age group (≤ 50 years old versus > 50 years old) | SR 3-03[1] | Cochran-Mantel-Haenszel (CMH) test |
| Success based on the completion of SDP without need for rescue by injection of local anesthetic by dose cohort (0.1 mL, 0.2 mL, or 0.4 mL) | SR 3-04[1] | CMH test, stratifying by dose |
| Success based on the completion of SDP without need for rescue by injection of local anesthetic by age group (3-5 years, 6-11 years, and 12-17 years, inclusive) | SR 3-04[1] | CMH test, stratifying by age group |
| Exploratory subgroup analysis by tooth location (anterior/premolar) | SR 3-02[1]<br>SR 3-03[1]<br>SR 3-04[1] | CMH test, stratifying by treatment group |

Source: SR 2-04, SR 2-05, SR 3-02, SR 3-03 and SR 3-04 Individual Study Reports (Module 5.3.5.1)
[1] Pivotal studies
CMH: Cochran-Mantel-Haenszel

(Source: NDA 208032 Applicant's table page 18 of Summary of Clinical Efficacy)

Note that "success based on the completion of SDP without need for rescue by injection of local anesthetic" is the endpoint for all three pivotal studies. (Source: NDA 208032 Applicant's table page 18 of Summary of Clinical Efficacy)

### 6.1.2 Demographics

Subject demographics for SR 3-02 can be found in section 5.3.3.2.11 of this review.
Subject demographics for SR 3-03 can be found in section 5.3.3.3.11 of this review.

Subject demographics for SR 3-04 can be found in section 5.3.3.4.11 of this review.

### 6.1.3 Subject Disposition

Subject disposition for SR 3-02 can be found in section 5.3.3.2.11 of this review.
Subject disposition for SR 3-03 can be found in section 5.3.3.3.11 of this review.
Subject disposition for SR 3-04 can be found in section 5.3.3.4.11 of this review.

### 6.1.4 Analysis of Primary Endpoints

SR 3-02, SR 3-03, and SR 3-04 have the same primary endpoint (see table below). SR 3-02 and SR 3-03 were trials conducted in adult dental patients. SR 3-04 was a trial conducted in pediatric dental patients. Below is a table of pre-determined efficacy endpoints for pivotal phase 3 trials with Kovanaze.

**Table 25 Summary of pre-determined efficacy endpoints for pivotal phase 3 trials with Kovanaze**

| Trial | Primary efficacy endpoint | Secondary efficacy endpoints | Comparator |
|---|---|---|---|
| SR 3-02 | "completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no)."<br><br>(Source: NDA 208032 page 18 of SR 3-02 protocol version 3.0) | "Intraoral soft-tissue anesthesia (yes/no) and the onset and duration of such soft-tissue anesthesia. "Onset" shall be defined as the time from the completion of dosing (T8) to the time that the subject reports no pain upon soft-tissue probing. "Duration" shall be defined as the time from Onset to the time the subject reports pain upon soft-tissue probing."<br><br>(Source: NDA 208032 page 18 of SR 3-02 protocol version 3.0) | Tetracaine alone and placebo |
| SR 3-03 | "completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no)."<br><br>(Source: NDA 208032 page 21 of SR 3-03 protocol version 2.0) | "completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by age group (≤50 and >50 years)."<br><br>(Source: NDA 208032 page 21 of SR 3-03 protocol version 2.0) | Placebo |
| SR 3-04 | "completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no)"<br><br>(Source: NDA 208032 page 24 of SR 3-04 protocol version 1.0) | • "Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by dose (100 µL, 200 µL or 400 µL).<br>• Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by age group (3-5, 6-11, and 12-17 years old, inclusive)."<br><br>(Source: NDA 208032 page 24 of SR 3-04 protocol version 1.0) | Placebo |

### 6.1.4.1 Results of SR 3-02 for primary efficacy endpoint

In trial SR 3-02, Kovanaze had a higher success rate for the primary efficacy endpoint when compared to either tetracaine spray alone or placebo. Below is a table of anesthetic success by treatment group for trial SR 3-02.

**Table 26 Anesthetic Success Rate by Treatment Group (mITT Population) (SR 3-02)**

| | Patient Count (Percent) By Treatment | | | | | |
|---|---|---|---|---|---|---|
| | (b) (4) (N = 44) | | TET (N = 44) | | PBO (N=22) | |
| **Anesthetic Response** | **Count (%)** | **95% CI** | **Count (%)** | **95% CI** | **Count (%)** | **95% CI** |
| Success | 37/44 (84.1%) | (69.9%, 93.4%) | 12/44 (27.3%) | (15.0%, 42.8%) | 6/22 (27.3%) | (10.7%, 50.2%) |
| Failure | 7/44 (15.9%) | - | 32/44 (72.7%) | - | 16/22 (72.7%) | - |
| *P*-value (b) (4) vs. TCC* | < 0.0001 | | | | | |
| *P*-value (b) (4) vs. PBO* | < 0.0001 | | | | | |

Source data: Table 14.2.1, Table 14.2.2
TET: Tetracaine alone; PBO: Placebo
* One-sided Fisher's Exact Test at 2.5% Type-1 Error
(Source: NDA 208032 Applicant's table page 62 of SR 3-02 Clinical Study Report)

### 6.1.4.2 Results of SR 3-03 for primary efficacy endpoint

In trial SR 3-03, Kovanaze had a higher success rate for the primary efficacy endpoint when compared to placebo. Below is a table of anesthetic success by treatment group for trial SR 3-03.

**Table 27 Success Rates by Treatment Group (mITT) (SR 3-03)**

| Anesthetic Outcome | (b) (4) (N = 100) | | PBO (N = 50) | | *P*-value* |
|---|---|---|---|---|---|
| | **Count (%)** | **95% CI** | **Count (%)** | **95% CI** | |
| Success | 88 (88.0%) | (80.0, 93.6%) | 14 (28.0%) | (16.2, 42.5%) | < 0.0001 |
| Failure | 12 (12.0%) | | 36 (72.0%) | | |

Source data: Table 14.2.1
PBO: placebo
* One-sided Fisher's Exact Test at 2.5% type-1 error
(Source: NDA 208032 Applicant's table page 66 of SR 3-03 Clinical Study Report)

### 6.1.4.3 Results of SR 3-04 for primary efficacy endpoint

In trial SR 3-04, when all age groups are assembled together, Kovanaze had a higher success rate for the primary efficacy endpoint when compared to placebo. Below is a table of anesthetic success by treatment group for trial SR 3-04.

**Table 28 Summary of Success and Failure Rates (mITT) (SR 3-04)**

| Anesthetic Response | (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value |
|---|---|---|---|
| **Success** | | | 0.023 |
| N (%) | 46 (76.7%) | 16 (53.3%) | |
| 95% CI | (64.0%, 86.6%) | (34.3%, 71.7%) | |
| **Failure *** | | | |
| N (%) | 14 (23.3%) | 14 (46.7%) | |

Source data: Table 14.2.1 and Listing 16.2.6.1
Success = Dental procedure completed without rescue injections; Failure = Required rescue anesthesia or discontinued after receiving at least one spray of study drug and before completion of SDP.
* Includes Patient 5-123 who withdrew after one spray of (b) (4) and prior to SDP, as treatment failure.
(Source: NDA 208032 Applicant's table page 55 of SR 3-04 Clinical Study Report)

Although there is successful result for the primary endpoint when all the age groups are lumped together, the intended population will be limited to pediatrics weighing 40 kg or greater (b) (4) No one below the age of three-years-old was studied.

## 6.1.5 Analysis of Secondary Endpoints

### 6.1.5.1 Secondary efficacy endpoint for SR 3-02

The secondary efficacy endpoint for SR 3-02 was to have been "intraoral soft-tissue anesthesia (yes/no) and the onset and duration of such soft-tissue anesthesia."(Source: NDA 208032 page 18 of SR 3-02 protocol version 3.0) In this trial, study drug was administered at $T_0$, $T_4$, and $T_8$. For further detail of the trial SR 3-02, see section 5.3.3.2 of this review. The efficacy of Kovanaze was to have been assessed by a soft tissue anesthesia assessment (STAA). See section 9.4.5 of this review for more detail of the STAA. Below is a table of STAA results at the Incisive Papilla.

**Table 29 Soft Tissue Anesthesia Assessment for Incisive Papilla (mITT Population) (SR 3-02)**

| Measurement Visit | Anesthetic Response | Patient Count (Percent) | | |
|---|---|---|---|---|
| | | (b) (4) (N=44) N (%) | TET (N=44) N (%) | PBO (N=22) N (%) |
| | Without Pain | 16 (36.4%) | 13 (29.5%) | 8 (36.4%) |

| Measurement Visit | Anesthetic Response | Patient Count (Percent) | | |
|---|---|---|---|---|
| | | (b) (4) (N=44) N (%) | TET (N=44) N (%) | PBO (N=22) N (%) |
| Pre-Study | With Pain | 28 (63.6%) | 31 (70.5%) | 14 (63.6%) |
| $T_{15}$ | Without Pain | 34 (77.3%) | 21 (47.7%) | 8 (36.4%) |
| | With Pain | 10 (22.7%) | 23 (52.3%) | 14 (63.6%) |
| $T_{30}$ | Without Pain | 23 (52.3%) | 5 (11.4%) | 2 (9.1%) |
| | With Pain | 2 (4.5%) | 0 | 2 (9.1%) |
| | Missing[a] | 19 (43.2%) | 39 (88.6%) | 18 (81.8%) |
| $T_{45}$ | Without Pain | 37 (84.1%) | 14 (31.8%) | 11 (50.0%) |
| | With Pain | 3 (6.8%) | 22 (50.0%) | 9 (40.9%) |
| | Missing[a] | 4 (9.1%) | 8 (18.2%) | 2 (9.1%) |
| $T_{60}$ | Without Pain | 32 (72.7%) | 16 (36.4%) | 10 (45.5%) |
| | With Pain | 12 (27.3%) | 27 (61.4%) | 12 (54.5%) |
| | Missing | 0 | 1 (2.3%) | 0 |
| $T_{90}$ | Without Pain | 25 (56.8%) | 12 (27.3%) | 9 (40.9%) |
| | With Pain | 19 (43.2%) | 32 (72.7%) | 13 (59.1%) |
| $T_{120}$ | Without Pain | 19 (43.2%) | 10 (22.7%) | 9 (40.9%) |
| | With Pain | 25 (56.8%) | 34 (77.3%) | 13 (59.1%) |
| $T_{Next\ Day}$ | Without Pain | 11 (25.0%) | 11 (25.0%) | 8 (36.4%) |
| | With Pain | 31 (70.5%) | 32 (72.7%) | 13 (59.1%) |
| | Missing | 2 (4.5%) | 1 (2.3%) | 1 (4.5%) |

Source: Table 14.2.3
TET: Tetracaine alone; PBO: Placebo
[a] Missing data points were due to ongoing SDP that were not interrupted for assessments at these time points.
(Source: NDA 208032 Applicant's table page 64 of SR 3-02 Clinical Study Report; header row added by reviewer)

Below is a table of STAA results at the Greater Palatine Foramen.

**Table 30 Soft Tissue Anesthesia Assessment for Greater Palatine Foramen (SR 3-02)**

| Measurement Visit | Anesthetic Response | Patient Count (Percent) | | |
|---|---|---|---|---|
| | | (b) (4) (N=44) N (%) | TET (N=44) N (%) | PBO (N=22) N (%) |
| Pre-Study | Without Pain | 14 (31.8%) | 12 (27.3%) | 7 (31.8%) |
| | With Pain | 30 (68.2%) | 32 (72.7%) | 15 (68.2%) |
| $T_{15}$ | Without Pain | 21 (47.7%) | 19 (43.2%) | 9 (40.9%) |
| | With Pain | 23 (52.3%) | 25 (56.8%) | 13 (59.1%) |

| Measurement Visit | Anesthetic Response | Patient Count (Percent) | | |
|---|---|---|---|---|
| | | (b) (4) (N=44) N (%) | TET (N=44) N (%) | PBO (N=22) N (%) |
| $T_{30}$ | Without Pain | 15 (34.1%) | 3 (6.8%) | 2 (9.1%) |
| | With Pain | 10 (22.7%) | 2 (4.5%) | 2 (9.1%) |
| | Missing[a] | 19 (43.2%) | 39 (88.6%) | 18 (81.8%) |
| $T_{45}$ | Without Pain | 19 (43.2%) | 20 (45.5%) | 10 (45.5%) |
| | With Pain | 21 (47.7%) | 16 (36.4%) | 10 (45.5%) |
| | Missing[a] | 4 (9.1%) | 8 (18.2%) | 2 (9.1%) |
| $T_{60}$ | Without Pain | 16 (36.4%) | 18 (40.9%) | 9 (40.9%) |
| | With Pain | 28 (63.6%) | 25 (56.8%) | 13 (59.1%) |
| | Missing | 0 | 1 (2.3%) | 0 |
| $T_{90}$ | Without Pain | 15 (34.1%) | 15 (34.1%) | 8 (36.4%) |
| | With Pain | 29 (65.9%) | 29 (65.9%) | 14 (63.6%) |
| $T_{120}$ | Without Pain | 12 (27.3%) | 12 (27.3%) | 8 (36.4%) |
| | With Pain | 32 (72.7%) | 32 (72.7%) | 14 (63.6%) |
| $T_{NextDay}$ | Without Pain | 10 (22.7%) | 12 (27.3%) | 7 (31.8%) |
| | With Pain | 32 (72.7%) | 31 (70.5%) | 14 (63.6%) |
| | Missing | 2 (4.5%) | 1 (2.3%) | 1 (4.5%) |

Source: Table 14.2.3
TET: Tetracaine alone; PBO: Placebo
[a] Missing data points were due to ongoing SDP that were not interrupted for assessments at these time points.
(Source: NDA 208032 Applicant's table page 65 of SR 3-02 Clinical Study Report; header row added by reviewer)

The above tables demonstrate that Kovanaze is more effective at the Incisive Papilla than at the Greater Palatine Foramen.

Unfortunately, the STAA assessment in this clinical trial was confounded by one of the two study sites that participated in this clinical trial. Two study sites participated in trial SR 3-02, study site #2 and study site #4. All subjects were asked at baseline, "Do you feel any pain?" (Source: NDA 208032 page 66 of SR 3-02 Clinical Study Report) The expected response (if the subject has normal innervation) is "yes." However, at study site #4, St. Renatus contends that study personnel may have been confused, leading to a number of subjects answering "no" to this question. Therefore, St. Renatus did not think that the onset and duration of Kovanaze, as measured by the STAA, could be accurately assessed at site #4.For this reason, St. Renatus performed a post-hoc analysis of STAA for site #2. In this post-hoc analysis of site #2, onset of Kovanaze at the incisive papilla was 9.7 ± 7.5 minutes and duration of Kovanaze action was 79.2 ± 27 minutes. Onset of Kovanaze was time from the last dose of Kovanaze, $T_8$. Duration of action was defined as the time of onset of Kovanaze to "the smaller of the time the

patient reported pain upon soft-tissue probing and $T_{120}$." (Source: NDA 208032 page 68 of SR 3-02 Clinical Study Report)

6.1.5.2 Secondary efficacy endpoint for SR 3-03

The secondary efficacy endpoint for SR 3-03 is "completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by age group (≤50 and >50 years)." (Source: NDA 208032 page 21 of SR 3-03 protocol version 2.0) There does not appear to be an appreciable difference in efficacy for adults based on age greater than 50-years-old compared to age less than or equal to 50-years-old. Below is a table of anesthetic success with Kovanaze stratified by age.

**Table 31 Anesthetic Success Rates Stratified by Age (mITT) (SR 3-03)**

| Stratification Factor | Anesthetic success rate | | | | *P*-value[a] |
|---|---|---|---|---|---|
| | (b) (4) (N = 100) | | PBO (N = 50) | | |
| | N | Count (%) | N | Count (%) | |
| Age [years] | | | | | |
| ≤ 50 | 69 | 60 (87.0%) | 34 | 7 (20.6%) | < 0.0001 |
| > 50 | 31 | 28 (90.3%) | 16 | 7 (43.8%) | |

Source data: Tables 14.2.2
[a] Stratified by Cochran-Mantel-Haenszel test
PBO: placebo
(Source: NDA 208032 Applicant's table page 67 of SR 3-03 Clinical Study Report)

6.1.5.3 Secondary endpoint for SR 3-04

The secondary efficacy endpoints for SR 3-04 are:

- "Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by dose (100 µL, 200 µL or 400 µL).
- Completion of the Study Dental Procedure without need for rescue by injection of local anesthetic (yes/no) by age group (3-5, 6-11, and 12-17 years old, inclusive)."

(Source: NDA 208032 page 24 of SR 3-04 protocol version 1.0)

In this trial, subjects with greater weight received a larger dose of trial drug. Those who received a larger dose of trial drug had a higher success rate compared to placebo. Below is a table of success rate by dosage.

**Table 32 Success Rates by Dosage Cohort (mITT) (SR 3-04)**

| Successful Anesthetic Response by Dosage Strata N (%) | Volume/Spray x Spray no. | (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|---|
| 10 to < 20 kg (n = 24) | (b) (4) | | | | 0.020 |
| 20 to < 40 kg (n = 36)* | | | | | |
| 40 kg or more (n = 30) | 0.2 mL x 2 | 18/20 (90.0%) | 4/10 (40.0%) | 0.0072 | |

Source data: Table 14.2.2 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across dosage strata p = 0.17.
(Source: NDA 208032 Applicant's table page 56 of SR 3-04 Clinical Study Report)

(b) (4)

**Table 33 Success Rates by Age Group (mITT)**

| Successful Anesthetic Response by Age Strata N (%) | (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|
| (b) (4) | | | | |

Source data: Table 14.2.3 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across age group strata p = 0.15.
(Source: NDA 208032 Applicant's table page 57 of SR 3-04 Clinical Study Report)

(b) (4) if success rate by dosage cohort is examined, Kovanaze appears to be efficacious in those weighing 40 kg or more (b) (4) .

(b) (4)


### 6.1.6 Other Endpoints

There were no additional pre-specified efficacy endpoints for SR 3-02, SR 3-03, or SR 3-04.

### 6.1.7 Subpopulations

The Applicant provided subgroup analysis of the primary endpoint for trials SR 3-02, SR 3-03, and SR 3-04 by age (3 to 5-years-old, 6 to 11-years-old, 12 to 17-years-old, 18 to 50-years-old, and > 50 years-old), gender (male and female), and ethnicity (Hispanic or Latino and Non-Hispanic or Latino).

### 6.1.7.1 Subgroup analysis for SR 3-02 and SR 3-03 (adult dental patients)

In adult dental patients in SR 3-02 and SR 3-03, there was a significant treatment effect for Kovanaze regardless of age, gender, ethnicity, and race. The eight tables below display subgroup analysis for SR 3-02 and SR 3-03 by age, gender, ethnicity, and race.

#### *6.1.7.1.1 Subgroup analysis for SR 3-02 and SR 3-03 (adult dental patients) by age*

**Table 34 Anesthetic Success Rate Stratified by Age Group (mITT): Pivotal Study SR 3-02**

| | | | Patient Count (Percent) | | | |
|---|---|---|---|---|---|---|
| **Stratified by** | **Category** | **Anesthetic Response** | **(b) (4) (N=44)** | **TET (N=44)** | **PBO (N=22)** | ***P*-value*** |
| Age Strata | ≤ 50 years | N | 34 | 39 | 16 | < 0.0001 |
| | | Success | 27 (79.4%) | 8 (20.5%) | 3 (18.8%) | |
| | | Failure | 7 (20.6%) | 31 (79.5%) | 13 (81.3%) | |
| | > 50 years | N | 10 | 5 | 6 | |
| | | Success | 10 (100.0%) | 4 (80.0%) | 3 (50.0%) | |
| | | Failure | 0 | 1 (20.0%) | 3 (50.0%) | |

Source: SR 3-02 Individual Study Report Module 5.3.5.1
TET: Tetracaine alone; PBO: Placebo
* Stratified Cochran-Mantel-Haenszel Test.
Breslow-Day Test of Homogeneity Across Age Strata *P*-Values 0.68 ((b) (4) vs. Tetracaine) and 0.46 ((b) (4) vs. Placebo).
(Source: NDA 208032 Applicant's table page 55 of Summary of Clinical Efficacy)

**Table 35 Anesthetic Success Rates Stratified by Age (mITT): Pivotal Study SR 3-03**

| **Stratification factor** | **Anesthetic Success Rate** | | | | ***P*-value[a]** |
|---|---|---|---|---|---|
| | **(b) (4) (N = 100)** | | **PBO (N = 50)** | | |
| | **N** | **Count (%)** | **N** | **Count (%)** | |
| Age [years] | | | | | |
| ≤ 50 | 69 | 60 (87.0%) | 34 | 7 (20.6%) | <0.0001 |
| > 50 | 31 | 28 (90.3%) | 16 | 7 (43.8%) | |

Source: SR 3-03 Individual Study Report Module 5.3.5.1
PBO: placebo
[a] Stratified by CMH test
(Source: NDA 208032 Applicant's table page 56 of Summary of Clinical Efficacy)

### *6.1.7.1.2 Subgroup analysis for SR 3-02 and SR 3-03 (adult dental patients) by gender*

**Table 36 Anesthetic Success Rate Stratified by Gender (mITT): Pivotal Study SR 3-02**

| | | | Patient Count (Percent) | | | |
|---|---|---|---|---|---|---|
| **Stratified by** | **Category** | **Anesthetic Response** | **(b) (4) (N=44)** | **TET (N=44)** | **PBO (N=22)** | ***P*-Value*** |
| Gender | Male | N | 14 | 28 | 10 | < 0.0001 |
| | | Success | 13 (92.9%) | 6 (21.4%) | 3 (30.0%) | |
| | | Failure | 1 (7.1%) | 22 (78.6%) | 7 (70.0%) | |
| | Female | N | 30 | 16 | 12 | |
| | | Success | 24 (80.0%) | 6 (37.5%) | 3 (25.0%) | |
| | | Failure | 6 (20.0%) | 10 (62.5%) | 9 (75.0%) | |

Source: SR 3-02 Individual Study Report Module 5.3.5.1
TET: Tetracaine alone; PBO: Placebo
* Stratified Cochran-Mantel-Haenszel Test.
Homogeneity Across Gender Strata P-Values 0.12 ( (b) (4) vs. Tetracaine) and 0.53 ( (b) (4) vs. Placebo).
(Source: NDA 208032 Applicant's table page 58 of Summary of Clinical Efficacy)

**Table 37 Subgroup Analysis of Success Rates by Gender (mITT): Pivotal Study SR 3-03**

| **Stratified by** | **Anesthetic Success Rate** | | | | ***P*-Value[a]** |
|---|---|---|---|---|---|
| | **(b) (4) (N = 100)** | | **PBO (N = 50)** | | |
| | **N** | **Count (%)** | **N** | **Count (%)** | |
| **Gender** | | | | | |
| Male | 43 | 38 (88.4%) | 25 | 9 (36.0%) | <0.0001 |
| Female | 57 | 50 (87.7%) | 25 | 5 (20.0%) | |

Source: SR 3-03 Individual Study Report Module 5.3.5.1
[a] Stratified by CMH test
[b] Breslow-Day test of homogeneity P-value = 0.40.
(Source: NDA 208032 Applicant's table page 59 of Summary of Clinical Efficacy)

### *6.1.7.1.3 Subgroup analysis for SR 3-02 and SR 3-03 (adult dental patients) by race and ethnicity*

Most adult dental patients in Phase 3 clinical trials in support of this NDA were White and non-Hispanic.

**Table 38 Need for Rescue Anesthesia Stratified by Racial Subcategories (Study SR 3-02)**

| | | Subject Count (Percent) | | |
|---|---|---|---|---|
| **Race** | **Anesthetic Response** | **(b) (4) (N=44)** | **TET (N=44)** | **Placebo (N=22)** |
| | N | 35 | 36 | 13 |

| | | Subject Count (Percent) | | |
|---|---|---|---|---|
| **Race** | **Anesthetic Response** | **(b) (4) (N=44)** | **TET (N=44)** | **Placebo (N=22)** |
| White | Success[a] | 30 (85.7%) | 10 (27.8%) | 4 (30.8%) |
| | Failure[b] | 5 (14.3%) | 26 (72.2%) | 9 (69.2%) |
| Asian | N | 1 | 2 | 4 |
| | Success[a] | 1 (100%) | 1 (50.0%) | 1 (25.0%) |
| | Failure[b] | 0 | 1 (50.0%) | 3 (75.0%) |
| Black / African American | N | 2 | 3 | 2 |
| | Success[a] | 1 (50.0%) | 1 (33.3%) | 1 (50.0%) |
| | Failure[b] | 1 (50.0%) | 2 (66.7%) | 1 (50.0%) |
| Native Hawaiian / Other Pacific Islander | N | 2 | 0 | 1 |
| | Success[a] | 1 (50.0%) | 0 | 0 |
| | Failure[b] | 1 (50.0%) | 0 | 1 (100%) |
| Other | N | 4 | 3 | 2 |
| | Success[a] | 4 (100%) | 0 | 0 |
| | Failure[b] | 0 | 3 (100%) | 2 (100%) |

Source: Listing 16.2.6.1

[a] Success: able to complete the study dental procedure without rescue medication

[b] Failure: unable to complete the study dental procedure without rescue medication, including subjects who discontinued or withdrew after at least one spray of study drug and before completion of the dental procedure.

(Source: NDA 208032 Applicant's table page 62 of Summary of Clinical Efficacy; header row added by reviewer)

**Table 39 Need for Rescue Anesthesia Stratified by Racial Subcategories (Study SR 3-03)**

| | | Subject Count (Percent) | |
|---|---|---|---|
| **Race** | **Anesthetic Response** | **(b) (4) (N=100)** | **Placebo (N=50)** |
| White | N | 64 | 30 |
| | Success[a] | 59 (92.2%) | 10 (33.3%) |
| | Failure[b] | 5 (7.8%) | 20 (66.7%) |
| Asian | N | 16 | 4 |
| | Success[a] | 14 (87.5%) | 0 |
| | Failure[b] | 2 (12.5%) | 4 (100%) |
| Black / African American | N | 16 | 14 |
| | Success[a] | 11 (68.8%) | 4 (28.6%) |
| | Failure[b] | 5 (31.3%) | 10 (71.4%) |
| Other | N | 4 | 2 |
| | Success[a] | 4 (100%) | 0 |

| | | | |
|---|---|---|---|
| | Failure[b] | 0 | 2 (100%) |

Source: Listing 16.2.6.1
[a] Success: able to complete the study dental procedure without rescue medication
[b] Failure: unable to complete the study dental procedure without rescue medication, including subjects who discontinued or withdrew after at least one spray of study drug and before completion of the dental procedure.
(Source: NDA 208032 Applicant's table page 63 of Summary of Clinical Efficacy)

**Table 40 Anesthetic Success Rate Stratified by Ethnicity (mITT): Pivotal Study SR 3-02**

| | | | Patient Count (Percent) | | | |
|---|---|---|---|---|---|---|
| **Stratified by** | **Category** | **Anesthetic Response** | **(b) (4) (N=44)** | **TET (N=44)** | **PBO (N=22)** | ***P*-Value*** |
| Ethnicity | Hispanic or Latino | N | 3 | 2 | 1 | < 0.0001 |
| | | Success | 2 (66.7%) | 0 | 0 | |
| | | Failure | 1 (33.3%) | 2 (100.0%) | 1 (100.0%) | |
| | Not Hispanic or Latino | N | 41 | 42 | 21 | |
| | | Success | 35 (85.4%) | 12 (28.6%) | 6 (28.6%) | |
| | | Failure | 6 (14.6%) | 30 (71.4%) | 15 (71.4%) | |

Source: SR 3-02 Individual Study Report Module 5.3.5.1
TET: Tetracaine alone; PBO: Placebo
* Stratified Cochran-Mantel-Haenszel Test.
Homogeneity Across Ethnicity Strata P-Values 0.61 ( (b) (4) vs. Tetracaine) and 0.71 ( (b) (4) vs. Placebo).
(Source: NDA 208032 Applicant's table page 65 of Summary of Clinical Efficacy)

**Table 41 Anesthetic Success Rate Stratified by Ethnicity (mITT): Pivotal Study SR 3-03**

| | Anesthetic Success Rate | | | | |
|---|---|---|---|---|---|
| | Kovanaze (N=100) | | Placebo (N=50) | | |
| Ethnicity | N | Count (%) | N | Count (%) | *P*-value[a] |
| Hispanic/Latino | 12 | 11 (91.7%) | 7 | 0 (0%) | <0.0001 |
| Not Hispanic/ not Latino | 88 | 77 (87.5%) | 43 | 14 (32.6%) | |

[a]Stratified by Cochran-Mantel-Haenszel test
(Source: NDA 208032 Reviewer-generated table derived from Applicant's table page 69 of SR 3-03 Clinical Study Report

6.1.7.2 Subgroup analysis for SR 3-04 (pediatric dental patients)

*6.1.7.2.1 Subgroup analysis for SR 3-04 (pediatric dental patients) by age*

(b) (4)

**Table 42 Success Rates by Age Group (mITT): Pivotal Study SR 3-04**

| Successful Anesthetic Response by Age Strata N (%) | (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|
| (b) (4) | | | | |

Source: SR 3-04 Individual Study Report Module 5.3.5.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across age group strata P = 0.15.
PBO: Placebo; CMH: Cochran-Mantel-Haenszel
(Source: NDA 208032 Applicant's table page 57 of Summary of Clinical Efficacy)

(b) (4)

*6.1.7.2.2 Subgroup analysis for SR 3-04 (pediatric dental patients) by tooth age, gender, and ethnicity*

In pediatric dental patients in SR 3-04, the efficacy of Kovanaze does not appear to be substantially effected by gender or ethnicity. The sample size was too small to detect a difference in pediatric efficacy based on race. Below are tables that demonstrate success rates of Kovanaze in SR 3-04 by tooth age, gender, ethnicity, and race. Of note, success with primary teeth compared to success with permanent teeth was confounded by subject age and the dose received.

**Table 43 Success Rates by Tooth Age, Gender, and Ethnicity (SR 3-04)**

| Strata | (b) (4) (N = 60) | PBO (N = 30) |
|---|---|---|
| **Tooth Age** | | |
| Primary (n = 66)* | 31/44 (70.5%) | 13/22 (59.1%) |
| Permanent (n = 24) | 15/16 (93.8%) | 3/8 (37.5%) |
| **Gender** | | |
| Male (n = 46) | 23/32 (71.9%) | 6/14 (42.9%) |
| Female (n = 44)* | 23/28 (82.1%) | 10/16 (62.5%) |
| **Ethnicity** | | |
| Hispanic or Latino (n = 41) | 21/28 (75.0%) | 9/13 (69.2%) |
| Not Hispanic or Latino (n = 49)* | 25/32 (78.1%) | 7/17 (41.2%) |

Source data: Table 14.2.8, Table 14.2.9, Table 14.2.10, and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
(Source: NDA 208032 Applicant's table page 61 of SR 3-04 Clinical Study Report)

*6.1.7.2.3 Subgroup analysis for SR 3-04 (pediatric dental patients) by race*

Below is a table of need for rescue anesthesia by race in SR 3-04. Conclusions about efficacy as it relates to race in the pediatric population cannot be made because of the small number of non-White subjects.

**Table 44 Need for Rescue Anesthesia Stratified by Race (SR 3-04)**

| | | Subject Count (Percent) | |
|---|---|---|---|
| **Race** | **Anesthetic Response** | (b) (4) **(N=60)** | **PBO (N=30)** |
| White | N | 54 | 26 |
| | Success[a] | 42 (77.8%) | 12 (46.2%) |
| | Failure[b] | 12 (12.2%) | 14 (53.8%) |
| Asian | N | 1 | 0 |
| | Success[a] | 0 | 0 |
| | Failure[b] | 1 (100%) | 0 |
| American Indian | N | 0 | 1 |
| | Success[a] | 0 | 1 (100%) |
| | Failure[b] | 0 | 0 |
| Black / African American | N | 3 | 1 |
| | Success[a] | 3 (100%) | 1 (100%) |
| | Failure[b] | 0 | 0 |
| Native Hawaiian/Other Pacific Islander | N | 0 | 1 |
| | Success[a] | 0 | 1 (100%) |
| | Failure[b] | 0 | 0 |
| Other | N | 2 | 1 |
| | Success[a] | 1 (50.0%) | 1 (100%) |
| | Failure[b] | 1 (50.0%) | 0 |

Source: Listing 16.2.6.1

[a] Success: able to complete the study dental procedure without rescue medication

[b] Failure: unable to complete the study dental procedure without rescue medication, including subjects who discontinued or withdrew after at least one spray of study drug and before completion of the dental procedure.

(Source: NDA 208032 Applicant's table page 64 of Summary of Clinical Efficacy; header row added by reviewer)

## 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

St. Renatus has recommended the following dosing for Kovanaze:

| Age Group | Dose | Total Tetracaine HCl Content | Total Oxymetazoline HCl Content |
|---|---|---|---|
| Adults (≥ 18 years old) | 2 sprays (0.2 mL per spray) | 12 mg | 0.2 mg |
| | 1 additional spray (0.2 mL) if adequate anesthesia to initiate the dental procedure has not been achieved 10 minutes after the second spray | 6 mg | 0.1 mg |
| (b) (4) | | | |
| Children (b) (4) weighing ≥ 40 kg) | 2 sprays (0.2 mL per spray) | 12 mg | 0.2 mg |

(Source: NDA 208032 Applicant's table page 1 of Introduction to Summary)

Thirteen clinical trials were performed and submitted in support of this NDA. Throughout these trials, different combinations of oxymetazoline and tetracaine were tested as well as different dosing regimens of the oxymetazoline and tetracaine formulation that is proposed to-be-marketed.

The following clinical trials in adults were used to determine the appropriate dose and dosing regimen:

Trial SR 2-04 demonstrated that unilateral and bilateral Kovanaze dosing is comparable.

Trial SR 2-05 demonstrated that Kovanaze can provide adequate anesthesia for procedures of maxillary teeth 4 through 13 in unilateral doses of one spray (tetracaine 6 mg/ oxymetazoline 0.1 mg) or two sprays (tetracaine 12 mg/ oxymetazoline 0.2 mg).

Trial SR 2-06 was a pharmacokinetic study in adults in which all subjects received three unilateral sprays of Kovanaze with each spray separated by a period of four minutes.

Trial SR 3-02, in which subjects received three sprays of Kovanaze, had an 84.1% anesthetic success rate for Kovanaze compared to placebo success rate of 27.3%.

In trial SR 3-03, subjects received 2 sprays of Kovanaze with an optional third spray of Kovanaze given if the first 2 sprays failed. 98.6% of subjects receiving 2 sprays had anesthetic success, while 59.3% of subjects who received three Kovanaze sprays were able to achieve anesthetic success. The only conclusion that can be made from this is that if Kovanaze does not work after two sprays, there is only a 59.3% chance of success after the third spray.

The following clinical trials in pediatric subjects were used to determine the appropriate dose and dosing regimen:

SR 2-07 was a pharmacokinetic trial in pediatric subjects aged 3 to 17-years-old. Subjects were given Kovanaze unilaterally. In SR 2-03, subjects were divided into three age cohorts: 12-17-years-old who weighed at least 40 kg, 7-11-years-old who weighed at least 20 kg, and 3-6-years-old who weighed at least 12 kg. Below are the results for trial SR 2-03:

**Table 45 Incidence (N, %) of Anesthetic Success Rate by Cohort (mITT Population) (SR 2-03)**

| Anesthetic Assessment Result | Cohort A 12-17 years | | | Cohort B 7-11 years | | Cohort C 3-6 years |
|---|---|---|---|---|---|---|
| | 0.12 mL (n = 8) | 0.2 mL (n = 8) | 0.4 mL (n = 8) | 0.12 mL (n = 8) | 0.2 mL (n = 8) | 0.12 mL (n = 8) |
| Success | 6 (75.0%) | 7 (87.5%) | 8 (100.0%) | (b) (4) | | |
| Failure | 2 (25.0%) | 1 (12.5%) | 0 (0.0%) | | | |

Source data: Table 14.2.1

(Source: NDA 208032 Applicant's table page 58 of SR 2-03 Clinical Study Report; header row added by reviewer)

The above table demonstrates that in SR 2-03, success with Kovanaze was more likely in the (b) (4) with larger doses of Kovanaze (0.4 mL of Kovanaze in Cohort A (b) (4)

In SR 3-04, subjects were assigned to treatment group based on weight, as demonstrated in the table below.

**Table 46 Kovanaze dosing for trial SR 3-04**

| Subject Weight | Treatment Group: Kovacaine Mist or Placebo | Volume per Spray | Number of Sprays | Kovacaine Mist Total Dose | |
|---|---|---|---|---|---|
| | | | | Tetracaine HCl | Oxymetazoline HCl (Oxymetazoline Equivalent) |
| 10 kg to <20 kg | 100 µL | 100 µL | 1 | 3 mg | 0.05 mg (0.044 mg) |
| 20 kg to <40 kg | 200 µL | 100 µL | 2 | 6 mg | 0.1 mg (0.088 mg) |
| 40 kg or more | 400 µL | 200 µL | 2 | 12 mg | 0.2 mg (0.175 mg) |

(Source: NDA 208032 Applicant's table page 25 of SR 3-04 protocol version 1.0)

Below is a table of the success rates in SR 3-04 by dosage cohort. These results demonstrate that success relative to placebo was significantly higher in those subjects weighing greater than 40 kg. (b) (4)

**Table 47 Success Rates by Dosage Cohort (mITT) (SR 3-04)**

| Successful Anesthetic Response by Dosage Strata N (%) | Volume/Spray x Spray no. | (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|---|
| 10 to < 20 kg (n = 24) | [redacted] | | | (b) (4) | 0.020 |
| 20 to < 40 kg (n = 36)* | | | | | |
| 40 kg or more (n = 30) | 0.2 mL x 2 | 18/20 (90.0%) | 4/10 (40.0%) | 0.0072 | |

Source data: Table 14.2.2 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across dosage strata p = 0.17.
(Source: NDA 208032 Applicant's table page 56 of SR 3-04 Clinical Study Report)

After completion of the trial, in order to fulfill one of the secondary endpoints, results were analyzed by age. (b) (4) [redacted]

**Table 48 Success Rates by Age Group (mITT) (SR 3-04)**

| Successful Anesthetic Response by Age Strata N (%) | (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|
| 3 to 5 years (n = 31) | [redacted] | | (b) (4) | 0.046 |
| 6 to 11 years (n = 38)* | | | | |
| 12 to 17 years (n = 21) | 15/16 (93.8%) | 2/5 (40.0%) | 0.028 | |

Source data: Table 14.2.3 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of (b) (4) and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across age group strata p = 0.15.
(Source: NDA 208032 Applicant's table page 57 of SR 3-04 Clinical Study Report)

Because Kovanaze was demonstrated to be efficacious in adults and in pediatric subjects weighing 40 kg or more with doses administered in clinical trials, it will be recommended for approval in this group with doses identical to those used in clinical trials.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Onset and duration of action of Kovanaze were assessed in trials SR 2-04, SR 3-02 and SR 3-03. In SR 2-04, electronic pulp test (EPT) and Subjective Numbness Assessment

(SNA) were used to attempt to determine the onset and duration of Kovanaze action. In trial SR 3-02, Soft-Tissue Anesthesia Assessment (STAA) was used to evaluate the onset and duration of Kovanaze. For additional details of SR 2-04, see section 9.6.3 of this review. For further details of SR 3-02, see section 5.3.3.2 of this review. For further detail of STAA, see section 9.4.5 of this review.

From the results of EPT in trial SR 2-04, St. Renatus concluded that the onset time for Kovanaze is 3 to 13 minutes and the duration of Kovanaze is 5 to 55 minutes. From the results of SNA in trial SR 2-04, St. Renatus concluded that the onset time for Kovanaze is 3 to 8 minutes after the last spray of Kovanaze and the duration of Kovanaze is 65 to 110 minutes.

Because of problems with trial conduct at one of the SR 3-02 trial sites, St. Renatus performed a post-hoc analysis of STAA for site #2. In this post-hoc analysis of STAA results from site #2, St. Renatus concluded that the mean onset time for Kovanaze is 9.7 minutes after the last dose of Kovanaze and the mean duration of action of Kovanaze is 79.2 minutes.

From the SNA results of trial SR 3-02, St. Renatus concluded that the onset time for Kovanaze is 7 minutes after the last dose of Kovanaze and the duration of action of Kovanaze is 45 to 60 minutes.

A table of the onset and duration of Kovanaze as assessed by EPT, SNA, and STAA is below.

**Table 49 Observed Onset and Duration from the Secondary Assessments in Studies SR 2-04 and SR 3-02**

| Observation | Study SR 2-04 | | Study SR 3-02 | |
|---|---|---|---|---|
| | EPT | SNA | STAA | SNA |
| Onset range (min) | 3-13 | 3-8 | 6-37<br>Mean: 9.7 | 7 |
| Duration range (min) | 5-55 | 65-110 | 16-107<br>Mean: 79.2 | 45-60 |

EPT: electric pulp test; SNA: subject numbness assessment; STAA: soft tissue anesthesia assessment
(Source: NDA 208032 Applicant's table page 76 of Summary of Clinical Efficacy)

As is appropriate, the proposed package insert seeks to make claims about the (b) (4) duration of Kovanaze as they pertain to dental procedures in patients.

The proposed package insert states:

> Wait 10 minutes after administration of KOVANAZE to perform a test drill to confirm that the tooth involved is anesthetized. A patient may not experience the same sensations of numbness or tingling of the lips and cheeks associated with injectable dental anesthetics.

(Source: NDA 208032 applicant's proposed package insert June 2016)

The implication that 10 minutes may be an adequate time for onset of Kovanaze, but that practitioners should perform a check to assess the adequacy of anesthesia, is supported by clinical trials SR 3-02 and SR 3-03 in which most subjects were able to have the dental procedure started at 7 and 11 minutes after the last spray of Kovanaze. Below is a table demonstrating the onset and duration of Kovanaze in clinical trials.

Unfortunately, the results in the below table that pertain to the duration of the procedure may be misleading for two reasons:

1. The Applicant states that in SR 3-03, the start time "is confounded by the fact that a third spray is given instead of waiting additional time like in Study SR 3-02." (Source: NDA 208032 page 76 of Summary of Clinical Efficacy) For this reason, the duration of procedure was only analyzed for SR 3-02.

2. The duration of the procedure for SR 3-02 as it appears in the table below is only for those who successfully completed the dental procedure without need for rescue medication.

**Table 50 Onset and Duration Times in Studies SR 3-02 and SR 3-03**

| Observation | Study SR 3-02 | Study SR 3-03 |
|---|---|---|
| Start time after last spray [a,b] | 7 min (83.8%)<br>12 min (16.2%) | 11 min (81.8%)<br>21 min (18.2%) |
| Duration of procedure | 4-43 min | 7-48 min |

[a] For Study SR 3-02, The dental procedure started at either T15 or T20, 7 minutes and 11 minutes after the last spray respectively. The results display the percentage that started at each time point.
[b] For Study SR 3-03, for patients who were able to start after two sprays, the procedure began at T15, 11 minutes after the last spray. For patients who were able to start after three sprays, the procedure began at T25, 21 minutes after last spray. The results display the percentage that started at each time point.

(Source: NDA 208032 Applicant's table page 76 of Summary of Clinical Efficacy)

In the proposed package insert, St. Renatus would like to include a statement that:

(b) (4)

(Source: NDA 208032 applicant's proposed package insert revised June 2016)

(b) (4)

The mean time for duration

of procedure in those who successfully completed the dental procedure without need for rescue medication in SR 3-02 was 15.24 minutes. (b) (4) I propose the following language pertaining to SR 3-02 to be in the proposed package insert:

> the mean duration of a dental procedure successfully completed with KOVANAZE was 15 minutes, although one successfully completed dental procedure was as long as 43 minutes.

## 6.1.10 Additional Efficacy Issues/Analyses

### 6.1.10.1 SR 2-01

Trial SR 2-01 took place in 45 adult dental patients having an amalgam or composite restoration of one tooth of the maxilla (not a second or third molar). Subjects were randomized 2:1 to Kovanaze with sham injection or 2% Lidocaine with epinephrine injection with isotonic saline spray (placebo).

Treatment success was the ability to complete the dental procedure without rescue medication. In this trial, Kovanaze had a success rate of 83.3% and lidocaine injection had a success rate of 93.3%. Below is a table summarizing treatment success.

**Table 51 Summary of Treatment Success (Trial SR 2-01)**

| Need for Rescue Medication | (b) (4) | Lidocaine Injection |
|---|---|---|
| Intent-to-treat analysis, N | 30 | 15 |
| No | 25 (83.3%) | 14 (93.3%) |
| Yes | 5 (16.7%) | 1 (6.7%) |
| Post hoc per-protocol analysis, N | 25* | Same as above |
| No | 22 (88.0%) | |
| Yes | 3 (12.0%) | |

* Subjects 0001, 0007, 0011, 0016, and 0020 were excluded due to protocol deviations.

(Source: NDA 208032 page 30 of SR 2-01 Clinical Study Report)

### 6.1.10.2 Spray pattern and variation in droplet size

Some batches used in clinical trials with Kovanaze had variation in droplet size distribution, while other batches had variation in spray pattern parameter. Kovanaze batch 804007, used in trial SR 2-01, was the only Kovanaze batch used in Phase 2 and 3 clinical trials with Kovanaze that did not demonstrate variation in droplet size distribution or spray pattern parameter. Of those batches that displayed variation in droplet size distribution or spray pattern parameter, no batches of Kovanaze had variation in both droplet size distribution and spray pattern parameter.

As an estimate of whether or not variation in droplet size distribution or spray pattern parameter affected the efficacy of a batch of Kovanaze, anesthetic success with Kovanaze batch 804007 (which did not demonstrate variation in droplet size or spray pattern) in SR 2-01 was compared to anesthetic success with Kovanaze for pivotal studies SR 3-02 and SR 3-03. Batch 006775, which had variation in droplet size, was used in SR 3-02. Batch 200093, which had variation in spray pattern, was used in SR 3-03. The proportion of success in those receiving Kovanaze in the ITT population in SR 2-01 was 83.3%. The proportion of success in those receiving Kovanaze in the mITT population in SR 3-02 was 84.1%. The proportion of success in those receiving Kovanaze in the mITT population in SR 3-03 was 88%.

There is insufficient evidence to draw a definitive conclusion about the impact of variation in droplet size distribution or spray pattern parameter between batches. However, preliminarily, there does not appear to be a decrease in efficacy related to variation in droplet size distribution or spray pattern parameter.

6.1.10.3 Success by Target Tooth

The Applicant performed an exploratory analysis on Phase 3 trials of success pf Kovanaze by target tooth. Below is a table of results by individual tooth in SR 3-02 and SR 3-03. As demonstrated by the table, the largest percentage of successes appears to be connected to teeth 5 through 12.

**Table 52 Analysis of Individual Tooth Results in Phase 3 (SR 3-02 and SR 3-03)**

| | Tooth No. | Study SR 3-02: 3x0.2 mL Unilateral | | | Study SR 3-03: 2 or 3x0.2 mL Unilateral | | | Both 3-02 and 3-03 |
|---|---|---|---|---|---|---|---|---|
| | | No. Success | No. Failure | *% Success* | No. Success | No. Failure | *% Success* | *% Success* |
| Right Side | **4** | 5 | 1 | *83* | 10 | 5 | *67* | *71* |
| | **5** | 6 | 1 | *86* | 11 | 1 | *92* | *89* |
| | **6** | 3 | | *100* | 5 | | *100* | *100* |
| | **7** | 3 | | *100* | 13 | | *100* | *100* |
| | **8** | 2 | | *100* | 16 | | *100* | *100* |
| Left Side | **9** | 3 | | *100* | 7 | 1 | *88* | *91* |
| | **10** | 5 | | *100* | 4 | 1 | *80* | *90* |
| | **11** | 1 | | *100* | 6 | | *100* | *100* |
| | **12** | 4 | | *100* | 10 | | *100* | *100* |
| | **13** | 5 | 5 | *50* | 6 | 4 | *60* | *55* |
| | **Total** | 37 | 7 | *84* | 88 | 12 | *88* | *87* |
| | | | | | | | | |
| Both Sides | **6-11** | 17 | 0 | *100* | 51 | 2 | *96* | *97* |
| | **5&12** | 10 | 1 | *91* | 21 | 1 | *95* | *94* |

| | Tooth No. | Study SR 3-02: 3x0.2 mL Unilateral | | | Study SR 3-03: 2 or 3x0.2 mL Unilateral | | | Both 3-02 and 3-03 |
|---|---|---|---|---|---|---|---|---|
| | | No. Success | No. Failure | *% Success* | No. Success | No. Failure | *% Success* | *% Success* |
| | **4&13** | 10 | 6 | *63* | 16 | 9 | *64* | *63* |
| | **Total** | 37 | 7 | *84* | 88 | 12 | *88* | *87* |

Source: SR 3-02 and SR 3-03 Individual Study Reports Module 5.3.5.1
(Source: NDA 208032 Applicant's table page 52 of Summary of Clinical Efficacy; header row added by reviewer)

Below is a table of results by individual tooth in SR 3-04. As demonstrated by the table, the largest percentage of successes appears to be connected to anterior teeth.

**Table 53 Success Rates by Tooth Location (mITT) (SR 3-04)**

| **Successful Anesthetic Response by Tooth Location Strata** N (%) | (b) (4) **(N = 60)** | **PBO (N = 30)** | **One-Sided Fischer's Exact Test P-Value** | **Stratified CMH P-Value**** |
|---|---|---|---|---|
| Anterior Teeth: C to H and # 6 to 11 (n = 25) | 17/18 (94.4%) | 5/7 (71.4%) | 0.18 | 0.034 |
| Premolar Teeth: A, B, I, J, and # 4, 5, 12, 13 (n = 65)* | 29/42 (69.0%) | 11/23 (47.8%) | 0.079 | |

Source data: Table 14.2.4 and Listing 16.2.6.1
* Includes Patient 5-123 as a treatment failure. Patient withdrew after one spray of (b) (4)
** Breslow-Day test of homogeneity across tooth location strata p = 0.46.
(Source: NDA 208032 Applicant's table page 58 of SR 3-04 Clinical Study Report)

# 7 Review of Safety

## ***Safety Summary***

Four hundred forty-four adult and pediatric subjects received at least one dose of Kovanaze. Among the most common adverse events in subjects who received Kovanaze in the Integrated Safety Database are rhinorrhea, nasal congestion, nasal discomfort, increased lacrimation, headache, and sneezing. While the occurrence of these adverse events was frequent, only nasal congestion, nasal discomfort, and sneezing were ever assessed as being severe. See section 7.3.4.1 for details on severe adverse events. More troublesome adverse events with Kovanaze that will be mentioned as warnings in the product package insert include epistaxis and dysphagia.

There were no deaths in any of the clinical trials submitted to support this NDA, and there were no serious adverse events (SAEs) in any subjects who received Kovanaze.

Among other things, this review of safety addresses the risk: benefit profile of receiving two sprays of Kovanaze compared to three sprays of Kovanaze. This is described more in section 7.2.2 of this review and concludes that if two sprays of Kovanaze are inadequate, adult patients may benefit from a third spray of Kovanaze.

## 7.1 Methods

Thirteen clinical trials were conducted in support of Kovanaze. Eleven of these clinical trials were pooled in a safety database for Kovanaze. For information on the conduct of these clinical trials, see section 5.0 of this review.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Trials conducted to evaluate the safety of Kovanaze are summarized in section 5.1 of this review.

### 7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 15.0.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The submitted safety database is comprised of safety data from 11 clinical trials conducted by St. Renatus: SR 2-01, SR 2-02, SR 2-03, SR 2-04, SR 2-05, SR 2-06, SR 2-07, SR 3-01, SR 3-02, SR 3-03, and SR 3-04.

The Integrated Summary of Safety (ISS) tables that were submitted by the Applicant represent the data from those 11 clinical trials conducted by St. Renatus. Two Phase 1 trials are not included in the submitted safety database. Subjects in this database received varying doses of Kovanaze or a comparator (placebo, lidocaine, or tetracaine spray alone). Adult and pediatric patients and volunteers are included in the Integrated Safety Database. According to the Applicant, the Integrated Safety Database included 444 individuals who were treated with Kovanaze with 526 Kovanaze exposures. This difference in the number of individuals (444) and the number of exposures (526) is due to studies SR 2-02 and SR 2-04 being crossover studies. The Applicant writes that “Safety data for subjects in crossover studies are analyzed for each of the individual dosing regimens administered.” (Source: NDA 208032 page 16 of Summary of Clinical Safety)

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The formulation of Kovanaze that is to be marketed contains tetracaine 6 mg and oxymetazoline 0.1 mg in every 0.2 mL spray. Below is the proposed dosing of Kovanaze from the proposed Kovanaze package insert:

| Age Group | Dose |
|---|---|
| Adults (≥ 18 years old) | 2 sprays (0.2 mL per spray), 4-5 minutes apart |
| | 1 additional spray (0.2 mL) if adequate anesthesia has not been achieved 10 minutes after the second spray |
| Children (b) (4), weighing ≥ 40 kg) | 2 sprays (0.2 mL per spray), 4 minutes apart |
| (b) (4) | |

(Source: NDA 208032 proposed package insert version revised 8/2015)

Below is a table of clinical trials with differing oxymetazoline/ tetracaine formulations.

**Table 54 Summary of Highest Kovanaze Doses Administered by Study Protocol**

| Study | Age Group | Population | Number of subjects in trial | Number of subjects exposed to a given dose of tetracaine (mg)/ oxymetazoline (mg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 3-3.6/ 0.05-0.06 | 6 /0.1 | 9 /0.15 | 12/0.2 | 18 /0.3 | 36/0.6 |
| **AP 1-02** | **adult** | **volunteer** | 23 | 0 | 0 | 10 | 5 | 5 | 0 |
| **SR 2-01** | **adult** | **patient** | 45 | 0 | 0 | 0 | 0 | 30 | 0 |
| **SR 2-02*** | **adult** | **volunteer** | 12 | 0 | 0 | 0 | 0 | 0 | 12 |
| **SR 2-03** | **pediatric** | **patient** | 48 | 24 | 16 | 0 | 8 | 0 | 0 |
| **SR 2-04*** | **adult** | **volunteer** | 48 | 0 | 0 | 2 | 0 | 46 | 0 |
| **SR 2-05** | **adult** | **patient** | 30 | 0 | 10 | 0 | 20 | 0 | 0 |
| **SR 2-06** | **adult** | **volunteer** | 24 | 0 | 0 | 0 | 0 | 24 | 0 |
| **SR 2-07** | **pediatric** | **volunteer** | 18 | 3 | 9 | 0 | 6 | 0 | 0 |
| **SR 3-01** | **adult** | **patient** | 26 | 0 | 0 | 0 | 0 | 10 | 0 |
| **SR 3-02** | **adult** | **patient** | 110 | 0 | 0 | 0 | 0 | 44 | 0 |
| **SR 3-03** | **adult** | **patient** | 150 | 0 | 0 | 0 | 73 | 27 | 0 |
| **SR 3-04** | **pediatric** | **patient** | 90 | 16 | 24 | 0 | 20 | 0 | 0 |
| **Total** | | | 704 | 43 | 59 | 12 | 132 | 186 | 12 |

*SR 2-02 and SR 2-04 were both crossover studies and the only the highest dose received is reported. In SR 2-02, all 12 subjects received both the 18/0.3 dose and the 36/0.6 dose, separated by a wash-out period. In SR 2-04, 46 subjects received the 18/0.3 bilateral dose, while 47 subjects also received the 9/0.15 left naris dose, 45 subjects received the 9/0.15 right naris dose after wash-out periods between each dose.

(Source: From NDA 208032 Applicant's table page 2 of Response to FDA Information Request received December 7, 2015; table modified by clinical reviewer to remove trial AP 1-01)

The Applicant also states:

> "198 adult subjects received the maximum to-be-marketed dose (i.e., 18 mg tetracaine/ 0.3 mg oxymetazoline). Note, in the table provided… the column only shows 186 subjects receiving the18/0.3 dose; this is because in the cross-over study SR 2-02, 12 subjects received both the 18/0.3 and 36/0.6 dose, and therefore, only the highest dose received (i.e., 36/0.6 mg) is shown... Further, the pooled dataset for the ISS does not include either AP 1-01 or AP 1-02, and therefore, in the ISS analysis only 193 subjects received the 18 mg tetracaine/ 0.3 mg oxymetazoline dose. (AP 1-01 and 1-02 utilized slightly different formulations of the investigational product, and therefore, their results were reported only as individual studies and were not compiled within the ISS)."

(Source: NDA 208032 page 1 of Response to FDA Information Request received December 7, 2015)

Therefore, in the ISS analysis, 193 adults received the to-be-marketed Kovanaze formulation of 18 mg tetracaine/ 0.3 mg oxymetazoline. Twelve adults received greater than the to-be-marketed Kovanaze formulation (36/0.6). Thirty-four pediatric subjects received the Applicant's proposed maximum to-be-marketed formulation of Kovanaze for pediatric subjects.

Below is an excerpt from the EOP2 meeting minutes (meeting date March 3, 2011):

> *Question 13*
> *The total planned safety database for the product is a minimum of 305 subjects with 239 to receive the maximum to be marketed dose (and with 12 of these 239 receiving twice the maximum dose). The source of these exposures is: 10 healthy subjects in AP 1-02 (5 of whom received the highest to-be-marketed dose); 10 healthy subjects in AP 1-02 who received a half "ipsilateral" dose; 30 dental patients in SR 2-01 (all receiving maximum dose); 12 healthy volunteers in SR 2-02 (receiving twice the maximum dose); 192 adult dental patients; 96 in Phase 3 studies (across 2 studies and all receiving maximum dose); and a minimum of 51 pediatric dental patients (across 2 studies). Does the Division confirm that the size of this safety database is adequate to support marketing approval as was agreed in the pre-IND meeting June 6, 2005?*
>
> **FDA Response**
> **A safety database this size could be adequate, given the widespread use of these products for many years. However, should a safety signal be noted in your database, additional information may be required to adequately characterize the safety profile of** (b) (4)**.**
> (Source: IND 070868 Meeting Minutes for EOP2 meeting dated March 3, 2011. meeting minutes finalized April 1, 2011.)

St. Renatus has fulfilled their obligation for exposure of subjects to Kovanaze in clinical trials.

According to the Applicant, demographic characteristics in the Integrated Safety Database were mostly balanced across all treatment groups, and, to some extent, I agree. However, there were more female dental patients than male dental patients who received Kovanaze in clinical trials and subjects were mostly White. In healthy volunteers who received Kovanaze, there was a slightly higher percentage of males who received Kovanaze compared to females. Healthy volunteers were mostly White. Below are demographic tables submitted by the Applicant.

**Table 55 Demographic Profile by Extent of Exposure -- Dental Patients**

| Demographic Variable | Tet/Oxy 18/0.3 mg (N=111) | Tet/Oxy 12/0.2 mg (N=121) | Tet/Oxy 6/0.1 mg (N=50) | Tet/Oxy 3-3.6/ 0.05-0.06 mg (N=40) | Total [(b) (4)] Exposures (N=322) | Active Comparator (N=69) | Placebo (N=108) |
|---|---|---|---|---|---|---|---|
| Gender | | | | | | | |
| Male | 41 (36.9%) | 55 (45.5%) | 17 (34.0%) | 22 (55.0%) | 135 (41.9%) | 42 (60.9%) | 51 (47.2%) |
| Female | 70 (63.1%) | 66 (54.5%) | 33 (66.0%) | 18 (45.0%) | 187 (58.1%) | 27 (39.1%) | 57 (52.8%) |
| Race | | | | | | | |
| White | 87 (78.4%) | 91 (75.2%) | 44 (88.0%) | 36 (90.0%) | 258 (80.1%) | 57 (82.6%) | 75 (69.4%) |
| Black | 10 (9.0%) | 11 (9.1%) | 2 (4.0%) | 0 (0.0%) | 23 (7.1%) | 4 (5.8%) | 17 (15.7%) |
| Asian | 6 (5.4%) | 14 (11.6%) | 0 (0.0%) | 0 (0.0%) | 20 (6.2%) | 4 (5.8%) | 8 (7.4%) |
| Other | 8 (7.2%) | 5 (4.1%) | 4 (8.0%) | 4 (10.0%) | 21 (6.5%) | 4 (5.8%) | 8 (7.4%) |
| Age - Years | | | | | | | |
| 3-5 | 0 (0.0%) | 0 (0.0%) | 5 (10.0%) | 20 (50.0%) | 25 (7.8%) | 0 (0.0%) | 10 (9.3%) |
| 6-11 | 0 (0.0%) | 4 (3.3%) | 27 (54.0%) | 12 (30.0%) | 43 (13.4%) | 0 (0.0%) | 15 (13.9%) |
| 12-17 | 0 (0.0%) | 24 (19.8%) | 8 (16.0%) | 8 (20.0%) | 40 (12.4%) | 0 (0.0%) | 5 (4.6%) |
| 18-50 | 91 (82.0%) | 53 (43.8%) | 4 (8.0%) | 0 (0.0%) | 148 (46.0%) | 59 (85.5%) | 55 (50.9%) |
| 50+ | 20 (18.0%) | 40 (33.1%) | 6 (12.0%) | 0 (0.0%) | 66 (20.5%) | 10 (14.5%) | 23 (21.3%) |
| Weight - categories | | | | | | | |
| 10 kg to < 20 kg | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 20 (50.0%) | 20 (6.2%) | 0 (0.0%) | 8 (7.4%) |
| 20 kg to < 40 kg | 0 (0.0%) | 0 (0.0%) | 32 (64.0%) | 8 (20.0%) | 40 (12.4%) | 0 (0.0%) | 12 (11.1%) |
| 40 kg or more | 111 (100.0%) | 111 (91.7%) | 18 (36.0%) | 12 (30.0%) | 252 (78.3%) | 69 (100.0%) | 88 (81.5%) |
| Missing | 0 (0.0%) | 10 (8.3%) | 0 (0.0%) | 0 (0.0%) | 10 (3.1%) | 0 (0.0%) | 0 (0.0%) |

Source data: ISS Table 1.1

[a] Four patients in SR 2-05 erroneously received twice their assigned dose (Tet/Oxy 24/0.4 mg instead of 12/0.2 mg). These subjects are counted within the treatment group to which they were originally assigned.

[b] Active comparator group is a combination of the lidocaine group (SR 2-01) and tetracaine only groups (SR 3-01 and SR 3-02)

(Source: NDA 208032 Applicant's table page 21 of Summary of Clinical Safety)

**Table 56 Subject Demographics -- Healthy Volunteers**

| Demographic Variable | Tet/Oxy 36/0.6 mg (N=12) | Tet/Oxy 18/0.3 mg (N=82)* | Tet/Oxy 12/0.2 mg (N=6) | Tet/Oxy 9/0.15 mg (N=92)* | Tet/Oxy 6/0.1 mg (N=9) | Tet/Oxy 3/0.05 mg (N=3) | Total (b) (4) Exposures (N=204) | Placebo (N=47)* |
|---|---|---|---|---|---|---|---|---|
| Gender | | | | | | | | |
| Male | 6 (50.0%) | 44 (53.7%) | 2 (33.3%) | 50 (54.3%) | 6 (66.7%) | 1 (33.3%) | 109 (53.4%) | 25 (53.2%) |
| Female | 6 (50.0%) | 38 (46.3%) | 4 (66.7%) | 42 (45.7%) | 3 (33.3%) | 2 (66.7%) | 95 (46.6%) | 22 (46.8%) |
| Race | | | | | | | | |
| White | 10 (83.3%) | 73 (89.0%) | 5 (83.3%) | 87 (94.6%) | 5 (55.6%) | 2 (66.7%) | 182 (89.2%) | 44 (93.6%) |
| Black | 1 (8.3%) | 2 (2.4%) | 1 (16.7%) | 2 (2.2%) | 4 (44.4%) | 1 (33.3%) | 11 (5.4%) | 1 (2.1%) |
| Asian | 1 (8.3%) | 2 (2.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (1.5%) | 0 (0.0%) |
| Other | 0 (0.0%) | 5 (6.1%) | 0 (0.0%) | 3 (3.3%) | 0 (0.0%) | 0 (0.0%) | 8 (3.9%) | 2 (4.3%) |
| Age - Years | | | | | | | | |
| 3-5 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (22.2%) | 3 (100.0%) | 5 (2.5%) | 0 (0.0%) |
| 6-11 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 7 (77.8%) | 0 (0.0%) | 7 (3.4%) | 0 (0.0%) |
| 12-17 | 0 (0.0%) | 0 (0.0%) | 6 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 6 (2.9%) | 0 (0.0%) |
| 18-50 | 12 (100.0%) | 82 (100.0%) | 0 (0.0%) | 92 (100.0%) | 0 (0.0%) | 0 (0.0%) | 186 (91.2%) | 47 (100.0%) |
| 50+ | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Weight - categories | | | | | | | | |
| 10 kg to < 20 kg | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (100.0%) | 3 (1.5%) | 0 (0.0%) |
| 20 kg to < 40 kg | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 9 (100.0%) | 0 (0.0%) | 9 (4.4%) | 0 (0.0%) |
| 40 kg or more | 12 (100.0%) | 82 (100.0%) | 6 (100.0%) | 92 (100.0%) | 0 (0.0%) | 0 (0.0%) | 192 (94.1%) | 47 (100.0%) |

Source data: ISS Table 1.2

*48 subjects enrolled in SR 2-04 and received 4 distinct doses at 1-3 week intervals: Tet/Oxy 18 mg/ 0.3 mg (bilateral); Tet/Oxy 9 mg/0.15 mg (unilateral, right); Tet/Oxy 9 mg/0.15 mg (unilateral, left); and Placebo. Subjects are counted for each dose received.

[b] Twelve patients enrolled in SR 2-02 and received 2 distinct doses of (b) (4) (Tet/Oxy: 18 mg / 0.3 mg and 36 mg/ 0.6 mg) at least one week apart. Subjects are counted for each dose received.

(Source: NDA 208032 Applicant's table page 23 of Summary of Clinical Safety)

Below are tables of concomitant medications by preferred term and Anatomical Therapeutic Chemical (ATC) classification taken by at least 3% of subjects receiving Kovanaze.

**Table 57 Common Concomitant Medications in Dental Patients**

| ATC Classification / Preferred Term [a] | Total (b) (4) Exposures (N=322) | Active Comparator (N=69) | Placebo (N=108) |
|---|---|---|---|
| Amides | 58 (18.0%) | 41 (59.4%) | 72 (66.7%) |
| Articaine HCl / Epinephrine | 29 (9.0%) | 40 (58.0%) | 57 (52.8%) |
| Propionic Acid Derivatives | 21 (6.5%) | 8 (11.6%) | 4 (3.7%) |
| Ibuprofen | 17 (5.3%) | 8 (11.6%) | 3 (2.8%) |
| HMG CoA Reductase Inhibitors | 20 (6.2%) | 2 (2.9%) | 7 (6.5%) |
| Simvastatin | 11 (3.4%) | 0 | 3 (2.8%) |
| Multivitamins | 15 (4.7%) | 0 | 2 (1.9%) |
| Vitamins (nos) | 15 (4.7%) | 0 | 2 (1.9%) |
| Anilides | 14 (4.3%) | 4 (5.8%) | 3 (2.8%) |
| Paracetamol | 11 (3.4%) | 3 (4.3%) | 1 (0.9%) |
| Other Antihistamines (systemic) | 14 (4.3%) | 0 | 5 (4.6%) |
| Loratadine | 7 (2.2%) | 0 | 3 (2.8%) |
| Aminoalkyl Ethers | 12 (3.7%) | 1 (1.4%) | 1 (0.9%) |
| Diphenhydramine HCl | 12 (3.7%) | 1 (1.4%) | 1 (0.9%) |
| Progestogens and Estrogens (fixed combinations) | 12 (3.7%) | 5 (7.2%) | 7 (6.5%) |
| Drospirenone/Ethinylestradiol | 2 (0.6%) | 0 | 1 (0.9%) |
| Proton Pump Inhibitors | 12 (3.7%) | 3 (4.3%) | 3 (2.8%) |
| Omeprazole | 7 (2.2%) | 1 (1.4%) | 3 (2.8%) |
| ACE Inhibitors | 11 (3.4%) | 1 (1.4%) | 6 (5.6%) |
| Lisinopril | 8 (2.5%) | 0 | 6 (5.6%) |
| Selective Serotonin Reuptake Inhibitors | 10 (3.1%) | 3 (4.3%) | 5 (4.6%) |
| Citalopram | 2 (0.6%) | 0 | 0 |

Source data: ISS Table 7.1
[a] WHODRUG Dictionary version March 2012
(Source: NDA 208032 Applicant's table page 128 of Summary of Clinical Safety)

**Table 58 Common Concomitant Medications in Healthy Volunteers**

| ATC Classification / Preferred Term [a] | Total (b) (4) Exposures (N=204) | Placebo (N=47) |
|---|---|---|
| Multivitamins, combinations | 21 (10.3%) | 4 (8.5%) |
| Ascorbic and other ingredients | 21 (10.3%) | 4 (8.5%) |
| Progestogens and Estrogens (fixed combinations) | 19 (9.3%) | 5 (10.6%) |

| ATC Classification / Preferred Term [a] | Total [(b) (4)] Exposures (N=204) | Placebo (N=47) |
|---|---|---|
| Ethinylestradiol/Norgestimate | 6 (2.9%) | 2 (4.3%) |
| Propionic Acid Derivatives | 11 (5.4%) | 1 (2.1%) |
| Ibuprofen | 11 (5.4%) | 1 (2.1%) |
| Anilides | 8 (3.9%) | 0 |
| Paracetamol | 4 (2.0%) | 0 |
| Progestogens | 8 (3.9%) | 2 (4.3%) |
| Medroxyprogesterone Acetate | 8 (3.9%) | 2 (4.3%) |

Source data: ISS Table 7.2
[a] WHODRUG Dictionary version March 2012
(Source: NDA 208032 Applicant's table page 129 of Summary of Clinical Safety; header row added by reviewer)

An evaluation of adverse events by common concomitant medications was undertaken and explained in more detail in section 7.5.5 of this review.

In trial SR 3-03, the Applicant planned to analyze the success rates of Kovanaze for those subjects taking intranasal anti-allergy medications. In this trial, two subjects receiving Kovanaze and three subjects receiving placebo were using intranasal medications. Below is a chart describing subjects who received Kovanaze and were also taking a concomitant intranasal medication and whether or not treatment with Kovanaze was successful.

**Table 59 Subjects in the Kovanaze treatment group on intranasal anti-allergy medication**

| Subject | Concomitant intranasal medication | Treatment Success |
|---|---|---|
| 06-072 | Flonase® | Treatment was successful after 2 Kovanaze sprays |
| 07-130 | Saline nasal spray | Treatment was a failure after 3 sprays of Kovanaze |

Unfortunately, the number of subjects on concomitant intranasal allergy medication who received Kovanaze was too small to draw conclusions about the efficacy of Kovanaze in those taking intranasal allergy medications.

### 7.2.2 Explorations for Dose Response

SR 3-03 was a trial in adult dental patients in which the Study Dental Procedure was to commence 15 minutes after the first spray of Kovanaze. If anesthesia was insufficient at that time, after two sprays of Kovanaze had been given, a third spray of Kovanaze was to have been administered. See section 5.3.3.3.3 of this review for further details of trial SR 3-03. Trial SR 3-03 included an analysis of success rates for those receiving two

sprays of Kovanaze compared with three sprays of Kovanaze. Below is an analysis of success rates by number of Kovanaze sprays.

**Table 60 Subgroup Analysis of Success Rates by Number of Sprays (mITT) (SR 3-03)**

| Stratification Stratum | Anesthetic Success Rate | | | |
|---|---|---|---|---|
| | (b) (4) (N = 100) | | PBO (N = 50) | |
| | N | Count (%) | N | Count (%) |
| Number of sprays | | | | |
| 2[a] | 73 | 72 (98.6%) | 17 | 14 (82.4%) |
| 3 | 27 | 16 (59.3%) | 33 | 0 (0.0%) |

Source data: Table 14.2.7
[a] In a few cases for this group, a third spray was not administered if the SDP had been initiated but anesthesia proved to be insufficient, as allowed by the protocol
PBO: placebo
(Source: NDA 208032 Applicant's table page 71 of SR 3-03 Clinical Study Report)

The above findings demonstrate that, of 100 subjects who received Kovanaze in trial SR 3-03, only 72 received two sprays and were considered to be an anesthetic success. Of the subjects who received three sprays of Kovanaze, 16 of 27 subjects (59.3%) were considered to be an anesthetic success. Anesthetic success in this clinical trial was defined as "completion of the Study Dental Procedure without need for rescue anesthetic." (Source: NDA 208032 page 40 of SR 3-03 protocol version 2.0) These results can be interpreted to mean that, if a third spray of Kovanaze is necessary, there is a decreased likelihood of successful completion of the dental procedure without rescue anesthetic compared to if only two sprays of Kovanaze were required. This observation may be reflective of the fact that patients in whom two sprays were not effective were recalcitrant to treatment with Kovanaze.

To examine the risk: benefit profile of a third spray of Kovanaze, the incidence of adverse events in those who received two sprays of Kovanaze was compared with the incidence of adverse events in those who received three sprays of Kovanaze. The incidence of adverse events was not consistently higher in those who received three sprays compared to two sprays. Some individual adverse events had a higher incidence in individuals who received two sprays, while other adverse events had a higher incidence those who received three sprays. For example, the adverse events of bradycardia, hypertension, headache, nasal congestion, and throat irritation all occurred with an increased incidence in those who received three sprays compared with those who received two sprays. The adverse events of increased diastolic blood pressure, dizziness, dysgeusia, nasal discomfort, nasal dryness, oropharyngeal pain, and rhinorrhea occurred with an increased incidence in those who received two sprays of Kovanaze compared with three. Therefore, from a risk: benefit standpoint, if two sprays of Kovanaze fails, a third spray may be worthwhile.

The incidence of adverse events in subjects who received two sprays of Kovanaze compared to subjects who received three sprays of Kovanaze is more thoroughly described in section 7.5.1 of this review.

The Applicant performed trial SR 2-03 as a dose-ranging study in pediatric patients. Subsequently, trial SR 3-04 was a phase 3 efficacy trial in pediatric patients. In SR 3-04, 60 subjects were given Kovanaze doses based on weight. Below is a table of success rates by dosage cohort followed by a table of success rates by age group. The dosing proposed by St. Renatus in their proposed package insert takes [redacted] (b) (4) [redacted]. In SR 3-04, all 21 subjects aged 12-17-years-old in SR 3-04 weighed ≥ 40 kg.

**Table 61 SR 3-04 Success Rates by Dosage Cohort (mITT)**

| Successful Anesthetic Response by Dosage Strata N (%) | Volume/Spray x Spray no. | [redacted] (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|---|
| 10 to < 20 kg (n = 24) | [redacted] (b) (4) | | | | 0.020 |
| 20 to < 40 kg (n = 36)* | | | | | |
| 40 kg or more (n = 30) | 0.2 mL x 2 | 18/20 (90.0%) | 4/10 (40.0%) | 0.0072 | |

Source data: Table 14.2.2 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of [redacted] (b) (4) [redacted] and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across dosage strata p = 0.17.
(Source: NDA 208032 Applicant's table page 56 of SR 3-04 Clinical Study Report)

**Table 62 SR 3-04 Success Rates by Age Group (mITT)**

| Successful Anesthetic Response by Age Strata N (%) | [redacted] (b) (4) (N = 60) | PBO (N = 30) | One-Sided Fischer's Exact Test P-Value | Stratified CMH P-Value** |
|---|---|---|---|---|
| 3 to 5 years (n = 31) | [redacted] (b) (4) | | | 0.046 |
| 6 to 11 years (n = 38)* | | | | |
| 12 to 17 years (n = 21) | 15/16 (93.8%) | 2/5 (40.0%) | 0.028 | |

Source data: Table 14.2.3 and Listing 16.2.6.1
* Includes Patient 5-123, withdrew after one spray of [redacted] (b) (4) [redacted] and no SDP, as treatment failure.
** Breslow-Day test of homogeneity across age group strata p = 0.15.
(Source: NDA 208032 Applicant's table page 57 of SR 3-04 Clinical Study Report)

Four subjects in SR 3-04 were under the age of 12, weighed 40 kg or greater, and were in the Kovanaze treatment group. A table of these subjects is below.

**Table 63 Efficacy of Kovanaze in subjects younger than 12-years-old weighing >40 kg (SR 3-04)**

| Subject | Age (years) | Anesthetic Success (yes/no) |
|---|---|---|
| 5-133 | 7 | no |

| Subject | Age (years) | Anesthetic Success (yes/no) |
|---|---|---|
| 5-126 | 8 | yes |
| 5-101 | 9 | yes |
| 5-140 | 10 | yes |

While the sample size is small, the above table demonstrates a 75% success rate of Kovanaze in subjects younger than 12-years-old, but weighing 40 kg or greater.

### 7.2.3 Special Animal and/or In Vitro Testing

See section 4.3 of this review.

### 7.2.4 Routine Clinical Testing

Safety testing in Phase 3 trials included:

- Vital sign measurements
- Oral and naris exams
- Periapical and/or bitewing radiographs
- Diagnostic radiograph
- Urine pregnancy testing, if applicable

Laboratory testing is discussed in section 7.4.2 of this review.
Vital sign measurements are discussed in section 7.4.3 of this review.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.4 of this review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Section 9.1 of this review contains a summary of the results of the literature review performed by St. Renatus in which adverse events associated with oxymetazoline and tetracaine were identified.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths appear to have occurred in any subjects that received Kovanaze.

### 7.3.2 Nonfatal Serious Adverse Events

Only one subject in clinical trials conducted for this NDA had a serious adverse event (SAE): patient 04-005 in clinical trial SR 3-02.

Patient 04-005
This patient was a 29-year-old male in the tetracaine only treatment group. On January 9, 2013, he was treated for dental caries on tooth #9 and received three sprays of 0.2 mL tetracaine. On January 19, 2013, he experienced severe intensity orbital cellulitis and moderate intensity sinusitis and headache. The investigator determined that these events were "remotely related to the study treatment (tetracaine)." (Source: NDA 208032 page 92 of Applicant's Summary of Clinical Safety) "Remote" is a term designated by the Applicant to describe the relationship of an adverse event to the study drug. (Source: NDA 208032 page 97 of SR 3-02 protocol version 3.0)

### 7.3.3 Dropouts and/or Discontinuations

The Applicant states that no subjects treated with Kovanaze discontinued a trial because of an adverse event. However, two subjects withdrew informed consent from clinical trials: Subject 5-123 in study SR 3-04 and Subject 07-164 in study SR 3-03.

Subject 5-123 is an 8-year-old female who had stinging in her nostril after one spray of study medication.

Subject 07-164 is a 52-year-old male who received placebo and an injection of rescue medication, from which he achieved inadequate pain relief.

### 7.3.4 Significant Adverse Events

The following are considered significant adverse events:

1. Severe adverse events
2. Adverse events leading to trial withdrawal (described in section 7.3.3 of this review)

#### 7.3.4.1 Severe Adverse Events

Twenty-three adverse events in the Integrated Safety Database were coded as severe. Many of the severe adverse events from Kovanaze will be mentioned in the package insert, including oropharyngeal pain, nasal congestion, nasal discomfort, throat irritation, sneezing, rhinalgia, sinus headache, dysgeusia, and nasal dryness. Other severe adverse events that were described in clinical trials with Kovanaze may not be considered adverse events; for example, hypoesthesia oral and hypoesthesia may be considered desired effects of the drug. Dry eye and dry mouth are two severe adverse events that occurred with Kovanaze that will not be included in the package insert because they resolved with no sequelae and they were not experienced by other subjects in clinical trials with Kovanaze. Severe adverse events in clinical trials of Kovanaze are described in the table below:

**Table 64 Severe adverse events in the Integrated Safety Database**

| Trial | Subject | Treatment group | Preferred term | Age (years) | Sex | Action required | Outcome | Relationship to drug per Investigator |
|---|---|---|---|---|---|---|---|---|
| SR 2-04 | 01-030 | Kovanaze | Oropharyngeal pain | 41 | F | None | Resolved, no sequelae | Possible |
| SR 2-04 | 01-033 | Kovanaze | Nasal congestion | 32 | M | None | Resolved, no sequelae | Possible |
| SR 2-04 | 01-045 | Kovanaze | Nasal discomfort | 21 | M | None | Resolved, no sequelae | Probable |
| SR 2-06 | 2-106 | Kovanaze | 1. Hypoesthesia oral<br>2. Hypoesthesia oral | 42 | F | None | Resolved, no sequelae | Probable |
| SR 2-06 | 2-121 | Kovanaze | Hypoesthesia | 27 | M | None | Resolved, no sequelae | Probable |
| SR 3-01 | 2-014 | Tetracaine only | Hypoesthesia | 24 | F | None | Resolved, no sequelae | Possible |
| SR 3-01 | 2-020 | Placebo | Hypoesthesia oral | 51 | M | None | Resolved, no sequelae | Probable |
| SR 3-02 | 4-005 | Tetracaine only | Cellulitis orbital | 29 | M | Hospitalized | Resolved, with sequelae | Remote |
| SR 3-02 | 4-007 | Tetracaine only | Procedural pain | 27 | M | Medication | Resolved, no sequelae | Unrelated |
| SR 3-02 | 4-013 | Kovanaze | Throat irritation | 56 | F | None | Resolved, no sequelae | Probable |
| SR 3-02 | 4-021 | Kovanaze | Sneezing | 28 | M | Medication | Resolved, no sequelae | Probable |
| SR 3-02 | 4-025 | Tetracaine only | Toothache | 25 | F | Medication | Resolved, no sequelae | Unrelated |
| SR 3-02 | 4-027 | Kovanaze | 1. Rhinalgia<br>2. Oropharyngeal pain | 53 | F | None | Resolved, no sequelae | Possible |
| SR 3-02 | 4-109 | Kovanaze | Nasal discomfort | 55 | M | Medication | Resolved, no sequelae | Probable |
| SR 3-03 | 5-035 | Kovanaze | Hypoesthesia oral | 27 | M | None | Resolved, no sequelae | Possible |
| SR 3-03 | 5-051 | Kovanaze | Sinus Headache | 55 | F | Medication | Resolved, no sequelae | Possible |
| SR 3-03 | 6-069 | Kovanaze | Dry mouth | 25 | F | Medication | Resolved, no sequelae | Possible |
| SR 3-03 | 6-072 | Kovanaze | Dysgeusia | 47 | F | None | Resolved, no sequelae | Possible |
| SR 3-03 | 6-080 | Kovanaze | Dry eyes | 47 | F | None | Resolved, no sequelae | Remote |
| SR 3-03 | 6-083 | Kovanaze | Nasal dryness | 23 | F | None | Resolved, no sequelae | Probable |
| SR 3-03 | 7-175 | Kovanaze | Oropharyngeal pain | 50 | F | None | Resolved, no sequelae | Possible |

### 7.3.5 Submission-Specific Primary Safety Concerns

Events of clinical concern in subjects receiving Kovanaze include:

- Dysphagia
- Dizziness
- Epistaxis
- Pharyngeal edema

**Table 65 Potentially Clinically Important AEs**

| SOC / Preferred Term | Total (b) (4) Exposures | Active Comparator | Placebo |
|---|---|---|---|
| **Dental Patients** | (N=322) | (N=69) | (N=108) |
| Dysphagia | 5 (1.6%) | 0 (0.0%) | 0 (0.0%) |
| Dizziness | 7 (2.2%) | 0 (0.0%) | 1 (0.9%) |
| Epistaxis | 9 (2.8%) | 2 (2.9%) | 0 (0.0%) |
| Pharyngeal Oedema | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
| **Healthy Volunteers** | (N=204) [a,b] | (N=0) | (N=47) [a,b] |
| Dysphagia | 10 (4.9%) | - | 0 |
| Dizziness | 5 (2.5%) | - | 0 |
| Epistaxis | 10 (4.9%) | - | 0 |

Source: ISS Tables 2.5 and 2.6

[a] 48 subjects enrolled in SR 2-04 and received 4 distinct doses at 1-3 week intervals: Tet/Oxy 18 mg/ 0.3 mg (bilateral); Tet/Oxy 9 mg/0.15 mg (unilateral, right); Tet/Oxy 9 mg/0.15 mg (unilateral, left); and Placebo. Subjects are counted for each dose received.

[b] 12 patients enrolled in SR 2-02 and received 2 distinct doses of (b) (4) (Tet/Oxy: 18 mg / 0.3 mg and 36 mg/ 0.6 mg) at least one week apart. Subjects are counted for each dose received.

(Source: NDA 208032 Applicant's table page 21 of Clinical Overview)

Dysphagia

Below is a table of subjects from the Integrated Safety Database with a preferred term of dysphagia. This table displays the relationship of dysphagia to Kovanaze as determined by St. Renatus and the relationship to Kovanaze as determined by this reviewer. All subjects with dysphagia received Kovanaze. All instances of dysphagia were mild or moderate and resolved without treatment. The exception was subject 3-044, in which no information is known about the intensity, outcome, or action required. Dysphagia will be included as a WARNING in the package insert for Kovanaze.

**Table 66 Subjects in Integrated Safety Database with dysphagia (preferred term)**

| Subject | Trial | Age/Sex | Kovanaze dose with which AE was associated | Time course/ duration | Relationship to drug per investigator | Relationship to drug per reviewer |
|---|---|---|---|---|---|---|
| 3-022 | SR 2-03 | 15-year-old male | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred two minutes after Kovanaze; lasted one minute | Possibly related | Potentially related |
| 3-044 | SR 2-03 | 14-year-old female | tetracaine 6 mg/ oxymetazoline 0.1mg | * | Probably related | * |
| 01-006 | SR 2-04, visit 1 | 36-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved within one hour | Probably related | Potentially related |
| 01-011 | SR 2-04, visit 3 | 18-year-old male | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved after about two hours | Probably related | Potentially related |
| 01-021 | SR 2-04, visit 3 | 45-year-old female | tetracaine 18mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved within 35 minutes | Probably related | Potentially related |
| 01-023 | SR 2-04, visit 1 | 20-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved on the same day that it occurred | Probably related | Potentially related |
| 01-023 | SR 2-04, visit 3 | 20-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved on the same day that it occurred | Probably related | Potentially related |
| 01-023 | SR 2-04, visit 4 | 20-year-old female | tetracaine 18mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved on the same day that it occurred | Probably related | Potentially related |
| 01-029 | SR 2-04, visit 2 | 25-year-old female | tetracaine 18mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved within one hour | Probably related | Potentially related |
| 01-029 | SR 2-04, visit 3 | 25-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved within one hour | Probably related | Potentially related |
| 01-034 | SR 2-04, visit 3 | 22-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved within three hours | Probably related | Potentially related |
| 01-034 | SR 2-04, visit 4 | 22-year-old female | tetracaine 18mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved within | Probably related | Potentially related |

| Subject | Trial | Age/Sex | Kovanaze dose with which AE was associated | Time course/ duration | Relationship to drug per investigator | Relationship to drug per reviewer |
|---|---|---|---|---|---|---|
| | | | | three hours | | |
| 01-030 | SR 2-05 | 68-year-old male | tetracaine 12 mg/ oxymetazoline 0.2 mg | Duration 27 minutes | Probably related | Potentially related |
| 4-019 | SR 3-02 | 51-year-old female | tetracaine 18mg/ oxymetazoline 0.3 mg | 34 minutes after dose and lasted for one hour | Probably related | Potentially related |
| 5-007 | SR 3-03 | 44-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred on the same day as Kovanaze dose; resolved within 2.5 hours | Possibly related | Potentially related |

Note: Trial SR 2-04 was a crossover trial
*Subject 3-044 was identified from the Comment Log; very little information was submitted

Dizziness

Below is a table of subjects from the Integrated Safety Database with a preferred term of dizziness. This table displays the relationship of dizziness to Kovanaze as determined by St. Renatus and the relationship to Kovanaze as determined by this reviewer. All subjects with dizziness received Kovanaze, except one subject who received placebo. All instances of dizziness with Kovanaze were mild or moderate in intensity and resolved without treatment. The subject with dizziness who received placebo is not included in the table below. Dizziness will be included in the proposed package insert as a common adverse reaction.

**Table 67 Subjects in Integrated Safety Database with dizziness (preferred term)**

| Subject | Trial | Age/Sex | Kovanaze dose with which AE was associated | Time course/ duration | Relationship to drug per investigator | Relationship to drug per reviewer |
|---|---|---|---|---|---|---|
| 01-019 | SR 2-04, visit 2 | 20-year-old female | tetracaine 18mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved after about one hour | Probably related | Potentially related |
| 01-031 | SR 2-04, visit 2 | 23-year-old male | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved within two hours | Unrelated | Potentially related |
| 01-034 | SR 2-04, visit 3 | 22-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred on the same day as Kovanaze dose; resolved on the same day | Remotely related | Potentially related |
| 01-0003; this subject had 2 episodes of dizziness | SR 2-05 | 50.5-year-old female | tetracaine 24 mg/ oxymetazoline 0.4 mg | One episode lasted for a few minutes; the other episode lasted for five hours | Probably related | Potentially related |
| 01-0017 | SR 2-05 | 69.5-year-old male | tetracaine 12 mg/ oxymetazoline 0.2 mg | Lasted for five minutes | Probably related | Potentially related |
| 2-107 | SR 2-06 | 24-year-old female | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved after about 10 hours | Probably related | Potentially related |
| 8-015 | SR 2-07 | 12-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred within one hour of Kovanaze and resolved within one hour | Remotely related | Potentially related |
| 2-022 | SR 3-01 | 22-year-old female | tetracaine 18 mg/ oxymetazoline 0.3 mg; this subject also received rescue anesthesia twice | Occurred on the same day as Kovanaze dose; resolved on the same day | Possibly related | Potentially related |
| 2-056 | SR 3-02 | 42-year-old female | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; resolved within less than one minute | Unrelated | Potentially related |
| 5-051 | SR 3-03 | 55-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred on the same day as Kovanaze dose; resolved after three days | Possibly related | Potentially related |
| 6-072; this subject had 2 AEs with preferred term dizziness | SR 3-03 | 47-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred on the same day as Kovanaze dose; resolved after eight minutes | Possibly related | Potentially related |
| 7-172 | SR 3-03 | 60-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred within 10 minutes; resolved three minutes later | Possibly related | Potentially related |

Note: Trial SR 2-04 was a crossover trial

Epistaxis

Below is a table of subjects from the Integrated Safety Database with a preferred term of epistaxis. This table displays the relationship of epistaxis to Kovanaze as determined by St. Renatus and the relationship to Kovanaze as determined by this reviewer. Nineteen subjects with epistaxis received Kovanaze, and two subjects with epistaxis received active comparator. All episodes of epistaxis with Kovanaze were mild or moderate in intensity and resolved without treatment. The exception was subject 3-008, for whom the intensity, outcome, and action required are unknown. Epistaxis will be including in the proposed package insert for Kovanaze as a WARNING.

**Table 68 Subjects in Integrated Safety Database with epistaxis (preferred term)**

| Subject | Trial | Age/Sex | Kovanaze dose or active comparator with which AE was associated | Time course/ duration | Relationship to drug per investigator | Relationship to drug per reviewer |
|---|---|---|---|---|---|---|
| 01-001 | SR 2-02 | 25-year-old male | tetracaine 36 mg/ oxymetazoline 0.6 mg | About 12 minutes | Probably related | Potentially related |
| 01-005 | SR 2-02 | 38-year-old female | tetracaine 18 mg/ oxymetazoline 0.3 mg | Lasted about five minutes | Probably related | Potentially related |
| 01-008 | SR 2-02 | 27-year-old male | tetracaine 18 mg/ oxymetazoline 0.3 mg | Unknown | Probably related | Potentially related |
| 3-008 | SR 2-03 | 5-year-old male | tetracaine 3.6mg/ oxymetazoline 0.06 mg | Unknown | Probable | *Potentially related |
| 3-038 | SR 2-03 | 13-year-old female | tetracaine 6 mg/ oxymetazoline 0.1 mg | Occurred the day after Kovanaze and resolved within six days | Unrelated | Potentially related |
| 01-003 | SR 2-04, visit 2 | 22-year-old female | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred the day after Kovanaze treatment; resolved after five minutes | Possibly related | Potentially related |
| 01-021 | SR 2-04, visit 3 | 45-year-old female | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred one day after Kovanaze and resolved the same day | Possibly related | Potentially related |
| 01-031 | SR 2-04, visit 2 | 23-year-old male | tetracaine 9 mg/ oxymetazoline 0.15 mg | Resolved after one hour | Possibly related | Potentially related |
| 01-045 | SR 2-04, visit | 21-year-old male | tetracaine 9 mg/ oxymetazoline 0.15 mg | Occurred the day after Kovanaze; epistaxis resolved on the same day that it started | Possibly related | Potentially related |
| 01-0003 | SR 2-05 | 50.5-year-old female | tetracaine 24 mg/ oxymetazoline 0.4 mg | Duration of a few minutes | Probably related | Potentially related |
| 01-0011 | SR 2-05 | 65.5-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Duration of one minute | Probably related | Potentially related |
| 2-109 | SR 2-06 | 21-year-old female | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred on the same day as the Kovanaze dose; duration less than one minute | Probably related | Potentially related |
| 2-117 | SR 2-06 | 29-year-old male | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred on the same day as the Kovanaze dose; duration of about one hour | Unrelated | Potentially related |
| 2-121 | SR 2-06 | 27-year-old male | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred on the same day as Kovanaze dose; duration of 11 minutes | Unrelated | Potentially related |
| 4-007 | SR 3-02 | 27-year-old male | Active comparator tetracaine nasal spray and 4% articaine rescue injection twice | Occurred 5.5 hours after dose; duration one minute | Probably related | Potentially related |
| 4-030 | SR 3-02 | 21-year-old | Active comparator tetracaine | Occurred 11 minutes after dose and was | Possibly related | Potentially |

| Subject | Trial | Age/Sex | Kovanaze dose or active comparator with which AE was associated | Time course/ duration | Relationship to drug per investigator | Relationship to drug per reviewer |
|---|---|---|---|---|---|---|
| | | female | nasal spray and 4% articaine rescue injection three times | intermittent for about one hour | | related |
| 4-105 | SR 3-02 | 47-year-old male | tetracaine 18 mg/ oxymetazoline 0.3 mg | Occurred two hours after Kovanaze; duration 14 hours | Probably related | Potentially related |
| 5-015 | SR 3-03 | 31-year-old male | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred the day after Kovanaze dose; duration one minute | Possibly related | Potentially related |
| 6-061 | SR 3-03 | 24-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred the day after Kovanaze; duration less than five minutes | Probably related | Potentially related |
| 6-096 | SR 3-03 | 34-year-old female | tetracaine 12 mg/ oxymetazoline 0.2 mg | Occurred in the same day as Kovanaze dose; resolved the next day | Probably related | Potentially related |
| 3-120 | SR 3-04 | 5-year-old male | tetracaine 3 mg/ oxymetazoline 0.5 mg | Occurred eight minutes after Kovanaze; Duration two minutes | Probably related | Potentially related |

Note: Trial SR 2-04 was a crossover trial
*Subject 3-008 was identified from the Comment Log; very little information was submitted

Pharyngeal Edema
Subject 01-0003 in SR 2-05 developed moderate pharyngeal edema lasting for a few minutes. This 50.5-year-old female had received tetracaine 24 mg/ oxymetazoline 0.4 mg. The investigator determined that this adverse event was probably related to Kovanaze and I agree.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Common adverse events in Phase 3 trials
SR 3-01, SR 3-02, and SR 3-03 were Phase 3 trials in adults administered Kovanaze, tetracaine spray, or placebo. SR 3-04 was a Phase 3 trial in pediatric patients.

Below is a table of adverse events incidence- head count for all subjects in Phase 3 trials, including adult and pediatric subjects. Adverse events occurring in 2% or greater of subjects who received Kovanaze have been included.

**Table 69 Adverse events in Phase 3 trials that occurred in 2% or more of subjects in the Kovanaze treatment group (adults and pediatrics)**

| Preferred term | # subjects who received Kovanaze n(%) | # subjects who received tetracaine spray n(%) | # subjects who received placebo n(%) |
|---|---|---|---|
| | N=214 | N=54 | N=108 |
| Rhinorrhea | 103 (48.13%) | 20 (37.04%) | 5 (4.63%) |
| Hypoesthesia oral | 68 (31.78%) | 35 (64.81%) | 15 (13.89%) |
| Nasal congestion | 66 (30.84%) | 34 (62.96%) | 9 (8.33%) |
| Hypoesthesia teeth | 57 (26.64%) | 17 (31.48%) | 13 (12.04%) |
| Procedural pain | 53 (24.77%) | 30 (55.56%) | 65 (60.19%) |
| Nasal discomfort | 48 (22.43%) | 7 (12.96%) | 6 (5.56%) |
| Lacrimation increased | 35 (16.36%) | 6 (11.11%) | 9 (8.33%) |
| Hypoesthesia | 30 (14.02%) | 18 (33.33%) | 10 (9.26%) |
| Oropharyngeal pain | 25 (11.68%) | 5 (9.26%) | 0 |
| Headache | 19 (8.88%) | 3 (5.56%) | 5 (4.63%) |
| Pharyngeal hypoesthesia | 19 (8.88%) | 10 (18.52%) | 0 |
| Intranasal hypoesthesia | 18 (8.41%) | 8 (14.81%) | 5 (4.63%) |
| Dysgeusia | 15 (7.01%) | 1 (1.85%) | 1 (0.93%) |
| Throat irritation | 15 (7.01%) | 1 (1.85%) | 0 |
| Rhinalgia | 14 (6.54%) | 3 (5.56%) | 5 (4.63%) |
| Sneezing | 13 (6.07%) | 2 (3.70%) | 3 (2.78%) |
| Paresthesia | 11 (5.14%) | 0 | 1 (0.93%) |
| Blood pressure systolic increased | 8 (3.74%) | 0 | 2 (1.85%) |
| Injection site pain | 7 (3.27%) | 0 | 8 (7.41%) |

| Preferred term | # subjects who received Kovanaze n(%) | # subjects who received tetracaine spray n(%) | # subjects who received placebo n(%) |
|---|---|---|---|
| Blood pressure diastolic increased | 6 (2.80%) | 0 | 1 (0.93%) |
| Bradycardia | 5 (2.34%) | 3 (5.56%) | 1 (0.93%) |
| Dizziness | 5 (2.34%) | 0 | 1 (0.93%) |
| Epistaxis | 5 (2.34%) | 2 (3.70%) | 0 |
| Hypertension | 5 (2.34%) | 1 (1.85%) | 1 (0.93%) |
| Sinus headache | 5 (2.34%) | 0 | 0 |

Common adverse events in SR 2-01

SR 2-01 was a randomized Phase 2 clinical trial in 45 adult dental patients aged 20 to 66-years-old having an amalgam or composite restoration of one tooth of the maxilla. Subjects were randomized to one of two treatment groups:

1. Kovanaze (18mg tetracaine/ 0.3 mg oxymetazoline) and sham injection in which the cap was left on the needle tip. (30 subjects)
2. 2% Lidocaine HCl with epinephrine Injection (1:100,000) and isotonic saline spray (placebo) (15 subjects)

I have included an analysis of common adverse events in SR 2-01 because it may be useful to compare common adverse events in the Kovanaze treatment group to common adverse events in the treatment group that, more or less, represents standard of care. The result of this analysis is the discovery that no adverse events occurred in the treatment group that received standard of care: 2% lidocaine HCl with epinephrine injection (1:100,000). Below is the table of adverse events by preferred term in those who received Kovanaze.

**Table 70 Adverse Events by preferred term in SR 2-01**

| Preferred term | # subjects who received Kovanaze n(%) |
|---|---|
| | N=30 |
| Nasal congestion | 6 (20%) |
| Rhinorrhea | 4 (13.33%) |
| Abdominal Discomfort | 1 (3.33%) |
| Headache | 1 (3.33%) |
| Hypertension | 1 (3.33%) |
| Hypoesthesia Oral | 1 (3.33%) |
| Lacrimation Increased | 1 (3.33%) |
| Sneezing | 1 (3.33%) |

Section 6.1.10.1 describes efficacy results for SR 2-01. It should be noted that, in addition to having less adverse events than the Kovanaze treatment group, the lidocaine injection treatment group also demonstrated increased efficacy over

Kovanaze. 83.3% of subjects in the Kovanaze treatment group and 93.3% of subjects in the lidocaine injection treatment group had treatment success. Therefore, according to the results of SR 2-01, lidocaine injection could be interpreted as being safer and more efficacious than Kovanaze for the proposed indication. A caveat of this finding is the small number of subjects in SR 2-01.

Despite the possibility that, based on the results of SR 2-01, Kovanaze is not as safe or efficacious as lidocaine injection for anesthesia during dental procedures, Kovanaze will still benefit some patients, particularly those who avoid dental care for fear of needles.

### 7.4.2 Laboratory Findings

Clinical laboratory data with Kovanaze was only included in studies SR 2-02, SR 2-06, and SR 2-07. For a summary of these clinical trials, see section 9.5 of this review.

SR 2-02 is a Phase 1 study in 12 healthy adult volunteers in which pharmacokinetic parameters were obtained. Clinical laboratories were only evaluated at the screening visit.

SR 2-06 is a Phase 1 study in 24 healthy adults in which pharmacokinetic parameters were obtained. In this clinical trial, hematology, coagulation, serum chemistry, and urinalysis tests were obtained before study drug dosing and one day after drug dosing. On the day of drug dosing, all subjects received three sprays of Kovanaze to a total of 18 mg tetracaine and 0.3 mg oxymetazoline.

Below are summaries of lab results obtained in SR 2-06:

Hematology labs
Hematology labs included white blood cell, red blood cell, hematocrit, hemoglobin, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils. There were no clinically significant changes in hematology labs from before to after dosing.

Coagulation labs
Coagulation labs included activated prothrombin time, international normalized ratio, and prothrombin time. There were no clinically significant changes in coagulation labs from before to after dosing.

Serum chemistry labs
Serum chemistry labs included sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, albumin, total protein, alkaline phosphatase, alanine transaminase, aspartate transaminase, and direct, indirect, and total bilirubin. There were no clinically significant changes in serum chemistry labs from before to after dosing. No Hy's Law Cases have been identified from SR 2-06.

Urinalysis labs

Urine was analyzed for specific gravity, pH, glucose, ketones, blood, protein, bilirubin, urobilinogen, nitrites, leukocyte esterase, red blood cells, white blood cells, hyaline casts, granular casts, epithelium, bacteria, crystals, and mucous threads. Many of the results of urinalysis labs were outside of the range of normal when evaluated both before and after drug dosing. Urinalysis lab value abnormalities were reviewed by this reviewer and found to be of unclear clinical significance.

SR 2-07 is a Phase 1 clinical trial in 18 healthy pediatric subjects. Hematology, serum chemistry, coagulation, and urinalysis labs were to be obtained at screening (1 to 28 days before drug dosing), before drug dosing on the day of drug dosing, and 14 days after drug dosing. All subjects received a one-time dose of Kovanaze based on weight.

Below are summaries of lab results obtained in SR 2-07:

Hematology labs
Hematology labs included white blood cells, red blood cells, hematocrit, hemoglobin, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils. Overall, there were no clinically significant changes in hematology labs from before to after dosing.

Coagulation labs
Coagulation labs included partial thromboplastin time, international normalized ratio, and prothrombin time. Overall, there were no clinically significant changes in coagulation labs from before to after dosing.

Serum chemistry labs
Serum chemistry labs included sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, albumin, total protein, alkaline phosphatase, alanine transaminase, aspartate transaminase, and direct, indirect, and total bilirubin. Overall, there were no clinically significant changes in serum chemistry labs from before to after dosing. No Hy's Law Cases have been identified from SR 2-07.

Urinalysis labs
Urine was analyzed for specific gravity, pH, glucose, ketones, blood, protein, bilirubin, urobilinogen, nitrites, leukocyte esterase, red blood cells, white blood cells, hyaline casts, granular casts, epithelium, bacteria, crystals, and mucous threads.

Many of the results of urinalysis labs were outside of the range of normal when evaluated both before and after drug dosing. Urinalysis lab value abnormalities were reviewed and found to be of unclear clinical significance.

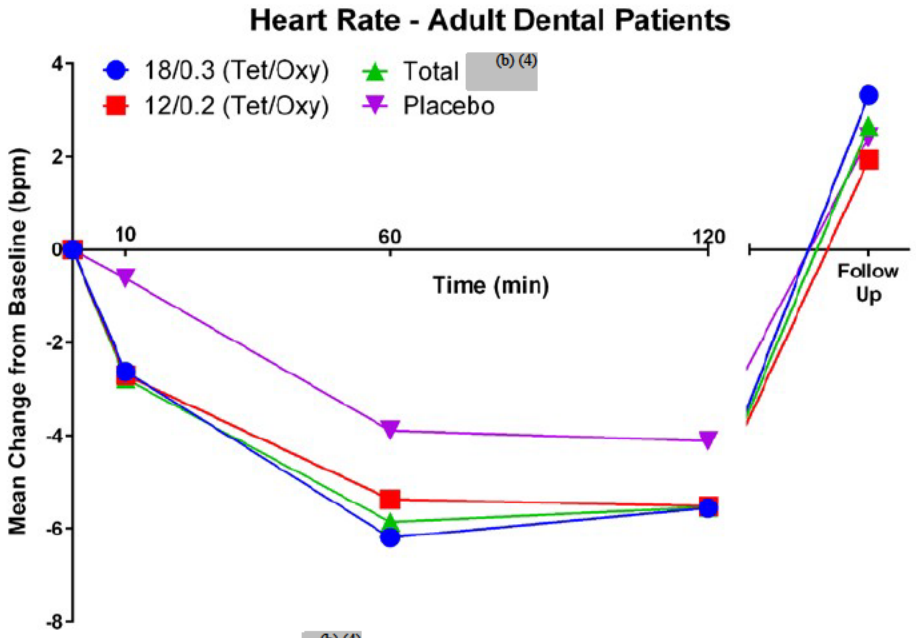
## 7.4.3 Vital Signs

### 7.4.3.1 Vital Signs in Adults

#### *7.4.3.1.1 Vital Signs in Adult Dental Patients*

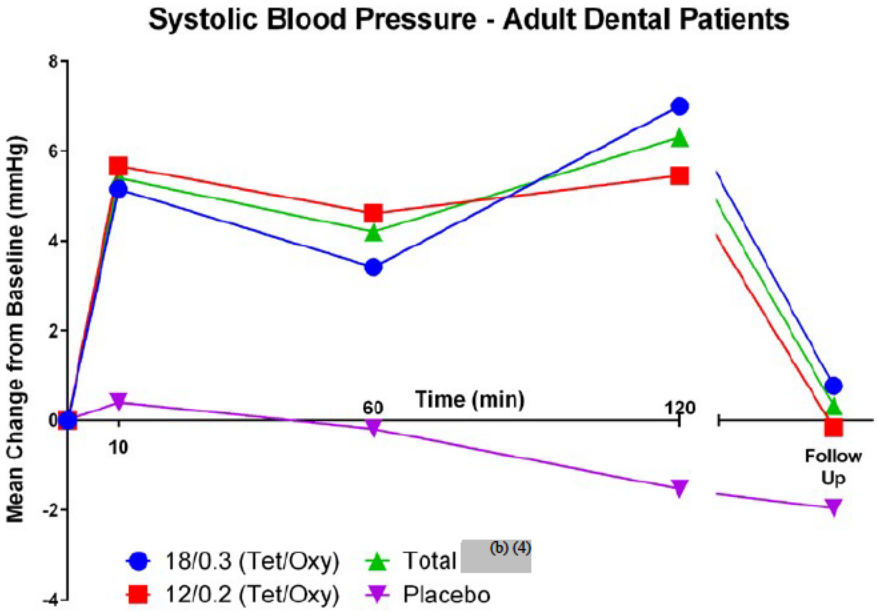
Oxymetazoline is known to cause hypertension and bradycardia. Bradycardia, tachycardia, and hypertension are all vital sign-related measures that are of particular interest with Kovanaze. In clinical trials with adult dental patients, vital signs were not recorded during the dental procedures, themselves, making these trials less useful for assessments of tachycardia, bradycardia, or hypertension from Kovanaze. However, as demonstrated in the figures below, at the time points when vital signs were recorded in patients in these trials, Kovanaze does appear to have caused a decrease in heart rate and elevation in systolic blood pressure in adult dental patients.

**Figure 1 HR Mean Changes from Baseline in Adult Dental Patients**




Only time points with N ≥ 60% of total (b) (4) population are shown.
Source data: ISS Table 3.1.1
(Source: NDA 208032 Applicant's figure page 23 of Clinical Overview)

**Figure 2 SBP Mean Changes from Baseline in Adult Dental Patients**




*Only time points with N ≥ 64% of total (b) (4) population are shown.
Source data: ISS Table 3.3.1
(Source: NDA 208032 Applicant's figure page 24 of Clinical Overview)

Hypertension in adult dental patients

Hypertension appears to be more frequent with Kovanaze compared to placebo and hypertension with Kovanaze appears to be more likely with patients over the age of 50-years-old.

Of adult dental patients receiving Kovanaze, 13.6% of subjects over 50-years-old experienced an increase in systolic blood pressure >160 mmHg and an increase of ≥ 25 mmHg after Kovanaze compared to only 1.4% of subjects ≤ 50-years-old.

In clinical trials, 11 adult dental patients who received Kovanaze had systolic blood pressure > 160 mmHg and an increase ≥ 25 mmHg compared with two subjects in the placebo treatment group who had such increase in systolic blood pressure.

Below is a table displaying the 11 adult dental patients who received Kovanaze and had systolic blood pressure > 160 mmHg and an increase ≥ 25 mmHg. This table displays the highest systolic blood pressure reading experienced by these subjects and the time in the trial during which this occurred.

**Table 71 Highest systolic blood pressure experienced by 11 adult dental patients who received Kovanaze had systolic blood pressure > 160 mmHg and an increase ≥ 25 mmHg**

| Trial | Subject | Age (years) | Kovanaze dose (tetracaine mg/ oxymetazoline mg) | Highest Systolic Blood Pressure | Time (minutes)* |
|---|---|---|---|---|---|
| SR 2-01 | 01-0007 | 72 | 18/0.3 | 179/93 | 40 and 50 |
| SR 2-05 | 01-0013 | 65 | 6/0.1 | 168/84 | 60 |
| SR 2-05 | 01-0016 | 74 | 12/0.2 | 164/96 | 60 |
| SR 2-05 | 01-0017 | 69 | 12/0.2 | 168/93 | 60 |
| SR 3-02 | 04-038 | 47 | 18/0.3 | 168/64 | 120 |
| SR 3-02 | 04-039 | 58 | 18/0.3 | 179/98; 179/110 | 30;90 |
| SR 3-03 | 05-047 | 62 | 12/0.2 | 164/95 | 45 |
| SR 3-03 | 05-055 | 63 | 12/0.2 | 175/96 | 10 |
| SR 3-03 | 07-163 | 67 | 12/0.2 | 179/96; 179/107 | 90; 120 |
| SR 3-03 | 07-175 | 50 | 18/0.3 | 164/86 | 120 |
| SR 3-03 | 07-176 | 78 | 18/0.3 | 163/82 | 10 |

*In SR 2-01, SR 3-02, and SR 3-03, time 0 minutes was when the first spray of Kovanaze was administered.

In clinical trials, two adult dental patients had diastolic blood pressure > 105 mmHg and an increase of ≥ 15 mmHg compared with one subject in the placebo treatment group. The two adult dental patients with diastolic blood pressure > 105 mmHg and an increase of ≥ 15 mmHg had maximum diastolic blood pressures of 115 and 107 occurring at 10 and 120 minutes after the first spray of Kovanaze, respectively.

Hypotension in adult dental patients

In clinical trials of adult dental patients, one subject in the Kovanaze treatment group and one subject in the placebo treatment group had systolic blood pressure < 90 mmHg and a decrease in ≥ 15 mmHg. In clinical trials of adults dental patients, two subjects in the Kovanaze treatment group and no placebo subjects had diastolic blood pressure < 50 mmHg and a decrease ≥ 10 mmHg. These cases were reviewed and did not appear to be of clinical significance. It does not appear that Kovanaze is causatively linked to an increased incidence of hypotension.

Tachycardia in adult dental patients

In clinical trials with adult dental patients, one subject in the Kovanaze treatment group (Subject 04-039 in SR 3-02) and no subjects in the placebo treatment group had a heart rate that was > 125 beats per minute. This subject had a pre-study heart rate of 100 beats per minute.

All other adult dental patients (aside from subject 04-039 described above) who received Kovanaze in clinical trials were examined to see if any subjects had

tachycardia recorded after receiving Kovanaze (excluding the next day follow-up), but not at one of the time points before Kovanaze. Of the 214 adult dental patients who received Kovanaze, five had tachycardia at a time point on the same day after receiving Kovanaze, but did not have tachycardia at screening, pre-treatment, or baseline.

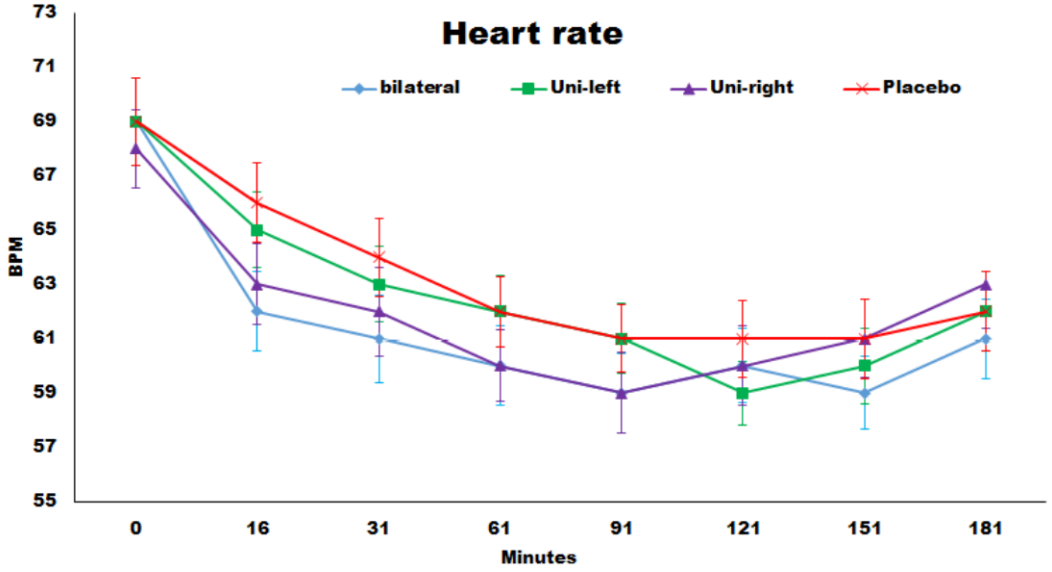
Because of the low incidence of tachycardia in adult dental patients who received Kovanaze, it does not appear that Kovanaze is causatively linked to an increased incidence of tachycardia.

*7.4.3.1.2 Vital Signs in Adult Volunteers*

As mentioned previously, in clinical trials with adult dental patients, vital signs were not recorded during the dental procedures, making these trials less useful for assessments of tachycardia, bradycardia, or hypertension from Kovanaze. However, vital signs were recorded regularly for volunteers in clinical trials who did not undergo a dental procedure. All trials conducted in healthy volunteers were Phase 1 trials with the exception of SR 2-04. SR 2-04 is a Phase 2 trial conducted in healthy adult volunteers.

For further details of SR 2-04 see section 9.6.3 of this review. Vital sign results for trial SR 2-04 confirm the trend of decrease in heart rate that appears to occur in adults following administration of Kovanaze. Below is a figure illustrating decreased heart rate from Kovanaze in SR 2-04.

**Figure 3 Mean Heart Rates (BPM) by Dosing Regimen in SR 2-04**

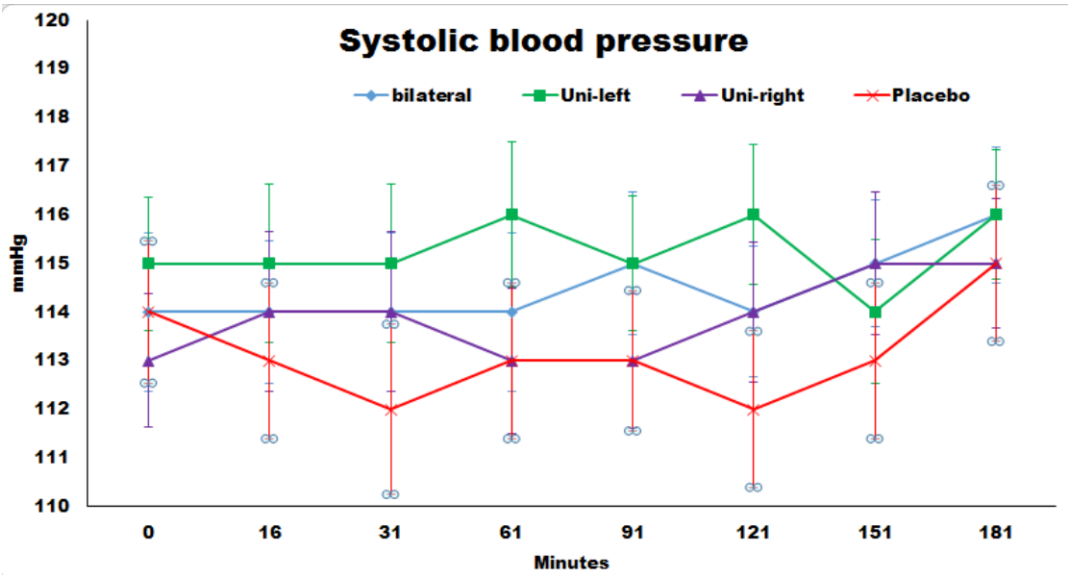



Source data: Table 14.3.6.1
(Source: NDA 208032 Applicant's figure page 75 of SR 2-04 Clinical Study Report)

In SR 2-04, there was a small increase in systolic blood pressure following Kovanaze dosing that St. Renatus determined was not statistically significant. The figure below demonstrates systolic blood pressure after Kovanaze in SR 2-04. I agree that, in SR 2-

04, if Kovanaze is associated with any increase in systolic blood pressure, this increase is small.

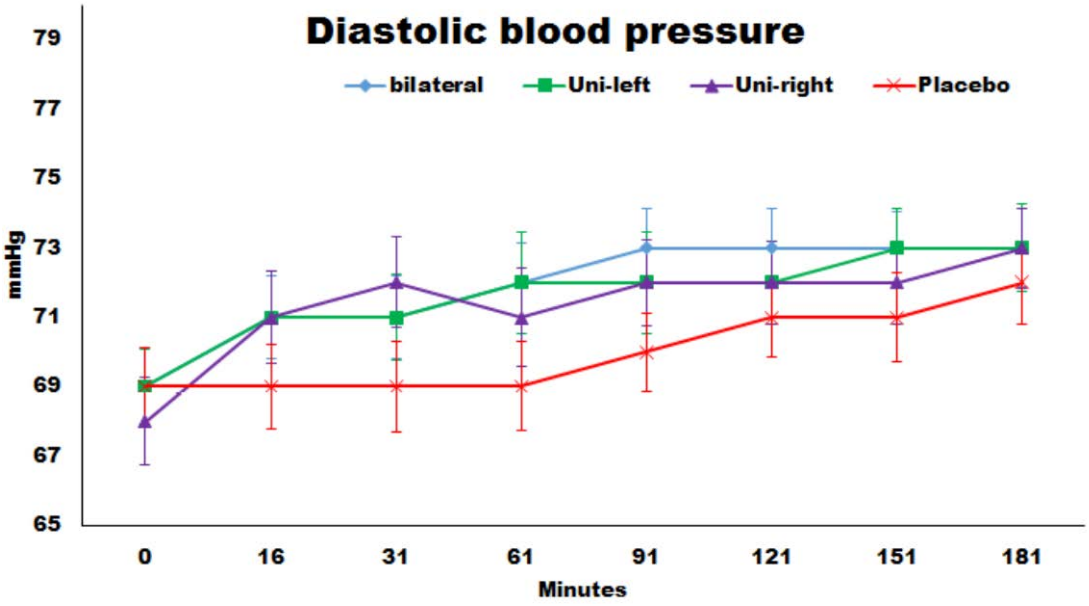
**Figure 4 Mean Systolic Blood Pressure Values (mmHg) by Dosing Regimen in SR 2-04**




Source data: Table 14.3.6.2
(Source: NDA 208032 Applicant's figure page 76 of SR 2-04 Clinical Study Report)

There was also an increase in diastolic blood pressure after Kovanaze dosing as illustrated in the table below. Similar to the increase in systolic blood pressure in SR 2-04 related to Kovanaze, any increase in diastolic blood pressure in SR 2-04 related to Kovanaze is small.

**Figure 5 Mean Diastolic Blood Pressure Values (mmHg) by Dosing Regimen in SR 2-04**



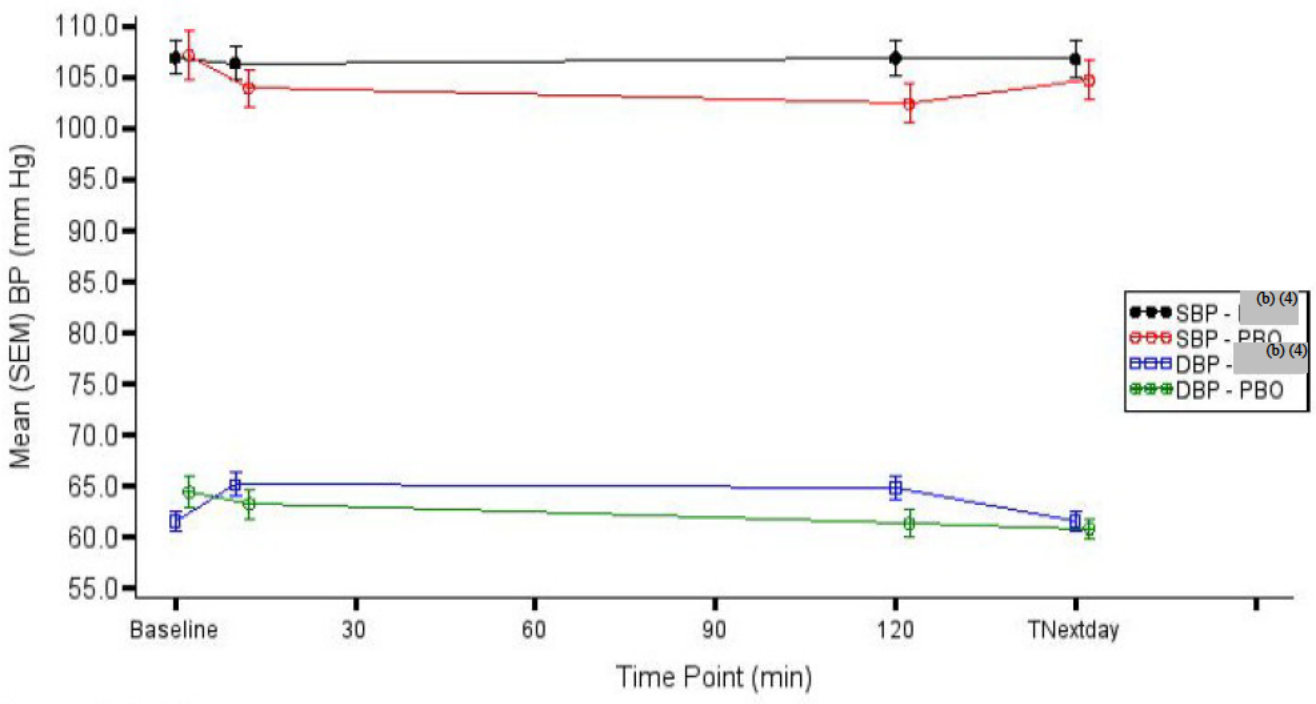
Source data: Table 14.3.6.3
(Source: NDA 208032 Applicant's figure page 77 of SR 2-04 Clinical Study Report)

7.4.3.2 Vital signs in Pediatrics

In pediatric patients who received Kovanaze, changes in heart rate and blood pressure appeared minor.

SR 3-04 was a clinical trial in pediatric dental patients. In SR 3-04, vital signs were measured before trial drug, at 10 minutes after the first spray of Kovanaze (T10), at 120 minutes after the first spray of Kovanaze (T120), and the next day. Below is a figure that displays mean systolic and diastolic blood pressure for subjects in the Kovanaze group compared with those in the placebo group in SR 3-04. Overall, mean systolic blood pressure was consistent from baseline to after treatment with Kovanaze. In the Kovanaze treatment group, mean diastolic blood pressures demonstrated an increase from baseline at T10 and T120. Mean diastolic blood pressure was slightly higher in the Kovanaze treatment group compared to the placebo treatment group at T10 and T20.

**Figure 6 Mean (SEM) Systolic and Diastolic BP Over Time - Pooled (b) (4) Safety Population (N=90) for SR 3-04**

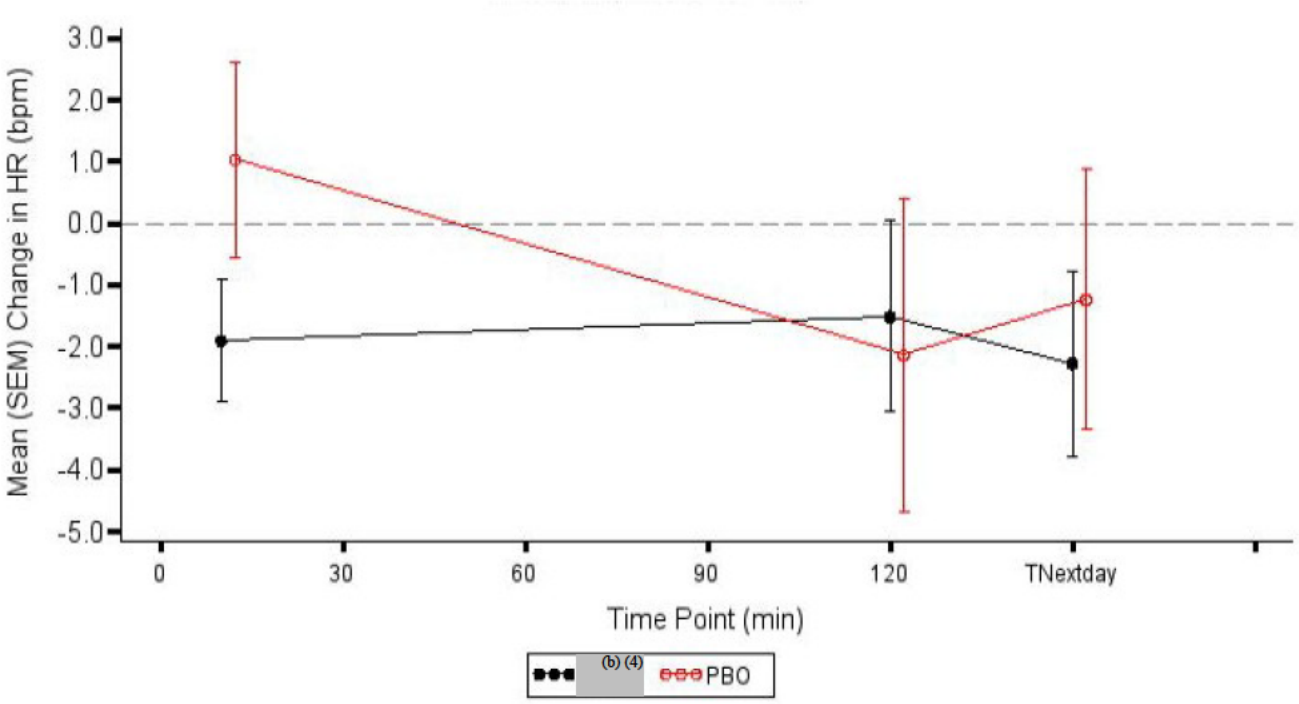



(Source: NDA 208032 Applicant's figure page 463 of SR 3-04 Clinical Study Report)

Below is a figure displaying the mean change from baseline of those in the Kovanaze treatment group compared to those in the placebo treatment group for SR 3-04. As

demonstrated in the figure below, there was no clinically significant change in mean heart rate from baseline in either the Kovanaze or placebo treatment group.

**Figure 7 Mean (SEM) Change from Baseline in Heart Rate Over Time - Pooled (b) (4) Safety Population (N=90) for SR 3-04**




(Source: NDA 208032 Applicant's figure page 467 of SR 3-04 Clinical Study Report)

## 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were obtained in 24 healthy adult volunteers in clinical trial SR 2-06 before dosing of trial drug (at screening) and the day after trial drug dosing. These data are in the table below:

**Table 72 12-lead ECG**

| | Findings | Statistics | Screening (n = 24) | Discharge/ Day 2 (n = 24) |
|---|---|---|---|---|
| Hear rate (bpm) | | N<br>Mean<br>SD<br>Median<br>(Min, Max) | 24<br>58.9<br>8.81<br>57.5<br>(45,80) | 24<br>62.3<br>10.96<br>60.0<br>(45,84) |

| | Findings | Statistics | Screening (n = 24) | Discharge/ Day 2 (n = 24) |
|---|---|---|---|---|
| Rhythm | Normal Sinus Rhythm | | 10 (41.7%) | 13 (54.2%) |
| | Sinus Bradycardia Sinus | | 13 (54.2%) | 10 (41.7%) |
| | Tachycardia Supraventricular | | 0 | 0 |
| | Tachycardia Junctional | | 0 | 0 |
| | Rhythm Idioventricular | | 0 | 0 |
| | Rhythm | | 0 | 0 |
| | First Degree AV Block | | 1 (4.2%) | 0 |
| | Second Degree AV Block/Mobitz I | | 0 | 0 |
| | Second Degree AV Block/Mobitz II | | 0 | 0 |
| | Third Degree AV Block | | 0 | 0 |
| | N/A | | 0 | 1 (4.2%) |
| Arrhythmias | Yes | | 5 (20.8%) | 2 (8.3%) |
| | No | | 19 (79.2%) | 22 (91.7%) |
| Normal limits | Within Normal Limits | | 5 (20.8%) | 10 (41.7%) |
| | Abnormal, NCS | | 19 (79.2%) | 14 (58.3%) |
| | Abnormal, CS | | 0 | 0 |

Source data: Table 14.3.7.1
NCS – not clinically significant; CS – clinically significant; N/A – not applicable; AV – atrioventricular
(Source: NDA 208032 Applicant's table page 88 of SR 2-06 Clinical Study Report; header row added by reviewer)

The above table demonstrates that ECG changes from Screening to one day after trial drug dosing do not appear to be clinically significant. ECGs were not obtained in pediatric subjects.

Subjects did not have continuous ECG monitoring during clinical trials with Kovanaze. St. Renatus has provided rationale for the minimal amount of ECG monitoring that occurred in subjects in their clinical trial program:

1. ECG parameters were studied in dogs at higher doses of oxymetazoline and tetracaine than those proposed in humans with "no treatment-related biologically significant changes were observed for heart rate, RR interval, PR interval, QRS duration, QT interval, or QTc." (Source: NDA 208032 pages 29 of Clinical Overview)

2. Tetracaine and oxymetazoline at the doses proposed in Kovanaze have a history of safe use. See section 2.4 of this review for further detail. St. Renatus identified two publications in which oxymetazoline was used and ECG was obtained: Katz et al., 1990 and Riegle et al., 1992.

Katz et al., 1990 documents a double-blind randomized clinical trial whose purpose was to evaluate 0.05% oxymetazoline, cocaine 10%, and lidocaine 4% with epinephrine 1:100,000 for the prevention of epistaxis that may occur with nasal intubation. Forty-two subjects over the age of 16-years-old were randomized to one of three treatment groups. Fourteen subjects were randomized to the oxymetazoline treatment group. Awake subjects in the oxymetazoline treatment group had cotton swabs saturated with

2 ml of 0.05% oxymetazoline applied to the nares for 5 minutes, after which time general anesthesia was induced. Subjects had continuous ECG monitoring. The article authors note that “No cardiac arrhythmias occurred in any patient either prior to or after intubation.” (Katz et al. 1990)

Two milliliters of 0.05% oxymetazoline (as is used in Katz et al. 1990) contains 1 mg of oxymetazoline. This is more oxymetazoline than in the maximum dose of Kovanaze (0.3 mg oxymetazoline). Therefore, although the trial was small, it is reassuring that no cardiac arrhythmia occurred.

Riegle et al, 1992 describes a double-blind randomized clinical trial whose purpose was to evaluate 0.05% oxymetazoline, cocaine 4%, and phenylephrine 0.25% for vasoconstriction during functional endoscopic sinus surgery in 57 children. Nineteen children received oxymetazoline 0.05%. According to the article authors, in regard to the amount of oxymetazoline or other study drug: “It was not possible to determine the cumulative dose received by each child.” (Riegle et al. 1992) After application of oxymetazoline, subjects had ECG monitoring, during which time no arrhythmias were seen.

While it is reassuring that no arrhythmias were seen, because the dose of oxymetazoline that subjects received is unknown, it is difficult to use this journal article as evidence in support of Kovanaze.

3. To decrease the likelihood of a patient experiencing an overdose of oxymetazoline, the package insert will advise against use of other products that contain oxymetazoline.

Reasoning that the components of Kovanaze have a history of safe use combined with advise in the package insert to avoid additional products containing oxymetazoline provide adequate rationale to forego additional ECG testing in adults receiving Kovanaze.

### 7.4.5 Special Safety Studies/Clinical Trials

The following special studies were performed:
1. Subject-Reported Safety Evaluation
2. Naris Examination
3. Alcohol Sniff Test

#### 7.4.5.1 Subject-related (referred to as “subject-reported” in SR 3-02) Safety Evaluation

This evaluation was performed in SR 2-03, SR 3-01, SR 3-02, SR 3-03, and SR 3-04. An example of this assessment is present in section 9.4 of this review. According to the Applicant, the results of the Subject-related Safety Evaluation in those given Kovanaze were similar to the results of those in placebo treatment groups.



Reference ID: 3952361

#### 7.4.5.2 Naris Examination

This evaluation was performed in SR 2-03, SR 3-01, SR 3-02, SR 3-03, and SR 3-04. For this examination, nostrils that received trial drug were evaluated for patency, ulceration, inflammation, bleeding, and color. Some subjects experienced ulceration and abnormal mucosal coloration.

The Naris Examination dataset was evaluated for incidence of ulceration. The following subjects had intranasal ulceration after trial drug administration, but not before trial drug administration. Nasal ulceration will be included in the package insert as a possible adverse event.

**Table 73 Subjects with ulceration present after trial drug, but not before trial drug**

| Subject | Study | Treatment group | Sex | Age (years) |
|---|---|---|---|---|
| 2-055 | SR 3-02 | Kovanaze | female | 21 |
| 4-018 | SR 3-02 | Kovanaze | female | 55 |
| 4-026 | SR 3-02 | placebo | female | 53 |
| 4-027 | SR 3-02 | Kovanaze | female | 53 |
| 4-105 | SR 3-02 | Kovanaze | male | 47 |
| 6-061 | SR 3-03 | Kovanaze | female | 24 |
| 6-063 | SR 3-03 | placebo | female | 24 |
| 6-078 | SR 3-03 | Kovanaze | female | 22 |
| 6-086 | SR 3-03 | Kovanaze | male | 27 |
| 6-105 | SR 3-03 | Kovanaze | male | 54 |
| 5-132 | SR 3-04 | Kovanaze | male | 12 |

#### 7.4.5.3 Alcohol Sniff Test

An alcohol sniff test was performed to evaluate olfactory sensitivity in trials SR 3-01, SR 3-02, and SR 3-03. Kovanaze does not appear to have a clinically significant impact on olfactory sensitivity.

### 7.4.6 Immunogenicity

No issues related to the immunogenicity of Kovanaze were addressed in this NDA submission.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

In trial SR 2-02, twelve subjects received 18 mg tetracaine/0.3 mg oxymetazoline (standard dose) and then at least a week later, received 36 mg tetracaine/0.6 oxymetazoline (high dose) (see appendix 9.5.2 for details of trial SR 2-02)

There were no clinically significant differences in the heart rate, blood pressure, or oxygen saturation that resulted from the 18 mg tetracaine/0.3 mg oxymetazoline dose compared to the 36 mg tetracaine/0.6 mg oxymetazoline dose. (Source: NDA 208032 pages 58-60 of SR 2-02 Clinical Study Report)

In SR 2-02, 24 hours after Kovanaze dosing, subjects were communicated with via telephone. At this telephone call, after Dose 1 (standard dose), 5/12 subjects reported nasal stuffiness. At the telephone call 24 hours after Dose 2 (high dose), 9/12 subjects reported nasal stuffiness and 2/12 subjects reported discomfort at the spray site. One possible interpretation of these results is that nasal stuffiness and discomfort at the spray site might be more likely with higher doses of Kovanaze. However, the dose of Kovanaze given at Visit 2 is double the maximum recommended dose and we cannot extrapolate this increase in adverse events with an excessive dose of Kovanaze to the doses of Kovanaze that will be recommended in the package insert. Results of SR2-02 are in the table below.

**Table 74 Telephone Follow-Up (Safety Population) (SR 2-02)**

| | Findings | Visit 1 (n = 12) | Visit 2 (n = 12) |
|---|---|---|---|
| Any Changes in Health Since Yesterdays Visit | Yes | 6 (50.0%) | 9 (75.0%) |
| | No | 6 (50.0%) | 3 (25.0%) |
| If Yes, (check all that apply) | | | |
| Nasal Stuffiness | Yes | 5 (41.7%)[a] | 9 (75.0%) |
| Discomfort at Spray Site | Yes | 0 | 2 (16.7%) |
| Rash | Yes | 0 | 0 |
| Swelling | Yes | 0 | 0 |
| Headache | Yes | 0 | 0 |
| Infection | Yes | 0 | 0 |
| Pain | Yes | 0 | 0 |
| Numbness | Yes | 0 | 0 |
| Tingling | Yes | 0 | 0 |

Source data: Table 14.3.7

[a] Subject 01-008 indicated a change in health since previous day's visit that was not included in the listed symptoms (hence the discrepancy between number of subjects with a change in health versus the number providing responses to the symptoms specified as part of the telephone follow-up).

(Source: NDA 208032 Applicant's table page 98 of SR 2-02 Clinical Study Report)

Adverse events were compared in all adult subjects in the Integrated Safety Database who received 18 mg tetracaine/ 0.3 mg oxymetazoline to all adult subjects in the Integrated Safety Database who received 12 mg tetracaine/ 0.2 mg oxymetazoline. Events were included in the table below if the incidence with which an adverse event occurred was 2.5% greater than in the alternate group.

**Table 75 Comparison or adverse events in adults who received tetracaine 18 mg/ oxymetazoline 0.3 mg or tetracaine 12 mg/oxymetazoline 0.2 mg. Events were included in this table if the incidence with which an adverse event occurred was 2.5% greater than in the alternate group.**

| System Organ Class | Preferred Term | # and incidence in adult subjects who received tetracaine 18mg/ oxymetazoline 0.3 mg n(%) | # and incidence in adult subjects who received tetracaine 12mg/ oxymetazoline 0.2 mg n(%) |
|---|---|---|---|
| | | N=193 | N=93 |
| Cardiac Disorders | | | |
| | Bradycardia | 7 (3.6%) | 1 (1.1%) |
| Gastrointestinal Disorders | | | |
| | Hypoesthesia oral | 47 (24.4%) | 14 (15.1%) |
| | Hypoesthesia teeth | 39 (20.2%) | 9 (9.7%) |
| Injury, Poisoning and Procedural Complications | | | |
| | Procedural pain | 36 (18.7%) | 1 (1.1%) |
| Investigations | | | |
| | Blood pressure diastolic increased | 3 (1.6%) | 4 (4.3%) |
| Nervous System Disorders | | | |
| | Dizziness | 4 (2.1%) | 5 (5.4%) |
| | Dysgeusia | 7 (3.6%) | 6 (6.5%) |
| | Headache | 25 (13.0%) | 6 (6.5%) |
| | Hypoesthesia | 20 (10.4%) | 20 (21.5%) |
| Respiratory, Thoracic and Mediastinal Disorders | | | |
| | Intranasal hypoesthesia | 11 (5.7%) | 8 (8.6%) |
| | Nasal congestion | 59 (30.6%) | 26 (28.0%) |
| | Nasal discomfort | 34 (17.6%) | 25 (26.9%) |
| | Nasal dryness | 4 (2.1%) | 5 (5.4%) |
| | Oropharyngeal pain | 16 (8.3%) | 16 (17.2%) |
| | Pharyngeal hypoesthesia | 22 (11.4%) | 8 (8.6%) |
| | Rhinorrhea | 83 (43.0%) | 55 (59.1%) |
| | Throat irritation | 15 (7.8%) | 4 (4.3%) |
| Vascular Disorders | | | |
| | Hypertension | 6 (3.1%) | 0 |

Not all of the differences in adverse events between subjects in the three Kovanaze spray(18 mg tetracaine/ 0.3mg oxymetazoline) treatment group compared to the two Kovanaze spray(12 mg tetracaine/ 0.2 mg oxymetazoline) treatment group can be explained. There are however, some differences in adverse event incidence between the two groups that would make logical sense based on the known physiologic effects of Kovanaze. Bradycardia and hypertension are known effects of oxymetazoline and therefore, it is logical that they occurred more frequently in subjects who received more Kovanaze. Headache, pharyngeal hypoesthesia, and throat irritation also occurred more frequently in the group that received a higher dose of Kovanaze, and it would be logical that a larger dose or a medication would lead to the increased incidence of an adverse event. Other adverse events occurred with a higher incidence in the two spray group. For example, blood pressure diastolic increased, dysgeusia, nasal discomfort, nasal dryness, and rhinorrhea.

It might be expected for the incidence of adverse events associated with local toxicity of Kovanaze to be consistently higher in subjects who received three sprays of Kovanaze. However, this is not the case. As can be noted from the table above, nasal congestion occurred with an increased incidence in those who received three sprays of Kovanaze compared to those who received two sprays of Kovanaze, but the incidence of numerous other adverse events that may be associated with the local toxicity of Kovanaze occurred with greater incidence in those who received two sprays of Kovanaze compared with three sprays. Those adverse events that may be manifestations of local toxicity that occurred with greater incidence in those who received two sprays include nasal discomfort, nasal dryness, and rhinorrhea.

Taking into consideration that a third spray of Kovanaze may provide efficacy benefit for some patients, a third spray of Kovanaze appears to be reasonable from a safety standpoint.

### 7.5.2 Time Dependency for Adverse Events

An assessment of time dependency for adverse events was performed. This assessment provides some insight into the time of onset of adverse events. However, as the Applicant states:

> Several caveats must be taken into consideration when interpreting the onset and duration times displayed in these tables. The primary caveat is that start and stop times were not always recorded for all adverse events. This is especially true for the AEs derived from the comment page as start and stop times were not recorded in the comments and are not part of the dataset. Therefore, AEs from the comment page are not included in these tables.
>
> Another important factor is the accuracy of the AE stop dates and times. While the start time of an AE usually occurred during the dental visit and could be accurately recorded, stop dates and times for a specific AE could have occurred after the dental visit. In these cases, a patient (or a parent) would be asked for an estimated stop date and time during a follow-up phone call. When no estimate was provided, then the date of the phone call would be recorded as the stop date. In some cases, this stop date would yield an AE duration of up to several days.

(Source: NDA 208032 pages 4 and 5 of Response to FDA Information Request received March 15, 2016)

Below are results of mean onset time to common adverse in adults and pediatrics derived from tables submitted by the Applicant and received on March 15, 2016. If the mean onset times are believed to be reliable, the incidence of most adverse events is relatively distant in time to the administration of Kovanaze. From a clinical standpoint, this may mean that dental patients will begin experiencing the manifestations of adverse events long after discharge from the dental office.

**Table 76 Estimated onset for the most frequently reported AEs related* to Kovanaze administration among adult subjects**

| Preferred Term | N | Mean onset (minutes) |
|---|---|---|
| Rhinorrhea | 180 | 70.7 |
| Nasal congestion | 108 | 324.8 |
| Nasal discomfort | 95 | 50.0 |
| Oropharyngeal pain | 29 | 146.8 |
| Sneezing | 30 | 73.1 |
| Rhinalgia | 16 | 262.4 |
| Throat irritation | 18 | 112.3 |
| Headache | 37 | 105.5 |
| Dysgeusia | 13 | 79.8 |
| Lacrimation Increased | 28 | 29.8 |

The Applicant notes that 2 subjects in this analysis who experienced rhinorrhea and 1 subject who experienced oropharyngeal pain had time of onset reassigned to 0
*In this table, AEs that are "Related" have been assigned a causality that is remote, possible, probable, or definite
(Source: Reviewer generated table based on Applicant's table pages 56-58 of Response to FDA Information Request SD 29 received March 15, 2016)

**Table 77 Estimated onset for the most frequently reported AEs related* to Kovanaze administration among pediatric subjects**

| Preferred Term | N | Mean onset (minutes) |
|---|---|---|
| Rhinorrhea | 28 | 155.9 |
| Nasal congestion | 31 | 80.1 |
| Nasal discomfort | 19 | 27.1 |
| Sneezing | 11 | 70.4 |
| Rhinalgia | 15 | 15.5 |
| Lacrimation Increased | 45 | 0.8 |

The Applicant notes that 1 subjects in this analysis who experienced lacrimation increased had time of onset reassigned to 0
*In this table, AEs that are "Related" have been assigned a causality that is remote, possible, probable, or definite
(Source: Reviewer generated table based on Applicant's table pages 59-60 of Response to FDA Information Request SD 29 received March 15, 2016)

### 7.5.3 Drug-Demographic Interactions

Adverse events experienced by subjects in the Integrated Safety Database were reviewed to determine if there was a correlation between the incidence of adverse events and age, sex, race, or BMI. Overall, age ≤ 50 years, age > 50 years, sex, race, and BMI do not appear to be linked to substantial clinically significant safety concerns with Kovanaze.

### 7.5.4 Drug-Disease Interactions

The Applicant submitted tables of the most commonly reported medical history conditions in subjects in clinical trials with Kovanaze. Adverse events experienced by these subjects in the Integrated Safety Database were reviewed to determine if there was a correlation between the incidence of adverse events and medical conditions in a subject's past medical history. For the most part, for adults, gastroesophageal reflux disease, seasonal allergies, alcohol use, tobacco use, drug hypersensitivity, headache, and post-menopausal status do not appear to be linked to substantial clinically significant safety concerns with Kovanaze.

Significantly, the subject who experienced pharyngeal edema, referred to in section 7.3.5 of this review, had a history of drug hypersensitivity. This is notable, but not surprising, because it is logical that patients with a hypersensitivity to drugs may be more likely to be sensitive to Kovanaze or other drugs. While anaphylaxis was not observed in the clinical trials with Kovanaze, a statement in the proposed package insert exists in which the possibility of anaphylaxis with Kovanaze is described as follows:

> Allergic or anaphylactic reactions have been associated with tetracaine, and may occur with other components of KOVANAZE. They are characterized by urticaria, angioedema, bronchospasm, and shock. If an allergic reaction occurs, seek emergency help immediately.

(Source: NDA 208032 Kovanaze proposed package insert)

Also not surprisingly, adults with a history of headache, when given Kovanaze had a 26.1% incidence of headache compared with a 10.4% incidence of headache in all adult dental patients who received Kovanaze in Phase 3 trials. This result could be logically expected and no action is indicated.

Overall, for pediatric subjects, drug hypersensitivity, food allergy, seasonal allergies, and asthma did not appear to be linked to substantial clinically significant safety concerns with Kovanaze.

### 7.5.5 Drug-Drug Interactions

The Applicant submitted tables of the most commonly used concomitant medications of subjects in clinical trials with Kovanaze (drugs taken by at least 5% of trial participants). Adverse events experienced by these subjects in the Integrated Safety Database were reviewed to determine if there was a correlation between the incidence of adverse events and concomitant medications. For adults, these medications include medications that act on the renin-angiotensin system, anesthetics, anti-inflammatory and anti-rheumatic products, calcium channel blockers, diuretics, drugs for functional gastrointestinal disorders, lipid-modifying agents, psychoanaleptics, vitamins, analgesics, antihistamines for systemic use, beta-blockers, cough and cold preparations, drugs for acid-related disorders, drugs for obstructive airway diseases, nasal preparations, and sex hormones and modulators of the genital system. The Applicant notes that adverse events in subjects with concomitant medication must be interpreted cautiously because it is unknown if subjects took these medications on the same day as Kovanaze administration. For pediatrics, these medications include anesthetics, cough and cold preparations, analgesics, antihistamines for systemic use, nasal preparations, and drugs for obstructive airway disease.

For the most part, concomitant medications listed in the paragraph above do not appear to be linked to substantial clinically significant safety concerns with Kovanaze.

As would be expected, adults taking medications that act on the renin-angiotensin system, calcium channel blockers, and beta-blockers appear to have had an overall higher incidence of increased blood pressure with Kovanaze when compared with all subjects who received Kovanaze. The correlation between adults with a history of hypertension requiring treatment with medication and hypertension with Kovanaze is logical. Hypertension is included in the proposed package insert.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Because Kovanaze is not intended to be used chronically, carcinogenicity studies are not applicable and were not performed with Kovanaze, oxymetazoline, or tetracaine.

### 7.6.2 Human Reproduction and Pregnancy Data

The Applicant identified five publications in their literature review that pertain to women receiving oxymetazoline during pregnancy: Asleton 1985, Rayburn 1990, Schatz 1997, Torfs 1996, and Holm 1985. (Aselton et al. 1985; Rayburn et al. 1990; Schatz et al. 1997; Torfs et al. 1996; Holm and Clarren 1985) However, Kovanaze has not been studied in pregnant women in adequate and well-controlled clinical trials and in all



Reference ID: 3952361

clinical trials performed for this NDA, women who were pregnant or lactating were excluded.

Tetracaine, *p*-butylaminobenzoic acid (PBBA), and oxymetazoline have been shown to be excreted in the milk of lactating rats after a combination of subcutaneous tetracaine and oxymetazoline. However, it is unknown if tetracaine is excreted in human milk and there does not appear to be published literature documenting controlled trials of the excretion of oxymetazoline in human milk.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Three clinical trials were conducted with Kovanaze in pediatric subjects: SR 2-03, SR 2-07, and SR 3-04. St. Renatus seeks an indication for pediatric patients (b) (4) St. Renatus submitted a pediatric study plan for Kovanaze after the NDA was submitted. A partial waiver has been requested for those 0 to 2 years of age. The pediatric program for Kovanaze is complete.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose has occurred with both oxymetazoline alone and tetracaine alone. Symptoms of oxymetazoline overdose that St. Renatus intends to describe in the proposed package insert include:

> dizziness, chest pain, headaches, myocardial infarction, stroke, visual disturbances, arrhythmia, hypertension, or hypotension

(Source: NDA 208032 proposed package insert)

Symptoms of tetracaine overdose that St. Renatus intends to describe in the proposed package insert include:

> rapid circulatory collapse, cardiac arrest, and cerebral events

(Source: NDA 208032 proposed package insert)

Kovanaze has no known drug abuse potential.

Withdrawal and rebound are not known to occur with tetracaine. Rebound congestion has been associated with intranasal oxymetazoline.

## 7.7 Additional Submissions / Safety Issues

### 7.7.1 Effect of variation in droplet size distribution or spray pattern parameter on the incidence of adverse events

As described in section 6.1.10.2 of this review, some batches used in clinical trials with Kovanaze had variation in droplet size distribution, while others had variation in spray pattern parameter. Kovanaze batch 804007 used in trial SR 2-01 was the only Kovanaze batch used in Phase 2 and 3 clinical trials that did not demonstrate variation in droplet size distribution or spray pattern parameter. Of those batches that displayed variation in droplet size distribution or spray pattern parameter, no batches of Kovanaze had variation in both droplet size distribution and spray pattern parameter.

Below is a table of batches, the trials in which they were used, and presence or absence of variation in droplet size distribution or spray pattern parameter.

**Table 78 Batches used in clinical trials with Kovanaze**

| Batch | Trials | Variation in droplet size distribution or spray pattern parameter |
|---|---|---|
| 804007 | SR 2-01 | No variation |
| 006773 | SR 2-03 | Variation in droplet size distribution |
| 006775 | SR 2-05, SR 2-06, SR 3-01, SR 3-02 | Variation in droplet size distribution |
| 200093 | SR 2-07, SR 3-03, SR 3-04 | Variation in spray pattern parameter |
| 004011 | SR 2-02, SR 2-04 | Variation in spray pattern parameter |

Because batch 804007, used in clinical trial SR 2-01 appeared to have no variation in droplet size distribution or spray pattern variation, it may have been considered an ideal comparator for assessing adverse events in clinical trials in which batches were used that did exhibit variation in droplet size distribution or spray pattern variation. However, St. Renatus identified potential problems with this approach:

1. Methods used to analyze batch 804007:
In their response to Information Request on March 15, 2016, St. Renatus stated that for batch 804007, “the spray property data was collected for this particular lot using the methods in place at that time and cannot be easily compared to more recent test data.” (Source: NDA 208032 page 3 of Response to FDA Information Request March 15, 2016)

2. Completeness of adverse event data:
As the clinical development program advanced, the collected adverse event data became more complete. SR 2-01 was one of the early clinical trials with Kovanaze, and St. Renatus states that “the ability to compare the AE incidence rates for this particular

lot with other lots is somewhat limited." (Source: NDA 208032 page 3 of Response to FDA Information Request March 15, 2016)

In the table of adverse events in adults by batch below, the overall incidence of adverse events appears to be lower with batch 804007. According to St. Renatus, the other batches analyzed(004011, 006775, and 200093) "were the most current lots manufactured for clinical studies and are the most comparable in manufacturing process and testing to the to be marketed product." (Source: NDA 208032 page 3 of Response to FDA Information Request March 15, 2016) Among these three lots, adverse events mostly occurred with an incidence of within 15% of each other with the exception of four adverse events. These adverse events and a possible explanation for this finding are below:

1. Hypoesthesia oral
2. Hypoesthesia teeth
3. Pharyngeal hypoesthesia

Hypoesthesia is an expected effect of Kovanaze. St. Renatus explains that the difference in the adverse event of hypoesthesia between Kovanaze batches is because "some sites consistently documented this as an AE while others did not." (Source: NDA 208032 page 3 of Response to FDA Information Request March 15, 2016)

4. Procedural pain:
St. Renatus explains that the difference in the incidence in procedural pain between the batches of Kovanaze may be related to the nature of the clinical trials for which the batches were used. For example, batch 200093 (26% incidence of procedural pain) was used in adults in trial SR 3-03, a clinical trial in which patients were receiving a dental procedure. Batch 004011 (0% incidence of procedural pain) was used in adults in clinical trials SR 2-02 and SR 2-04, which took place in healthy volunteers, not dental patients.

It is important that batches 004011, 006775, and 200093 had similar incidences of adverse events because these batches did not have variation in both droplet size distribution and spray pattern parameter, but in either one or the other. Because the incidence of adverse events is similar in batches regardless of droplet size distribution or spray pattern parameter, then neither droplet size distribution nor spray pattern parameter affects the safety of Kovanaze.

Below is a table of adverse events in adults by batch based on tables submitted by St. Renatus on March 15, 2016.

**Table 79 Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term for Adults who received Kovanaze (either tetracaine 18 mg/oxymetazoline 0.3mg or tetracaine 12mg/oxymetazoline 0.2mg)**

| Number of adults who received Kovanaze (tet/oxy 18 /0.3 or tet/oxy 12/0.2) | N=58 | N=98 | N=100 | N=30 |
|---|---|---|---|---|
| System Organ Class<br>Preferred Term | Batch 004011<br>n(%) | Batch 006775<br>n(%) | Batch 200093<br>n(%) | Batch 804007<br>n(%) |
| Variation | Spray pattern parameter | Droplet size distribution | Spray pattern parameter | No variation |
| Cardiac Disorders | | | | |
| Bradycardia | 3 (5.2%) | 4 (4.1%) | 1 (1%) | 0 (0%) |
| Tachycardia | 0 (0%) | 3 (3.1%) | 0 (0%) | 0 (0%) |
| Eye Disorders | | | | |
| Lacrimation Increased | 2 (3.4%) | 13 (13.3%) | 8 (8%) | 1 (3.3%) |
| Gastrointestinal Disorders | | | | |
| Dysphagia | 4 (6.9%) | 2 (2%) | 1 (1%) | 0 (0%) |
| Hypoesthesia oral | 0 (0%) | 46 (46.9%) | 14 (14%) | 1 (3.3%) |
| Hypoesthesia teeth | 0 (0%) | 37 (37.8%) | 11 (11%) | 0 (0%) |
| Nausea | 0 (0%) | 4 (4.1%) | 2 (2%) | 0 (0%) |
| Injury, Poisoning, and Procedural Complications | | | | |
| Procedural Pain | 0 (0%) | 11 (11.2%) | 26 (26%) | 0 (0%) |
| Investigations | | | | |
| Blood pressure systolic increased | 0 (0%) | 0 (0%) | 8(8%) | 0 (0%) |
| Nervous System Disorders | | | | |
| Dizziness | 1 (1.7%) | 5 (5.1%) | 3 (3%) | 0 (0%) |
| Dysgeusia | 0 (0%) | 4 (4.1%) | 9 (9%) | 0 (0%) |
| Headache | 8 (13.8%) | 13 (13.3%) | 9 (9%) | 1 (3.3%) |
| Hypoesthesia | 1 (1.7%) | 34 (34.7%) | 5 (5%) | 0 (0%) |
| Paresthesia | 4 (6.9%) | 11 (11.2%) | 7 (7%) | 0 (0%) |
| Sinus Headache | 1 (1.7%) | 4 (4.1%) | 2 (2%) | 0 (0%) |
| Respiratory, Thoracic, and Mediastinal Disorders | | | | |
| Epistaxis | 3 (5.2%) | 6 (6.1%) | 3 (3%) | 0 (0%) |
| Nasal Congestion | 19 (32.8%) | 32 (32.7%) | 28 (28%) | 6 (20%) |
| Nasal Discomfort | 9 (15.5%) | 26 (26.5% | 24 (24%) | 0 (0%) |
| Nasal Dryness | 4 (6.9%) | 1 (1%) | 4 (4%) | 0 (0%) |
| Oropharyngeal pain | 2 (3.4%) | 15 (15.3%) | 15 (15%) | 0 (0%) |
| Pharyngeal hypoesthesia | 4 (6.9%) | 21 (21.4%) | 5 (5%) | 0 (0%) |

| Number of adults who received Kovanaze (tet/oxy 18 /0.3 or tet/oxy 12/0.2) | N=58 | N=98 | N=100 | N=30 |
|---|---|---|---|---|
| System Organ Class<br>Preferred Term | Batch 004011<br>n(%) | Batch 006775<br>n(%) | Batch 200093<br>n(%) | Batch 804007<br>n(%) |
| Variation | Spray pattern parameter | Droplet size distribution | Spray pattern parameter | No variation |
| Rhinalgia | 2 (3.4%) | 6 (6.1%) | 5 (5%) | 0 (0%) |
| Rhinorrhea | 28 (48.3%) | 49 (50%) | 57 (57%) | 4 (13.3%) |
| Sneezing | 10 (17.2%) | 5 (5.1%) | 4 (4%) | 1 (3.3%) |
| Throat Irritation | 1 (1.7%) | 10 (10.2%) | 8 (8%) | 0 (0%) |
| Upper-Airway Cough Syndrome | 0 (0%) | 3 (3.1%) | 0 (0%) | 0 (0%) |
| Vascular Disorders | | | | |
| Hypertension | 0 (0%) | 5 (5.1%) | 0 (0%) | 1 (3.3%) |

Notes: An adverse event was not included in the above table if it did not occur in any batch at an incidence of ≥2.5%.

Below is a table of adverse events in pediatrics by batch based on tables submitted by St. Renatus on March 15, 2016.

Most of the adverse events occurred with similar frequencies in the two batches of Kovanaze analyzed, with variation in incidences of adverse events usually within 15%. Five adverse events occurred with variation in incidence greater than 15% between batches. These adverse events and a possible explanation for this finding are below:

1. Lacrimation increased
Batch 006773 had an incidence of "lacrimation increased" of 43.8%. Batch 200093 had an incidence of "lacrimation increased" of 21.8%. It is unclear what the cause for the increased incidence of lacrimation in batch 006773 is compared to batch 200093, but in the analysis of adult adverse events (above), the incidence of lacrimation was similar among the three more recently manufactured batches.

2. Hypoesthesia oral
3. Hypoesthesia teeth
4. Hypoesthesia
St. Renatus attributes the increased reporting of hypoesthesia for batch 006773 to variation in clinical trial site practices.

5. Nasal congestion
There is a higher incidence of nasal congestion with batch 006773 (47.9%) when compared to batch 200093 (19.2%). St. Renatus attributes the increased reporting of nasal congestion for batch 006773 to variation in clinical trial site practices.

**Table 80 Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term for Pediatrics who received Kovanaze**

| Number of pediatrics who received Kovanaze (with tetracaine quantities of 12,6, and 3-3.6mg) | N=48 | N=78 |
|---|---|---|
| System Organ Class<br>Preferred Term | Batch 006773<br>n(%) | Batch 200093<br>n(%) |
| Variation | Droplet size distribution | Spray pattern parameter |
| Eye Disorders | | |
| Lacrimation Increased | 21 (43.8%) | 17 (21.8%) |
| Gastrointestinal Disorders | | |
| Dysphagia | 2 (4.2%) | 0 (0%) |
| Hypoesthesia oral | 30 (62.5%) | 19 (24.4%) |
| Hypoesthesia teeth | 30 (62.5%) | 16 (20.5%) |
| Paresthesia oral | 0 (0%) | 3 (3.8%) |
| Vomiting | 2 (4.2%) | 0 (0%) |
| General Disorders and Administration Site Conditions | | |
| Injection Site Anaesthesia | 0 (0%) | 4 (5.1%) |
| Injection Site Pain | 1(2.1%) | 7 (9.0%) |
| Pain | 1 (2.1%) | 2 (2.6%) |
| Temperature Intolerance | 3 (6.3%) | 0 (0%) |

| Number of pediatrics who received Kovanaze (with tetracaine quantities of 12,6, and 3-3.6mg) | N=48 | N=78 |
|---|---|---|
| System Organ Class<br>Preferred Term | Batch 006773<br>n(%) | Batch 200093<br>n(%) |
| Variation | Droplet size distribution | Spray pattern parameter |
| Injury, Poisoning, and Procedural Complications | | |
| Post procedural discomfort | 2 (4.2%) | 1 (1.3%) |
| Procedural pain | 20 (41.7%) | 16 (20.5%) |
| Nervous System Disorders | | |
| Dysgeusia | 3 (6.3%) | 2 (2.6%) |
| Headache | 0 (0%) | 6 (7.7%) |
| Hypoesthesia | 33 (68.8%) | 19 (24.4%) |
| Respiratory, Thoracic, and Mediastinal Disorders | | |
| Epistaxis | 2 (4.2%) | 1 (1.3%) |
| Intranasal hypoesthesia | 3 (6.3%) | 0 (0%) |
| Nasal Congestion | 23 (47.9%) | 15 (19.2%) |
| Nasal Discomfort | 8 (16.7%) | 10 (12.8%) |
| Pharyngeal hypoesthesia | 3 (6.3%) | 3 (3.8%) |
| Rhinalgia | 5 (10.4%) | 6 (7.7%) |
| Rhinorrhea | 16 (33.3%) | 23 (29.5%) |
| Sneezing | 5 (10.4%) | 6 (7.7%) |
| Throat Irritation | 2 (4.2%) | 2 (2.6%) |

Notes: An adverse events was not included in the above table if it did not occur in any batch at an incidence of ≥2.5%.

St. Renatus states that the "various lots that were used over the clinical program do not appear to have been related to the frequency of reported TEAEs." (Source: NDA 208032 page 3 of Response to FDA Information Request March 15, 2016) This assessment of Kovanaze batches (lots) as they relate to the adverse event profile of Kovanaze appears reasonable. Variation in droplet size distribution and spray pattern parameter do not appear to affect the safety of Kovanaze.

### 7.7.2 Use of SR 3-02 to evaluate local safety of P-butylaminobenzoic acid

To assist in assessment of the local safety of P-butylaminobenzoic acid (PBBA) in Kovanaze, trial SR 3-02 was evaluated. SR 3-02 was chosen because, in this trial, the drug product batch may have contained an increased percentage of PBBA and olfactory function and local tissue reaction were assessed. In SR 3-02, 44 adult subjects received Kovanaze. SR 3-02 is described in section 5.3.3.2 and an analysis of the efficacy of Kovanaze demonstrated in this trial is in section 6.0 of this review. Evaluations that took place in this clinical trial that have assisted in demonstrating the local safety of the PBBA in Kovanaze include a naris examination, an alcohol sniff test, and certain adverse events reported. Below are details of these three assessments.

1. Naris examination
Naris examination (further described in section 9.4.3 of this review) was to have taken place during the screening period (up to 14 days before taking part in the clinical trial),

immediately before the procedure, 120 minutes after the first spray of Kovanaze (T120), and at the next-day follow-up visit. Naris examination was also performed in SR 2-03, SR 3-01, SR 3-03, and SR 3-04. Because SR 3-03 was also a Phase 3 clinical trial in adults, an identical naris examination was performed in both trials, and the level of PBBA in the batch of Kovanaze in SR 3-03 was lower than PBBA in the batch of Kovanaze in SR 3-02, the results of the nasal examination from SR 3-02 were compared with the results of the nasal examination from SR 3-03. The naris examination evaluated ulceration, patency, redness, inflammation, and bleeding.

Nasal ulceration in the treatment naris

In section 7.4.5.2 of this review, subjects were identified who had nasal ulceration after trial drug, but not before trial drug. Below is a table that compares the incidence in subjects in SR 3-02 and SR 3-03 who had nasal ulceration present after trial drug but not before. The incidence of nasal ulceration present after trial drug, but not before trial drug in SR 3-02 is higher (9%) than in SR 3-03 (4%). The significance of this finding is unclear. The incidence of nasal ulceration after trial drug, but not before trial drug was also approximately twice as high in SR 3-02 placebo subjects compared to SR-3-03 placebo subjects. (Of note, placebo in both SR3-02 and SR 3-03 consisted of an aqueous solution with all the parts of Kovanaze except the active ingredients.) This could suggest systematic differences in the way the assessments were done, leading to a higher incidence of nasal ulceration after trial drug in SR 3-02 that is not attributable to Kovanaze, itself.

**Table 81 Comparison of incidence of nasal ulceration present after trial drug but not before trial drug in SR 3-02 and SR 3-03**

| | SR 3-02 | SR 3-03 |
|---|---|---|
| Number of subjects who received Kovanaze who had ulceration after trial drug but not before (% from all subjects in this trial who received Kovanaze) | 4 of 44 (9%) | 4 of 100 (4%) |
| Number of subjects who received placebo who had ulceration after trial drug but not before (% from all subjects in this trial who received placebo) | 1 of 22 (4.5%) | 1 of 50 (2%) |

To assess for factors that may increase the likelihood of developing nasal ulceration, subjects in SR 3-02 and SR 3-03 who received Kovanaze and had nasal ulceration after trial drug, but not before trial drug were evaluated. Subjects who experienced nasal ulceration after Kovanaze (but not before Kovanaze) do not appear to share common demographic traits.

Patency of treatment naris

Of subjects in SR 3-02 and SR 3-03 who received Kovanaze, one subject in each group developed lack of patency in the treatment naris following Kovanaze administration. Below are details of these two subjects:

SR 3-02 Subject 2-055
Subject 2-055 is a 21-year-old female. She had a patent treatment naris at both screening and pre-study. At T120 after study treatment, her naris was not patent, but patency returned by the next-day examination. At T120, she also had nasal ulceration that was not present pre-study and was not present at the next-day naris examination. No inflammation was present at any of her naris examinations. The color of her nasal mucosa was slightly red at screening and pre-study, but was pink at T120. Her nasal mucosa was slightly red at the next-day naris examination.

SR 3-03 Subject 7-121
Subject 7-121 is a 34-year-old female. At screening, which was the same day as study treatment, she had a patent naris. At the screening naris examination, nasal mucosa was slightly red, had slight inflammation, and there were no ulcerations. At T120, mucosa was pink and there was no inflammation. At the next-day follow-up, mucosa was red and there was inflammation.

Redness of treatment naris
No subjects treated with Kovanaze or placebo in SR 3-02 had a pink treatment naris before study drug and a red treatment naris after study drug. One subject (6-096) treated with Kovanaze and one subject (6-063) treated with placebo in SR 3-03 had a pink treatment naris before study drug and a red treatment naris after study drug.

Inflammation of treatment naris
No subjects treated with Kovanaze or placebo in SR 3-02 developed the designation of “inflammation” after Kovanaze unless some degree of inflammation was present before Kovanaze. No subjects treated with Kovanaze in SR 3-03 developed the designation of “inflammation” after Kovanaze unless some degree of inflammation was present before Kovanaze. One subject (6-063) treated with placebo in SR 3-03 developed the designation of “inflammation” after Kovanaze even though inflammation was not present before Kovanaze. Of note, it does not appear that the Applicant formally defined “inflammation.”

Bleeding of treatment naris
The naris examination data set was reviewed for cases in SR 3-02 and SR 3-03 in which subjects had bleeding of the treatment naris after Kovanaze, but not before Kovanaze. Two subjects in SR 3-02 were reported as having slight/minor bleeding at a time point after Kovanaze administration, but not before Kovanaze administration. No subjects in SR 3-03 were reported as having bleeding at a time point after Kovanaze administration, but not before Kovanaze administration. However, epistaxis was an adverse event captured in subjects receiving Kovanaze in both SR 3-02 and SR 3-03. Epistaxis was an adverse event that occurred more frequently with Kovanaze in SR 3-03 than in SR 3-02. See section 7.3.5 of this review for details of epistaxis seen with Kovanaze.

2. Alcohol sniff test

The alcohol sniff test (further described in section 9.4.4 of this review) was to have taken place immediately before the procedure, 120 minutes after the first spray of Kovanaze, and at the next-day follow-up visit. The results of the alcohol sniff test for SR 3-02 are in the table below.

**Table 82 Alcohol Sniff Test Results (cm) Pre-Study through 24 h Post-Treatment (Safety Population)**

| Time Point | Statistic | (b) (4) (N=44) | TET (N=44) | PBO (N=22) |
|---|---|---|---|---|
| Pre-Study | n | 44 | 44 | 22 |
| | Mean (SD) | 19.2 (8.96) | 18.8 (10.00) | 21.2 (8.35) |
| | Median | 22.0 | 20.8 | 23.0 |
| | Min, Max | 2, 30 | 1, 30 | 2, 29 |
| $T_{120}$ min | n | 44 | 44 | 22 |
| | Mean (SD) | 18.0 (9.47) | 17.7 (9.48) | 20.9 (8.13) |
| | Median | 20.5 | 20.5 | 23.0 |
| | Min, Max | 0, 30 | 1, 30 | 1, 29 |
| $T_{Next\ Day}$ | n | 42 | 43 | 21 |
| | Mean (SD) | 18.2 (8.51) | 16.1 (8.74) | 20.4 (8.38) |
| | Median | 19.3 | 17.5 | 23.0 |
| | Min, Max | 2, 29 | 2, 30 | 2, 30 |

Source: Table 14.5.2.1
TET: Tetracaine alone; PBO: Placebo
(Source: NDA 208032 Applicant's table page 126 of SR 3-02 Clinical Study Report)

Because the results of the alcohol sniff test in the table above may have masked individual subject variation in results of the alcohol sniff test, the results of the alcohol sniff test in individual subjects were examined more closely. Below is a list of subjects who required alcohol to be moved 50% or more of their pre-study alcohol sniff test distance closer after Kovanaze at the next-day follow-up or at both 120 minutes and the next-day follow-up.

**Table 83 Subjects who received Kovanaze in SR 3-02 and SR 3-03 and required alcohol to be moved 50% or more of their pre-study alcohol sniff test distance closer after Kovanaze at either the next day follow-up or at both 120 minutes and at the next day follow-up**

| Subjects who received Kovanaze and required alcohol to be moved 50% or more of their pre-study alcohol sniff test distance closer after Kovanaze at either the next day follow-up or at both 120 minutes and at the next day follow-up | |
|---|---|
| SR 3-02 N=44 | SR 3-03 N=100 |
| 2-086 | 5-031 |
| 4-027 | 5-035 |
| | 6-072 |

| | |
|---|---|
| | 6-085 |
| | 6-095 |
| | 5-013 |
| | 6-069 |
| | 6-094 |

Below is a table with details of subjects who experienced a decrement in their alcohol sniff test results listed in the table above. All but two of the subjects who performed poorly on the alcohol sniff test after Kovanaze experienced some form of nasal congestion or rhinorrhea as an adverse event. None of these subjects experienced naris bleeding before or after Kovanaze.

**Table 84 Subjects in SR 3-02 and SR3-03 who experienced a decrement in their alcohol sniff test results**

| Subject | Naris color | Naris inflammation | Adverse events by verbatim term that may have contributed to a decrement in alcohol sniff test results |
|---|---|---|---|
| SR 3-02 N=44 | | | |
| 2-086 | Slightly red before and after Kovanaze | None before or after Kovanaze | Congestion, nasal congestion |
| 4-027 | Pink before and after Kovanaze | None before or after Kovanaze | Soft tissue lesion in right nostril, runny nose right side naris |
| SR 3-03 N=100 | | | |
| 5-013 | Pink before and after Kovanaze | None before or after Kovanaze | |
| 5-031 | Pink before and after Kovanaze | None before or after Kovanaze | Phlegm in throat, runny nose |
| 5-035 | Pink before and after Kovanaze | None before or after Kovanaze | Stuffy nose |
| 6-069 | Pink at screening and T120; slightly red the next day | No inflammation at screening and T20; slight inflammation the next day | Runny nose |
| 6-072 | Pink before and after Kovanaze | None before or after Kovanaze | Right nostril numb |
| 6-085 | Pink at screening and T120; slightly red the next day | No inflammation at screening and T120; slight inflammation the next day | Stuffiness in left nostril, mucous build-up in throat, |
| 6-094 | Slightly red at screening and T120 | No inflammation at screening and T120 | Runny nose right nostril |
| 6-095 | Slightly red at screening and T120; pink the next day | Slight inflammation at screening and T120; no inflammation the next day | Left nostril runny |

The increased incidence of a decrement of alcohol sniff test results in SR 3-03 compared to in SR 3-02 is reassuring because the purpose of this analysis is to demonstrate that the PBBA level in the Kovanaze batch in SR 3-02 did not contribute to an increase in adverse events in SR 3-02.The Kovanaze used in SR 3-02 does not appear to have had a clinically significant impact on olfactory sensitivity.

3. Select adverse events
Other indicators of local toxicity of PBBA may have been the incidence of certain adverse events listed below:

- rhinorrhea
- nasal congestion
- nasal discomfort
- rhinalgia

The incidence of these adverse events in SR 3-02 was compared to the incidence of these adverse events in SR 3-03 in the table below. Of the four adverse events that were examined, the incidence was similar between SR 3-02 and SR 3-03 for nasal congestion, nasal discomfort, and rhinalgia. The incidence of rhinorrhea was higher in SR 3-03 compared with SR 3-02.

**Table 85 Incidence of rhinorrhea, nasal congestion, nasal discomfort, and rhinalgia in SR 3-02 compared to SR 3-03**

| Preferred Term | # subjects who received Kovanaze in SR 3-02 n(%) | # subjects who received Kovanaze in SR 3-03 n(%) |
|---|---|---|
| | N=44 | N=100 |
| Rhinorrhea | 17 (38.64%) | 57 (57%) |
| Nasal congestion | 15 (34.09%) | 28 (28%) |
| Nasal discomfort | 11 (25%) | 24 (24%) |
| Rhinalgia | 3 (6.82%) | 5 (5%) |

In summary, the local safety of the Kovanaze batch used in SR 3-02 is supported by evaluation of the naris examination, the alcohol sniff test, and the incidence of certain adverse events in SR 3-02.

### 7.7.3 Methemoglobinemia

Methemoglobinemia is known to occur with local anesthetics, including tetracaine. Because Kovanaze contains tetracaine, those using Kovanaze will be cautioned in the package insert about the possibility of methemoglobinemia.

# 8 Postmarket Experience

No postmarketing safety data exists for Kovanaze because it has not been registered in any country.

# 9 Appendices

## 9.1 Literature Review/References

The Applicant identified publications from the following sources: PubMed, Cochrane database, Hazardous Substance Data Base, ToxNet, clinicaltrials.gov database and citations in important publications.

One hundred forty-five publications were submitted by St. Renatus to accompany this NDA submission.

Below is a list of adverse events identified in the literature by St. Renatus followed by the publication citation in which these adverse events were contained:

For a combination of tetracaine and oxymetazoline:

- Nasal pain, throat pain, gagging/nausea, unpleasant taste, globus sensation, dysphagia, dyspnea were common adverse events (Gaviola, Chen, and Chia 2013)
- Methemoglobinemia (Whited and Cohen 2012)

For tetracaine:

- Erythema, itching (Mazumdar, Tomlinson, and Faulder 1991)
- Minor skin reactions (Ogden, Love, and Basta 2008)
- Anaphylactic reaction in one subject, hypotension or seizures and agitation in two subjects (Tucker and al Haddad 1991)
- Unpleasant taste(Alterio et al. 2006)
- Erythema (Speirs et al. 2001)
- Erythema (Taddio et al. 2006)
- Erythema and edema (O'Brien et al. 2004)
- Erythema, edema, itching (Doyle et al. 1993)
- Erythema, blanching (Shah et al. 2008)
- Erythema (Lemyre et al. 2006; Lemyre et al. 2007)
- Death (Christie 1976)
- Death; syncope; circulatory collapse (Adriani and Campbell 1956)
- Seizure, cardiopulmonary arrest, dizziness, difficulty speaking, facial paresis, unresponsive to commands (Patel, Chopra, and Berman 1989)
- Methemoglobinemia (Lavergne et al. 2006)
- Pruritic lesions (Garcia-Gavin et al. 2011)
- From ophthalmic solution: corneal infiltrate, reduced visual acuity, erythematous dermatitis right side of face, corneal scarring, permanent loss of vision (Duffin and Olson 1984)

- Contact dermatitis (Warshaw et al. 2008)
- Death (Ireland, Ferguson, and Stark 1951)
- Vertigo; facial nerve weakness (Hoffman and Li 2001)
- Bradycardia (Maulidi et al. 2012)
- Skin irritation and pain (Wongprasartsuk and Main 1998)
- Erythema (Woolfson, McCafferty, and Boston 1990)
- Muscle spasm, convulsion; cardiac arrest (Zhijun et al. 2008)

For oxymetazoline:

- Nausea, vomiting, dizziness, abnormal coordination, somnolence (Perelman et al. 2013)
- Two subjects developed bilateral blepharitis with ophthalmic oxymetazoline (Duzman, Warman, and Warman 1986)
- Dry eyes and burning sensation were common adverse events with ophthalmic oxymetazoline (Dorn, Hofmann, and Knick 2003)
- Decreased tear volume and flow with ophthalmic oxymetazoline (Gobbels, Achten, and Spitznas 1991)
- Decrease in the resistivity index of the central retinal artery in the glaucoma patients with ophthalmic oxymetazoline (Arikan et al. 2006)
- Rebound congestion after continued oxymetazoline (Graf, Hallen, and Juto 1995; Graf 1997)
- Palpitations (Ferguson, Paramaesvaran, and Rubinstein 2001)
- Burning sensation (Green 1966)
- Chest pain, headache, hypertension, allergic rhinitis, ST-segment elevation, ballooning syndrome (Wang et al. 2009)
- Myocardial infarction (Rajpal, Morris, and Akkus 2014)
- Heart palpitations, dizziness (Khan and Dewhurst 1997)
- Depressed uterine contractions (Baxi et al. 1985)
- CNS vasculitis (Greene 2005)
- Decreased visual acuity (Magargal et al. 1985)
- Anxiety, hostility, paranoia, and hallucinations (Ticoll and Shugar 1994)
- Acute panic disorder (Saadah 1987)
- Hallucinations, psychosis, anxiety (Escobar and Karno 1982)
- Dizziness, bradycardia, hypotension, fall (Glazener, Blake, and Gradman 1983)
- Acute vision disturbance (Fivgas and Newman 1999)
- Cerebral infarct (Montalban et al. 1989)
- Headache, nausea, vomiting, sonophobia, photophobia; vasospasm on cerebral angiogram (Loewen, Hudon, and Hill 2004)
- Stroke (Cantu et al. 2003)
- Sedation, convulsive seizure, excitement, insomnia, hypothermia, tachycardia, peripheral vasoconstriction, anxiety, hallucinations (Soderman, Sahlberg, and Wiholm 1984)
- Hypertension, asystole (Thrush 1995)

- Hypotension, bradycardia (Fabi, Formigari, and Picchio 2009)
- Hypertensive crisis, decreased heart rate (Latham and Jardine 2013)

While it is useful to note the existence of the adverse events in the literature with tetracaine and oxymetazoline, most adverse events that will be included in the Kovanaze package insert will come directly from the clinical trials performed with Kovanaze. Some clinical issues with Kovanaze required further exploration that was not provided in clinical trials with Kovanaze alone. These issues required further articulation with published literature and include:

- ECG findings with oxymetazoline; see section 7.4.4 of this review
- Observational studies in pregnant women; see section 7.6.2 of this review
- Methemoglobinemia; see section 7.7.3 of this review

## 9.2 Labeling Recommendations

Labeling is still under internal discussion as well as discussion with the Applicant. From a clinical standpoint, the following sections will need extensive revisions:

- Highlights of Prescribing Information
- Full Prescribing Information: Contents
- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- WARNINGS AND PRECAUTIONS
- ADVERSE REACTIONS
- DRUG INTERACTIONS
- USE IN SPECIFIC POPULATIONS
- OVERDOSAGE
- CLINICAL STUDIES
- REFERENCES
- HOW SUPPLIED/ STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

## 9.3 Advisory Committee Meeting

No advisory committee meeting was conducted for this application.

## 9.4 Details of Some Assessments in SR 3-02 and SR 3-03

### 9.4.1 Subject-Reported Safety Evaluation (SRSE):

(Verbatim from NDA 208032 page 111 of SR 3-02 protocol version 3.0 and page 62 of SR3-02 protocol version 2.0)

To assess conditions that could be associated with the investigative drug, ask the subject the following questions.

- "Do you feel any different now than when you came in for treatment today?"
- "Are you currently feeling or exhibiting any of the following conditions?":

| | | | |
|---|---|---|---|
| A. | restlessness | Y | N |
| B. | dizziness | Y | N |
| C. | confusion | Y | N |
| D. | body numbness | Y | N |
| E. | tinnitus | Y | N |
| F. | blurred vision | Y | N |
| G. | tremors | Y | N |
| H. | nausea | Y | N |
| I. | itching | Y | N |
| J. | breathing problems | Y | N |
| K. | light headedness | Y | N |
| L. | metallic taste | Y | N |
| M. | numbness around mouth | Y | N |
| N. | agitation | Y | N |

## 9.4.2 Subjective Numbness Assessment (SNA)

(Verbatim from NDA 208032 page 112 of SR 3-02 protocol version 3.0)

To assess conditions that could be associated with investigative drug, ask the subject the following questions.

- "Do you notice any abnormal sensation when you tap your front teeth together?"
- "Do you notice any abnormal sensation in the roof of your mouth?"

Record the Yes/No response in the source documents.

## 9.4.3 Naris Examination (NE):

(The naris examination below is verbatim from NDA 208032 page 114 of SR 3-02 protocol version 3.0; an identical version of this naris examination is on page 62 of SR 2-03 protocol version 1.0. The following contain a nearly identical version with identical wording, but a slightly different format of item #3: page 63 of SR 3-03 protocol version 2.0 and page 67 of SR3-04 protocol version 1.0)

1. **Evaluate the patency of the naris**: On the same side of the head that will be dosed or was dosed during the procedure, manually occlude the nostril not used for dosing study drug and ask the subject to sniff gently. Record the response (Yes/No/Not Done) to the question, "Is the treatment nostril patent?"

2. **Examine the nasal vestibule and anterior nasal cavity**: Ask the subject to tilt his/her head backwards, and lift the tip of the nose.

3. **Perform a visual inspection**, assessing the color of the mucosa, inflammation and evaluate apparent bleeding or ulcerations. Record findings on the source documents.

**Naris Examination (NE)** ☐ **Left** ☐ **Right** *(the same side as the dental procedure)* ☐ Not Done

| Assessment | Result / Observation | | |
|---|---|---|---|
| Patency of the treatment naris | Is the treatment naris patent? | | ☐ No ☐ Yes |
| Ulceration | Does the treatment naris have ulcerations? | | ☐ No ☐ Yes |
| Color | ☐ Pink | ☐ Slightly red | ☐ Red |
| Inflammation | ☐ No inflammation | ☐ Slight inflammation | ☐ Inflammation |
| Bleeding | ☐ None | ☐ Slight/minor | ☐ Significant/ major |

**4. Record any abnormal findings.**

## 9.4.4 Alcohol Sniff Test (AST):

(Verbatim from NDA 208032 page 115 of SR 3-02 protocol version 3.0 and page 64 of SR 3-03 protocol version 2.0)

1) Open a standard 70% isopropyl alcohol preparation pad so that 0.5 cm of the entire pad is visible.

2) Place the alcohol pad beneath the subject's nostrils while the subject inspires twice to become familiar with the alcohol odor.

3) After the subject acknowledges the presence of the alcohol odor, withdraw the alcohol pad.

4) This is the start of the threshold test: Ask the subject to close the mouth and eyes, breathe normally through the nostril ipsilateral to the treatment tooth (closing the other nostril), and indicate when the odor is detected. NOTE: Discourage active sniffing and deep inspiration.

5) Hold a standard metric ruler in place extending inferiorly from the bridge of the nose.

6) Place the alcohol pad 30 cm below the nose and, with each expiration, move it 2 cm closer to the naris until the subject detects the presence of odor.

7) Measure the distance in centimeters from the anterior naris to the alcohol pad at the point at which the subject first detects the odor. Record this distance on the source documents.

| | |
|---|---|
| Alcohol Sniff Test Result: | __ __ . __ cm |

### 9.4.5 Soft-Tissue Anesthesia Assessment (STAA):

(Verbatim from NDA 208032 page 113 of SR 3-02 protocol version 3.0)

> To assess soft-tissue anesthesia, use a mechanical probe (i.e., Sensor Probe, Zila Pharmaceuticals, Inc.) to exert pressure on the:
>
> - Incisive papilla
> - Greater palatine foramen ipsilateral to the Study Dental Procedure
>
> For each site tested, ask the subject, "Do you feel any pain?" (Yes/No)
>
> Testing at each of the two soft-tissue sites will take place at baseline, and T15, T30, T45, T60, T90 and T120 (unless pain is detected) and at the Next-day Follow-Up Visit.

## 9.5 Phase 1 Clinical Trials

The following are Phase I clinical trials conducted for Kovanaze: AP 1-01, AP 1-02, SR 2-02, SR 2-06, and SR 2-07. Below are brief summaries of some of the Phase 1 trials. These summaries are meant to be brief and allow for an overview of the Phase 1 trials that took place. For the purpose of this NDA, Phase 1 trials provide supportive safety information described more thoroughly in section 7.0 of this review. Demonstration of efficacy of Kovanaze is dependent on Phase 3 trials, not the Phase 1 trials described below.

### 9.5.1 AP 1-02

This trial is notable because five subjects received 18 mg tetracaine/ 0.3 mg oxymetazoline and five subjects received 12 mg tetracaine/ 0.2mg oxymetazoline, but the safety results are not included in the Integrated Safety Database.

Title: A Phase 1 Single-Center Dose-Ranging Study of (b) (4) with Oxymetazoline Hydrochloride for Anesthetizing Maxillary Teeth in Healthy Subjects

Trial Design: Open-label dose-ranging trial

Trial Population: Twenty-three healthy adult subjects 18 to 30-years-old. Part 1 included 13 subjects. Part 2 included 10 subjects.

Trial Medications and Treatment Groups: trial medications included two formulations of tetracaine and oxymetazoline:
1. 3% tetracaine HCl with 0.05% oxymetazoline HCl
2. 4% tetracaine HCl with 0.05% oxymetazoline HCl

There were two parts to this trial: Part 1 and Part 2. In Part 1, three cohorts received the following total amount of drug as bilateral doses:

- Tetracaine 12 mg/0.2 mg oxymetazoline (6/0.1 in each nostril)
- Tetracaine 16 mg/0.2mg oxymetazoline (8/0.1 in each nostril)
- Tetracaine 18 mg/0.3mg oxymetazoline (9/0.15 in each nostril)

In Part 2, all subjects received a total dose of tetracaine 9 mg/0.15 mg oxymetazoline in the right nostril only.

Safety Assessments: Subjects were evaluated for the following:

- adverse events
- vital signs
- alcohol sniff test
- gag reflex
- swallowing function tests
- Three questionnaires

Relevant notable trial results:
The study report concluded that for "clinically significant anesthesia" to be achieved, bilateral dosing of Kovanaze was necessary. (Source: NDA 208032 page 4 of AP1-02 Clinical Study Report)

Because the Integrated Safety Database does not contain the results of this trial, but relevant doses 12 mg tetracaine/0.2mg oxymetazoline and 18 mg tetracaine/0.3 mg oxymetazoline were used in this trial, below is a discussion of the safety results of this trial.

Adverse Events: No serious adverse events were reported. All adverse events were mild with the exception of four adverse events that were moderate. Some events, such as "nasal/face numbness, nasal stuffiness, mild irritation, and mild pain" were considered to be "expected effects" and were not considered to be adverse events. (Source: NDA 208032 page 29 of AP1-02 Clinical Study Report) Below is a table of adverse events from Part 1 of trial AP 1-02

**Table 86 Adverse Events and Expected Effects in Part 1 (Bilateral Dosing)**

| | Tetracaine/Oxymetazoline, mg | | |
|---|---|---|---|
| | **12/0.2 mg** | **16/0.2 mg** | **18/0.3 mg** |
| No. of subjects with at least 1 AE/total no. subjects | 3/5 | 2/3 | 1/5 |
| No. of events: | | | |
| Bleeding from mesial papilla #7 | 1 | 0 | 0 |
| Cold symptoms | 0 | 1 | 0 |
| Difficulty breathing | 1 | 1 | 0 |
| Dizziness | 1 | 0 | 0 |
| Headache | 1 | 2 | 0 |
| Itching, itching on head, itching outside nose | 1 | 2 | 1 |

| | Tetracaine/Oxymetazoline, mg | | |
|---|---|---|---|
| | **12/0.2 mg** | **16/0.2 mg** | **18/0.3 mg** |
| Nasal irritation (moderate) | 0 | 0 | 1 |
| Sneeze pre-dose, post-dose | 0 | 2 | 0 |
| Teary eyes | 0 | 1 | 0 |
| Tiredness | 0 | 1 | 0 |
| No. of subjects with at least 1 expected effect/total no. subjects | 5/5 | 3/3 | 2/5 |
| No. of events: | | | |
| Mild nasal or throat irritation | 4 | 1 | 0 |
| Nasal itching (mild) | 1 | 0 | 0 |
| Runny nose (mild) | 1 | 0 | 1 |
| Mild pain (nasal) | 0 | 3 | 0 |
| Nasal stuffiness (mild) | 0 | 1 | 0 |
| Sniffling (mild) | 0 | 1 | 0 |

Source: Listings 5.1A (AEs) and 5.2A (expected effects)

(Source: NDA 208032 Applicant's table page 30 of AP1-02 Clinical Study Report; header row added by reviewer)

Alcohol sniff test: Below are tables of the summary of Mean Changes from baseline for alcohol sniff tests.

Results for Study AP 1-02
Table 3A: Summary of Mean Changes from Baseline for Alcohol Sniff Test by Total Dose and Time Period

---------- Dose: Tetra./Oxymet.=12/0.2 ----------

The MEANS Procedure

| Time Period | N Obs | Variable | Label | N | Mean | Std Dev |
|---|---|---|---|---|---|---|
| Baseline | 5 | ASTRES | Sniff Test Result | 5 | 20.60 | 6.07 |
| | | d_astres | Ch/BL Sniff Test Result | 0 | . | . |
| T_035_min | 5 | ASTRES | Sniff Test Result | 5 | 18.40 | 7.92 |
| | | d_astres | Ch/BL Sniff Test Result | 5 | -2.20 | 7.56 |
| T_END | 5 | ASTRES | Sniff Test Result | 5 | 22.80 | 3.35 |
| | | d_astres | Ch/BL Sniff Test Result | 5 | 2.20 | 4.82 |

---------- Dose: Tetra./Oxymet.=16/0.2 ----------

| Time Period | N Obs | Variable | Label | N | Mean | Std Dev |
|---|---|---|---|---|---|---|
| Baseline | 3 | ASTRES | Sniff Test Result | 3 | 15.33 | 9.45 |
| | | d_astres | Ch/BL Sniff Test Result | 0 | . | . |
| T_035_min | 3 | ASTRES | Sniff Test Result | 3 | 20.67 | 4.16 |
| | | d_astres | Ch/BL Sniff Test Result | 3 | 5.33 | 8.33 |
| T_END | 3 | ASTRES | Sniff Test Result | 3 | 12.00 | 7.21 |
| | | d_astres | Ch/BL Sniff Test Result | 3 | -3.33 | 5.03 |

Results for Study AP 1-02
Table 3A: Summary of Mean Changes from Baseline for Alcohol Sniff Test by Total Dose and Time Period

---------- Dose: Tetra./Oxymet.=18/0.3 ----------

The MEANS Procedure

| Time Period | N Obs | Variable | Label | N | Mean | Std Dev |
|---|---|---|---|---|---|---|
| Baseline | 5 | ASTRES | Sniff Test Result | 5 | 16.00 | 7.07 |
| | | d_astres | Ch/BL Sniff Test Result | 0 | . | . |
| T_035_min | 5 | ASTRES | Sniff Test Result | 5 | 10.80 | 5.59 |
| | | d_astres | Ch/BL Sniff Test Result | 5 | -5.20 | 9.55 |
| T_END | 5 | ASTRES | Sniff Test Result | 5 | 17.60 | 2.61 |
| | | d_astres | Ch/BL Sniff Test Result | 5 | 1.60 | 5.55 |

(Source: NDA 208032 Applicant's tables pages 75 and 76 of AP 1-02 Clinical Study Report)

Gag reflex: Gag reflex was normal for all subjects before study drug and after return of sensation after study drug.

Swallow test: Subject 01/025 received 18 mg tetracaine/0.3 mg oxymetazoline in Part 1. This subject did not swallow normally before study drug and swallowing worsened at the end of the test. All other subjects had normal swallowing before study drug and at the end of the test.

Numbness Questionnaire: Numbness of the lip, nose, cheek, or lower eyelid occurred in eight of 13 subjects in Part 1 and nine of 10 subjects in Part 2.

Nasal Symptoms Questionnaire:
In Part 1, nasal stuffiness occurred in eight of 13 subjects, nasal irritation occurred in four of 13 subjects, and mild or moderate nasal pain occurred in one of 13 subjects.

In Part 2, one of 10 subjects had nasal stuffiness and three of 10 subjects had nasal irritation.

Local Anesthesia Symptoms Questionnaire: Fifteen of 23 subjects reported no symptoms. The remaining eight of 23 subjects who reported symptoms had these symptoms recorded as adverse events.

9.5.2 SR 2-02

Title: Phase I, Open-Label, Dose-Escalation, Safety and Pharmacokinetic Study of (b) (4) in Healthy Volunteers

Trial Design: open-label, within-subject dose-escalation pharmacokinetic trial

Trial Population: Twelve healthy volunteer subjects aged 25 to 47-years-old completed the trial

Trial Medications and Trial Conduct: Subjects received two doses of Kovanaze separated by at least one week. Dose 1 represents a standard dose. Dose 2 represents twice the standard dose. For Dose 1, subjects received 18 mg tetracaine/0.3 mg oxymetazoline in 0.6 mL divided equally among two nostrils. Subjects received a total of six sprays: 0.1 mL bilaterally in each nostril three times separated by 4 minutes. Time 0 was the time at which the first set of bilateral nasal sprays was administered.

For Dose 2, subjects received 36 mg tetracaine/0.6 mg oxymetazoline in 1.2 mL divided equally among two nostrils. Subjects received 12 sprays: 0.1 mL bilaterally in each nostril six times separated by 4 minutes. Time 0 was the time at which the first set of bilateral nasal sprays was administered.

Safety Assessments: Subjects were evaluated for the following:

- Vital signs
- Adverse events
- Pharmacokinetic blood sampling

Relevant notable trial results: Plasma oxymetazoline and PBBA levels lasted for at least 120 minutes (this trial did not measure PK parameters beyond 120 minutes). For this reason, it was concluded that 120 minutes was not an adequate period of time for establishing pharmacokinetic parameters of Kovanaze.

Plasma tetracaine levels remained low after both Dose 1 and Dose 2 and were not always detectable.

Below is a table of oxymetazoline, tetracaine, and PBBA pharmacokinetic parameters from trial SR 2-02:

**Table 87 Oxymetazoline, Tetracaine, and PBBA PK Parameters (PK Population) (SR 2-02)**

| Analyte | Dose (mg) | Statistic[a] | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{1/2}$ (h) | $AUC_{0\text{-last}}$ (ng·h/mL) | $AUC_{0\text{-inf}}$ (ng·h/mL) |
|---|---|---|---|---|---|---|---|
| **Standard Dose** | | | | | | | |
| Oxymetazoline | 0.3 | Mean | 1.45[b] | 15[b] | 2.32[c] | 1.16[b] | 2.37[c] |
| | | SD | 0.473 | 10-20 | 0.86 | 0.281 | 0.705 |
| | | | | | | | |
| Tetracaine | 18 | Mean | 0.243[d] | 55[d] | ND | NR[e] | ND |
| | | SD | 0.113 | 20-80 | | | |
| | | | | | | | |
| PBBA | NA[f] | Mean | 492 | 35 | 1.00[g] | 610 | 861[g] |

| Analyte | Dose (mg) | Statistic[a] | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{1/2}$ (h) | $AUC_{0\text{-}last}$ (ng·h/mL) | $AUC_{0\text{-}inf}$ (ng·h/mL) |
|---|---|---|---|---|---|---|---|
| | | SD | 189 | 5-120 | 0.33 | 243 | 287 |
| **High Dose** | | | | | | | |
| Oxymetazoline | 0.6 | Mean | 2.05 | 25 | 1.72[c] | 1.95 | 3.51[c] |
| | | SD | 0.748 | 20-30 | 0.46 | 0.698 | 1.07 |
| | | | | | | | |
| Tetracaine | 36 | Mean | 1.15[c] | 100[c] | ND | 0.160[d,h] | ND |
| | | SD | 2.45 | 15-120 | | 0.032 | |
| | | | | | | | |
| PBBA | NA[i] | Mean | 886 | 45 | 1.01[b] | 1090 | 1770[b] |
| | | SD | 289 | 30-70 | 0.32 | 444 | 1070 |

Source data: Appendix 16.1.13; Table 2, Table 3 and Table 4 in Pharmacokinetic Analysis Report.
[a] Values represent mean and SD except for $t_{max}$, which is reported as median and range; n = 12 unless otherwise indicated
[b] n = 11
[c] n = 7
[d] n = 4
[e] Not reported; each subject had less than 3 samples with measurable tetracaine concentrations
[f] After subjects received 18 mg of tetracaine in a standard dose of (b) (4) at Visit 1
[g] n = 8
[h] Excludes 3 subjects who had less than 3 samples with measurable tetracaine concentrations
[i] After subjects received 36 mg of tetracaine in a high dose of (b) (4) at Visit 2
$AUC_{0\text{-}last}$ = Area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0\text{-}inf}$ = Area under the plasma concentration-time curve from time 0 extrapolated to infinity; $C_{max}$ = maximum observed plasma concentration; NA = not applicable; ND = parameter could not be determined due to insufficient data; NR = not reported; PBBA = p-butylaminobenzoic acid; $t_{1/2}$ = terminal half-life; $t_{max}$ = time of maximum concentration following the beginning of dosing.
(Source: NDA 208032 Applicant's table page 80 of SR 2-02 Clinical Study Report; header row added by reviewer)

In the above table, it is written that the median $t_{max}$ was 15 and 25 minutes after the start of dosing. Because Time 0 was the time at which the first set of bilateral nasal sprays was administered, this means that median $t_{max}$ occurred 7 and 5 minutes after dosing was complete.

### 9.5.3 SR 2-06

Title: Single-center, Open-label, Single-dose Study of the Pharmacokinetics and Safety of Intranasally Administered (b) (4) in Healthy Volunteers

Trial Design: open-label pharmacokinetic trial

Trial Population: Twenty-four healthy adult volunteers aged 18 to 47-years-old

Trial Medications and Conduct: Subjects received three sprays of Kovanaze separated by four minutes each so that the dosing period was eight minutes and the total dose was 18 mg tetracaine/0.3 mg oxymetazoline, only dosed into one nostril. Twelve subjects received Kovanaze in the right nostril and 12 subjects received Kovanaze in the left nostril. In this trial, $T_0$ was the time of the last dose of nasal spray.

Safety Assessments included:

- PK samples
- Vital signs
- Adverse events
- Physical examination
- Naris examination
- Hematology, coagulation, serum chemistry, and urinalysis tests obtained before study drug dosing and one day after drug dosing
- Electrocardiograms obtained before dosing of trial drug (at screening) and the day after trial drug dosing
- Drug, alcohol, and cotinine screen
- Pregnancy test, if applicable

Relevant notable Trial Results: Oxymetazoline and PBBA PK parameters were obtained in this trial. They are described in the table below. According to the Clinical Study Report, tetracaine was not detectable in enough samples to determine its pharmacokinetic parameters.

**Table 88 Plasma Pharmacokinetic Parameters for Oxymetazoline and PBBA after Intranasal Administration of (b) (4) to Healthy Volunteers**

| Analyte | Statistic | Pharmacokinetic Parameters | | | | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $\lambda_z$ ($h^{-1}$) | $t_{½}$ (h) | $AUC_{0-t}$ (ng·h/mL) | $AUC_{0-inf}$ (ng·h/mL) |
| Oxymetazoline | N | 24 | 24 | 24 | 24 | 24 | 24 |
| | Mean | 1.78 | 5.8 | 0.154 | 5.23 | 3.67 | 4.24 |
| | SD | 0.586 | 1.9 | 0.0575 | 2.20 | 1.79 | 2.09 |
| | CV(%) | 33 | 33 | 37 | 42 | 49 | 49 |
| | Minimum | 0.841 | 5.0 | 0.0655 | 2.27 | 1.45 | 1.98 |
| | Median | 1.73 | 5.0 | 0.150 | 4.63 | 3.13 | 3.45 |
| | Maximum | 2.88 | 10 | 0.306 | 10.6 | 7.00 | 8.39 |
| PBBA | N | 24 | 24 | 24 | 24 | 24 | 24 |
| | Mean | 465 | 22 | 0.346 | 2.60 | 960 | 973 |
| | SD | 122 | 6.6 | 0.184 | 1.23 | 509 | 513 |
| | CV(%) | 26 | 30 | 53 | 48 | 53 | 53 |
| | Minimum | 208 | 15 | 0.149 | 0.887 | 383 | 389 |
| | Median | 448 | 20 | 0.252 | 2.78 | 817 | 826 |
| | Maximum | 663 | 40 | 0.781 | 4.65 | 2500 | 2530 |

Source data: Appendix 16.1.13, Table 3 in Pharmacokinetic Analysis Report

(Source: NDA 208032 Applicant's table page 55 of SR 2-06 Clinical Study Report)

For details of lab results see section 7.4.2 of this review. For details of ECG results, see section 7.4.4 of this review.

### 9.5.4 SR 2-07

Title: A Single-center Study Evaluating the Pharmacokinetics of Tetracaine, Parabutylaminobenzoic Acid, and Oxymetazoline after Intranasal Administration of (b) (4) (tetracaine hydrochloride with oxymetazoline hydrochloride) to Healthy Pediatric Subjects

Trial Design: open-label pharmacokinetic trial

Trial Population: Eighteen subjects 3 to 17-years-old

Trial Medications and Treatment Groups:
Subjects were dosed by weight:

**Table 89 (b) (4) Doses Based on Subject Weight**

| Subject Weight | Treatment Group: (b) (4) | Volume per Spray | Number of Sprays | (b) (4) Total Dose | |
|---|---|---|---|---|---|
| | | | | Tetracaine HCl | Oxymetazoline HCl (Oxymetazoline Equivalent) |
| 10 kg to < 20 kg | 0.1 mL | 0.1 mL | 1[a] | 3 mg | 0.05 mg (0.044 mg) |
| 20 kg to < 40 kg | 0.2 mL | 0.1 mL | 2[b] | 6 mg | 0.1 mg (0.088 mg) |
| 40 kg or more | 0.4 mL | 0.2 mL | 2[b] | 12 mg | 0.2 mg (0.175 mg) |

[a] Administered at D0
[b] Administered at D0 and D4 (4 min apart)

(Source: NDA 208032 Applicant's table page 32 of SR 2-07 Clinical Study Report)

Trial Conduct:
Kovanaze was administered in the right nostril or the left nostril. Nine subjects received Kovanaze in the right nostril and nine subjects received Kovanaze in the left nostril. Below is a table of demographics for subjects in SR 2-07. This table demonstrates that three subjects were an appropriate weight to receive 0.1 mL of Kovanaze, nine subjects were an appropriate weight to receive 0.2 mL of Kovanaze, and six subjects were an appropriate weight to receive 0.4 mL of Kovanaze. The youngest subject was 4-years-old and the oldest subject was 15-years-old.

Table 14.1.4: Demographics - Safety Population

| Parameter | Category | Statistics | 100 ul N=3 | 200 ul N=9 | 400 ul N=6 |
|---|---|---|---|---|---|
| Gender | Male | | 1 (33.3%) | 6 (66.7%) | 2 (33.3%) |
| | Female | | 2 (66.7%) | 3 (33.3%) | 4 (66.7%) |
| Race | White | | 1 (33.3%) | 5 (55.6%) | 5 (83.3%) |
| | Asian | | 0 | 0 | 0 |
| | American Indian | | 0 | 0 | 0 |
| | Black or African American | | 2 (66.7%) | 4 (44.4%) | 1 (16.7%) |
| | Native Hawaiian or Pacific Islander | | 0 | 0 | 0 |
| | Alaska Native | | 0 | 0 | 0 |
| | Other | | 0 | 0 | 0 |
| Ethnicity | Hispanic or Latino | | 1 (33.3%) | 5 (55.6%) | 5 (83.3%) |
| | Not Hispanic or Latino | | 2 (66.7%) | 4 (44.4%) | 1 (16.7%) |
| Age (years) | | N | 3 | 9 | 6 |
| | | Mean | 4.3 | 8.4 | 13.5 |
| | | STD | 0.49 | 2.31 | 0.86 |
| | | Median | 4.1 | 8.2 | 13.4 |
| | | (Min,Max) | (4,5) | (5,12) | (12,15) |

(Source: NDA 208032 Applicant's table page 102 of SR 2-07 Clinical Study Report)

Safety Assessments:

- Pharmacokinetics
- Vital signs
- Adverse events
- Physical exam
- Labs: hematology, coagulation tests, serum chemistry, urinalysis
- Pregnancy test, if applicable

Relevant notable trial results:
After Kovanaze dosing, tetracaine was quickly converted to PBBA. Tetracaine was not detectable in any pharmacokinetic samples.
Below are plasma pharmacokinetic parameters for oxymetazoline and PBBA from Kovanaze:

**Table 90 Plasma Pharmacokinetic Parameters for Oxymetazoline after Intranasal Administration of (b) (4) to Healthy Pediatric Subjects**

| Group/ Oxymetazoline Dose | Statistic | Oxymetazoline Pharmacokinetic Parameters | | | | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{last}$ (h) | $t_{½}$ (h) | $AUC_{0-t}$ (ng·h/mL) | $AUC_{0-inf}$ (ng·h/mL) |
| 0.1 mL/0.05 mg | N | 3 | 3 | 3 | 1 | 3 | 1 |
| | Mean | 0.367 | 70 | 6.0 | 1.57 | 0.630 | 0.992 |
| | SD | 0.426 | 96 | 3.0 | - | 0.211 | - |
| | CV(%) | 116 | 138 | 50 | - | 33 | - |
| | | | | | | | |
| 0.2 mL/0.1 mg | N | 9 | 9 | 9 | 7 | 9 | 7 |
| | Mean | 0.846 | 10 | 9.9 | 4.32 | 1.88 | 2.53 |

| Group/ Oxymetazoline Dose | Statistic | Oxymetazoline Pharmacokinetic Parameters | | | | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{last}$ (h) | $t_{½}$ (h) | $AUC_{0-t}$ (ng·h/mL) | $AUC_{0-inf}$ (ng·h/mL) |
| | SD | 0.454 | 0 | 5.6 | 2.24 | 0.780 | 1.08 |
| | CV(%) | 54 | 0 | 57 | 52 | 42 | 43 |
| | | | | | | | |
| 0.4 mL/0.2 mg | N | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 1.20 | 10 | 9.0 | 3.49 | 2.27 | 2.64 |
| | SD | 0.387 | 0 | 1.9 | 0.814 | 0.390 | 0.405 |
| | CV(%) | 32 | 0 | 21 | 23 | 17 | 15 |

Abbreviations: CV - coefficient of variation; h – hours; N – number; SD – standard deviation
(Source: NDA 208032 Applicant's table page 6 of SR 2-07 Clinical Study Report; header row added by reviewer)

**Table 91 Plasma Pharmacokinetic Parameters for PBBA after Intranasal Administration of (b) (4) to Healthy Pediatric Subjects**

| Group/ Tetracaine Dose[a] | Statistic | PBBA Pharmacokinetic Parameters | | | | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $t_{max}$ (min) | $t_{last}$ (h) | $t_{½}$ (h) | $AUC_{0-t}$ (ng·h/mL) | $AUC_{0-inf}$ (ng·h/mL) |
| 0.1 mL/3 mg | N | 3 | 3 | 3 | 3 | 3 | 3 |
| | Mean | 166 | 30 | 12 | 2.81 | 515 | 529 |
| | SD | 70.5 | 0 | 0 | 0.384 | 220 | 222 |
| | CV(%) | 43 | 0 | 0 | 14 | 43 | 42 |
| | | | | | | | |
| 0.2 mL/6 mg | N | 9 | 9 | 9 | 9 | 9 | 9 |
| | Mean | 345 | 21 | 11 | 2.18 | 811 | 826 |
| | SD | 172 | 11 | 4.9 | 0.826 | 606 | 606 |
| | CV(%) | 50 | 50 | 43 | 38 | 75 | 73 |
| | | | | | | | |
| 0.4 mL/12 mg | N | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 365 | 20 | 8.8 | 1.57 | 647 | 665 |
| | SD | 29.9 | 11 | 0.41 | 0.283 | 63.2 | 85.7 |
| | CV(%) | 8 | 55 | 5 | 18 | 10 | 13 |

Abbreviations: CV - coefficient of variation; h – hours; N – number; SD – standard deviation
(Source: NDA 208032 Applicant's table page 6 of SR 2-07 Clinical Study Report)

## 9.6 Phase 2 Clinical Trials:

The following are Phase 2 clinical trials conducted for Kovanaze: SR 2-01, SR 2-03, SR 2-04, SR 2-05. Below are brief summaries of the Phase 2 trials. These summaries are meant to be brief and allow for an overview of the Phase 2 trials that took place. For the purpose of this NDA, Phase 2 trials provide supportive safety information described more thoroughly in section 7.0 of this review. Demonstration of efficacy of Kovanaze is dependent on Phase 3 trials, not the Phase 2 trials described below.

9.6.1 SR 2-01

Title: A Phase II, Single-Center, Randomized, Double-Blind Active-Treatment-Controlled Parallel-Group Study of the Efficacy of Kovacaine Nasal Spray for Anesthetizing Maxillary Teeth in Healthy Dental Patients

Trial Design: randomized, double-dummy

Trial Population: Forty-five adult dental patients aged 20 to 66-years-old having an amalgam or composite restoration of one tooth of the maxilla, but not a second or third molar.

Trial Medications and Treatment Groups: Subjects were randomized to Kovanaze or lidocaine injection. The specific treatment groups were:
1. Tetracaine 18 mg/oxymetazoline 0.3mg Kovanaze and sham injection in which the cap was left on the needle tip. (30 subjects)
2. 2% Lidocaine HCl with epinephrine Injection (1:100,000) and isotonic saline spray (placebo) (15 subjects)

Trial Conduct: At the time of 0 minutes, subjects received an injection of lidocaine or a sham injection and an intranasal spray of Kovanaze or placebo. Nasal spray was again given at the time of four and eight minutes. The dental procedure was to begin at the time of 15 minutes after the start of intranasal spray dosing. If the patient had pain at that time, the dental procedure was to begin at 20 minutes after the start of intranasal spray dosing.

Rescue Medication: If a subject did not have adequate anesthesia for the procedure, he or she was to have received 4% articaine with 1:100,000 epinephrine 0.85 to 1.7 mL.

Efficacy Assessments: The following assessments of efficacy were to have taken place during the trial:

1. Soft Tissue Anesthesia Assessment: (verbatim from NDA 208032 page 14 of SR 2-01 protocol version 2.0)

> In order to assess soft tissue anesthesia, a dental professional will use a pressure sensitive mechanical probe (i.e., Rotadent) and test the following areas for soft tissue anesthesia:
>
> - Distal to the apex of the tooth in the position of the maxillary first premolar at the deepest point in the buccal vestibule
> - Apical to the maxillary lateral incisor at the deepest point in the labial vestibule
> - Incisive papilla
> - At the confluence of the alveolar process and hard palate medial to the maxillary second premolar (near the greater palatine foramen)
>
> For each site tested, the subject will be asked, “Do you feel any pain?”
>
> After study drug administration, testing at each of the four soft tissue sites will only continue until the subject reports pain at that site when probed. Testing will continue as scheduled on a site-by-

site basis until each site has returned to baseline, or for a total of 120 minutes after dosing, whichever is sooner.

2. Heft-Parker Visual Analog Scale: (verbatim from NDA 208032 page 15 of SR 2-01 protocol version 2.0)

The efficacy of anesthesia will be assessed by use of the Heft-Parker VAS asking the subjects how much pain they experienced at the treatment site. Pain assessments will be taken at the start of the dental procedure (four minutes after the final nasal spray) and at the end of the treatment.

3. Global Assessment of Efficacy: (verbatim from NDA 208032 page 15 of SR 2-01 protocol version 2.0)

Global efficacy assessments will also be made at the end of treatment to determine the overall effectiveness of the study drugs. The Heft-Parker VAS will be used, and subjects will be asked, "Rate your overall level of pain during treatment."

Safety Assessments:

- Vital signs
- Adverse events

Relevant notable trial results:

Treatment success was the ability to complete the dental procedure without rescue medication. Below is a table summarizing treatment success. 83.3% of subjects who received Kovanaze completed the dental procedure without need for rescue medication and 93.3% of subjects who received lidocaine injection completed the procedure without need for rescue medication.

**Table 92 Summary of Treatment Success (Trial SR 2-01)**

| Need for Rescue Medication | (b) (4) | Lidocaine Injection |
|---|---|---|
| Intent-to-treat analysis, N | 30 | 15 |
| No | 25 (83.3%) | 14 (93.3%) |
| Yes | 5 (16.7%) | 1 (6.7%) |
| Post hoc per-protocol analysis, N | 25* | Same as above |
| No | 22 (88.0%) | |
| Yes | 3 (12.0%) | |

* Subjects 0001, 0007, 0011, 0016, and 0020 were excluded due to protocol deviations.

(Source: NDA 208032 Applicant's table page 30 of SR 2-01 Clinical Study Report)

Below are the results of the soft tissue anesthesia assessment:

**Table 93 Number of Subjects Reporting No Pain to Soft Tissue Stimulation by the Rotadent Algometer by Time point (SR 2-01)**

| Site[a] | Timepoint | (b) (4) (N = 30) | Lidocaine Injection (N = 15) |
|---|---|---|---|

| Site[a] | Timepoint | Kovacaine Mist (N = 30) | Lidocaine Injection (N = 15) |
|---|---|---|---|
| Site 1 | Prior to Dose | 3 (10.0%) | 0 ( 0.0%) |
| | 20 minutes | 15 (50.0%) | 12 (80.0%) |
| | 30 minutes | 13 (43.3%) | 11 (73.3%) |
| | 40 minutes | 10 (33.3%) | 10 (66.7%) |
| | 50 minutes | 6 (20.0%) | 8 (53.3%) |
| | 60 minutes | 5 (16.7%) | 2 (13.3%) |
| | 80 minutes | 2 ( 6.7%) | 2 (13.3%) |
| | 100 minutes | 2 ( 6.7%) | 1 ( 6.7%) |
| | 120 minutes | 0 ( 0.0%) | 0 ( 0.0%) |
| Site 2 | Prior to dose | 1 ( 3.3%) | 0 ( 0.0%) |
| | 20 minutes | 9 (30.0%) | 6 (40.0%) |
| | 30 minutes | 6 (20.0%) | 7 (46.7%) |
| | 40 minutes | 4 (13.3%) | 7 (46.7%) |
| | 50 minutes | 4 (13.3%) | 6 (40.0%) |
| | 60 minutes | 5 (16.7%) | 0 ( 0.0%) |
| | 80 minutes | 0 ( 0.0%) | 0 ( 0.0%) |
| | 100 minutes | 0 ( 0.0%) | 0 ( 0.0%) |
| | 120 minutes | 0 ( 0.0%) | 0 ( 0.0%) |
| Site 3 | Prior to dose | 1 ( 3.3%) | 0 ( 0.0%) |
| | 20 minutes | 22 (73.3%) | 3 (20.0%) |
| | 30 minutes | 20 (66.7%) | 2 (13.3%) |
| | 40 minutes | 18 (60.0%) | 2 (13.3%) |
| | 50 minutes | 11 (36.7%) | 2 (13.3%) |
| | 60 minutes | 6 (20.0%) | 1 ( 6.7%) |
| | 80 minutes | 5 (16.7%) | 0 ( 0.0%) |
| | 100 minutes | 0 ( 0.0%) | 0 ( 0.0%) |
| | 120 minutes | 0 ( 0.0%) | 0 ( 0.0%) |
| Site 4 | Prior to dose | 2 ( 6.7%) | 0 ( 0.0%) |
| | 20 minutes | 17 (56.7%) | 6 (40.0%) |
| | 30 minutes | 19 (63.3%) | 4 (26.7%) |
| | 40 minutes | 13 (43.3%) | 4 (26.7%) |
| | 50 minutes | 12 (40.0%) | 3 (20.0%) |
| | 60 minutes | 5 (16.7%) | 1 ( 6.7%) |
| | 80 minutes | 4 (13.3%) | 1 ( 6.7%) |
| | 100 minutes | 3 (10.0%) | 1 ( 6.7%) |
| | 120 minutes | 0 ( 0.0%) | 0 ( 0.0%) |

[a] Site 1 = distal to the apex of the tooth in the position of the maxillary first premolar at the deepest point in the buccal vestibule; site 2 = apical to the maxillary lateral incisor at the deepest point in the labial vestibule, site 3 = incisive papilla, and site 4 = at the confluence of the alveolar process and hard palate medial to the maxillary second premolar (near the greater palatine foramen).
Source: Section 14, Tables 3.8 to 3.43.

(Source: NDA 208032 Applicant's table page 31 of SR 2-01 Clinical Study Report; header row added by reviewer)

Below is a table describing the duration of soft tissue anesthesia in trial SR 2-01:

**Table 94 Duration of Soft Tissue Anesthesia (SR 2-01)**

| Site<br>Statistic | (b) (4)<br>(N = 30) | Lidocaine Injection<br>(N = 15) |
|---|---|---|
| Site 1, N<br>Mean ± SD<br>Min – Max | 18<br>21.1 ± 16.9<br>5 – 65 | 13<br>34.2 ± 21.0<br>5 – 85 |
| Site 2, N<br>Mean ± SD<br>Min – Max | 9<br>16.1 ± 16.9<br>5 – 45 | 7<br>32.1 ± 4.9<br>25 – 35 |
| Site 3, N<br>Mean ± SD<br>Min – Max | 22<br>31.8 ± 19.9<br>5 – 65 | 4<br>25.0 ± 18.3<br>4 – 45 |
| Site 4, N<br>Mean ± SD<br>Min – Max | 20<br>31.5 ± 24.1<br>5 – 85 | 7<br>29.3 ± 27.6<br>5 – 85 |

[a] Site 1 = distal to the apex of the tooth in the position of the maxillary first premolar at the deepest point in the buccal vestibule; site 2 = apical to the maxillary lateral incisor at the deepest point in the labial vestibule, site 3 = incisive papilla, and site 4 = at the confluence of the alveolar process and hard palate medial to the maxillary second premolar (near the greater palatine foramen).
Source: Section 14, Table 9.1
(Source: NDA 208032 Applicant's table page 32 of SR 2-01 Clinical Study Report)

## 9.6.2 SR 2-03

Title: A Phase 2, Single-Center, Open-Label, Randomized, Parallel-Groups, Dose-Ranging Study to Assess the Efficacy and Safety of Intranasally Administered (b) (4) for Anesthetizing Maxillary Teeth in Pediatric Subjects

Trial Design: open-label

Trial Population: Forty-eight pediatric dental patients aged 3 to 17-years-old having an operative restorative dental procedure on one maxillary tooth: either # A through J or # 4 through 13.

Trial Medications, Treatment Groups, and Trial Conduct: Three doses of Kovanaze were possibly given in one nostril on the same side as the treatment tooth:
1. 2 sprays of 0.2 mL
2. 2 sprays of 0.1 mL
3. 2 sprays of 0.06 mL

Kovanaze was to have been given at time 0 minutes and at time 4 minutes. The dental procedure was to have started at time 14 minutes. If pulpal anesthesia was not sufficient, the study dental procedure was to have started at time 19 minutes. At time 19 minutes, if pulpal anesthesia was not sufficient, rescue medication was given.

Subjects were divided into three age cohorts: 12 to 17-years-old who weighed at least 40 kg, 7 to 11-years-old who weighed at least 20 kg, and 3 to 6-years-old who weighed at least 12 kg. Subjects in each cohort were randomized to up to three treatment groups within each cohort. Subjects were given Kovanaze in one nostril on the same side as the treatment tooth. Below is a table describing assignment to treatment groups:

**Table 95 Decision Table for Assignment to Treatment Groups (SR 2-03)**

| Stage | Age Cohort | Age (years, inclusive) | Decision based on safe LED | Treatment groups (dose) | Number of treatment groups per cohort |
|---|---|---|---|---|---|
| A | Cohort A | 12-17 | N/A | 0.4 mL | 3 |
| | | | | 0.2 mL | |
| | | | | 0.12 mL | |
| B | Cohort B | 7-11 | If safe LED for Cohort A is 0.4 or 0.2 mL | 0.2 mL | 2 |
| | | | | 0.12 mL | |
| | | | If safe LED for Cohort A is 0.12 mL | 0.12 mL | 1 |
| C | Cohort C | 3-6 | N/A | 0.12 mL | 1 |

LED = lowest effective dose; N/A = Not applicable
(Source: NDA 208032 Applicant's table page 31 of SR 2-03 Clinical Study Report)

Rescue Medication: If Kovanaze did not allow for completion of the dental procedure, subjects were given injections of 2% lidocaine HCl with 1:100,000 epinephrine

Safety Assessments included:

- Intraoral examination
- Diagnostic radiographs
- Naris examination: see section 9.4.3 of this review for further description
- Urine pregnancy test, if applicable
- Vital signs
- Adverse events

Relevant notable trial results: In this trial, success was defined as completion of the dental procedure without need for rescue medication. Below is a table of success rates:

**Table 96 Incidence (N, %) of Anesthetic Success Rate by Cohort (mITT Population) (SR 2-03)**

| Anesthetic Assessment Result | Cohort A 12-17 years | | | Cohort B 7-11 years | | Cohort C 3-6 years |
|---|---|---|---|---|---|---|
| | 0.12 mL (n = 8) | 0.2 mL (n = 8) | 0.4 mL (n = 8) | 0.12 mL (n = 8) | 0.2 mL (n = 8) | 0.12 mL (n = 8) |
| Success | 6 (75.0%) | 7 (87.5%) | 8 (100.0%) | 5 (62.5%) | 7 (87.5%) | 4 (50.0%) |
| Failure | 2 (25.0%) | 1 (12.5%) | 0 (0.0%) | 3 (37.5%) | 1 (12.5%) | 4 (50.0%) |

Source data: Table 14.2.1

(Source: NDA 208032 Applicant's table page 58 of SR 2-03 Clinical Study Report)

### 9.6.3 SR 2-04

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 4-Period, Complete Crossover Comparison of the Dental Anesthetic Efficacy of Bilateral and Unilateral Application of (b) (4) (formerly (b) (4) in Healthy Volunteers

Trial Design: randomized, double-blind, cross-over

Trial Population: Forty-eight healthy adult volunteers; the youngest subject in this trial was 18-years-old. The oldest subject in this trial was 46-years-old.

Primary Endpoint:

> "The primary outcome measure for the study is achievement (yes/no) of Global Profound Pulpal Anesthesia (GPPA), defined as having all three target maxillary teeth [#s 4 (or 5), 6, and 8 for the right-side or #s 9, 11, and 13 (or 12) for the left-side] reach an EPT of 80 within 20 minutes of the final spray of study drug."

(Source: NDA 208032 Applicant's table pages 19 and 20 of SR 2-04 protocol version 1.0)

Secondary Endpoints:

- "For all individually EPT-tested teeth (one molar, one premolar, one canine and one incisor) the incidence of PPA, with unilateral and bilateral drug administration.
- For all individually EPT-tested teeth achieving PPA, time to onset and duration of PPA for unilateral and bilateral drug administration, where duration is defined as the time between the first EPT of 80 and the time of the first of two consecutive EPT values below 70.
- Mean highest EPT value reached for first molars (#3 and 14).
- Incidence of induction of PPA following the first, second and third doses of active drug administered unilaterally and bilaterally.
- The correlation between positive responses in a questionnaire of Subjective Numbness Assessment (SNA) and incidence of global EPT scores of 80.
- Systolic blood pressure, diastolic blood pressure, and heart rate recordings for three hours following administration of study medications.
- Adverse experiences spontaneously reported by subjects, or observed by study personnel including those encountered on nasal and airway examination (NAE), and incidence rates for systolic blood pressure, diastolic blood pressure, and heart rate exceeding +/- 25% of pre-study values."

(Source: NDA 208032 Applicant's table pages 20 of SR 2-04 protocol version 1.0)

Trial Medications, Treatment Groups, and Trial Conduct: Subjects received different doses of Kovanaze or placebo in four treatment periods separated by a washout period of 3 to 14 days. Below is a table of treatments that subjects received:

**Table 97 Summary of Treatments Administered (SR 2-04)**

| Time | Bilateral (b) (4) Regimen 1 # of sprays | | | | Unilateral (b) (4) left Regimen 2 # of sprays | | | | Unilateral (b) (4) right Regimen 3 # of sprays | | | | Bilateral PBO Regimen 4 # of sprays | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (b) (4) | | PBO | | (b) (4) | | PBO | | (b) (4) | | PBO | | (b) (4) | | PBO | |
| | L | R | L | R | L | R | L | R | L | R | L | R | L | R | L | R |
| $T_0$ | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| $T_4$ | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| $T_8$ | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| **Total # sprays** | **3** | **3** | **0** | **0** | **3** | **0** | **0** | **3** | **0** | **3** | **3** | **0** | **0** | **0** | **3** | **3** |

L = left nostril; R = right nostril; T = time in minutes; PBO = placebo
(Source: NDA 208032 Applicant's table page 28 of SR 2-04 Clinical Study Report)

Safety Assessments:

- Intraoral examination
- Nares and Airway Examination
- Pregnancy test, if applicable
- Vital signs
- Adverse events

Relevant notable trial results: The Applicant concluded that unilateral and bilateral dosing of Kovanaze appear to be comparable. Therefore, unilateral dosing is preferable.

### 9.6.4 SR 2-05

Title: A Two-part, Single Site, Open-label Investigation of Different Unilateral (b) (4) Dosing Regimens in Adult Dental Patients

Trial Design: open-label

Trial Population: Thirty adult dental patients having an operative restorative procedure on one maxillary tooth: # 4 to #13.

Trial Medications, Treatment Groups, and Trial Conduct: This trial took place in two Parts:
1. In Part 1, subjects were to have received four unilateral 0.1 mL sprays of Kovanaze separated by 4 minutes.

2. In Part 2, new subjects were to have been randomized to receive either two unilateral sprays of 0.2 mL of Kovanaze separated by 4 minutes or one spray of Kovanaze 0.2 mL.

Rescue Medication: 4% articaine with 1:200,000 epinephrine was to have been given to subjects if the dental procedure could not be completed with study drug alone.

Safety Assessments:

- Blood pressure
- Naris examination
- Adverse Events
- Pregnancy test, if applicable

Relevant notable trial results: The Applicant concluded that Kovanaze can provide adequate anesthesia for procedures of maxillary teeth 4 to13 in unilateral doses of one spray (tetracaine 6mg/oxymetazoline 0.1mg) or two sprays (tetracaine 12 mg/oxymetazoline 0.2mg).

## 9.7 Clinical Investigator Financial Disclosure

Application Number: NDA 208032

Submission Date: May 29, 2015

Applicant: St. Renatus

Product: Tetracaine HCl 3% and oxymetazoline HCl 0.05% nasal spray (Proposed trade name Kovanaze)

Reviewer: Amelia Luckett

Date of Review: February 12, 2016

Covered Clinical Studies (Name and/or Number): AP 1-01, AP 1-02, SR 2-01, SR 2-02, SR 2-03, SR 2-04, SR 2-05, SR 2-06, SR 2-07, SR 3-01, SR 3-02, SR 3-03, SR 3-04

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified: 13 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value | | |

| | | |
|---|---|---|
| could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in sponsor of covered study: 1 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒* | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from applicant) |

*The following was provided as an Attachment to Form 3455 for [redacted]

"[redacted] an employee of St. Renatus, LLC, [redacted] also has an ownership interest in St. Renatus, which is a non-publicly traded entity whose value cannot be readily established through reference to public prices.

Study SR 2-05 is an exploratory study, with findings that are informational in nature and not aimed at providing data to support approval of the drug. The investigation will be performed in a small group of subjects as a pilot design for the Phase 3 program to provide results that will facilitate company decision making and refine dosing technique. The scope and size of the study do not produce statistically significant results."

(Source: NDA 208032 page 2 of Form 3455 Disclosure: Financial Interests and Arrangements of Clinical Investigators)

It appears that the Applicant has adequately disclosed financial interests with Investigators.

SR 2-05 was a Phase 2 clinical trial in 30 healthy volunteers. For further detail of SR 2-05, see section 9.6.4 of this review. The efficacy of Kovanaze is not reliant on SR 2-05, however, subjects in SR 2-05 are included in the Integrated Safety Database. The adverse event profile of SR 2-05 has been reviewed and does not appear to skew the overall appearance of safety of Kovanaze.

## 9.8 References

Adriani, J., and D. Campbell. 1956. 'Fatalities following topical application of local anesthetics to mucous membranes', *J Am Med Assoc*, 162: 1527-30.

Alterio, D., B. A. Jereczek-Fossa, G. F. Zuccotti, M. E. Leon, E. Omodeo Sale, M. Pasetti, T. Modena, P. Perugini, L. Mariani, and R. Orecchia. 2006. 'Tetracaine oral gel in patients treated with radiotherapy for head-and-neck cancer: final results of a phase II study', *Int J Radiat Oncol Biol Phys*, 64: 392-5.

Arikan, O. K., C. Akarsu, B. Unal, A. Ergin, and C. Koc. 2006. 'Effect of oxymetazoline nasal spray on intraocular pressure and retrobulbar hemodynamics', *J Otolaryngol*, 35: 30-5.

Aselton, P., H. Jick, A. Milunsky, J. R. Hunter, and A. Stergachis. 1985. 'First-trimester drug use and congenital disorders', *Obstet Gynecol*, 65: 451-5.

Baxi, L. V., P. R. Gindoff, G. J. Pregenzer, and M. K. Parras. 1985. 'Fetal heart rate changes following maternal administration of a nasal decongestant', *Am J Obstet Gynecol*, 153: 799-800.

Cantu, C., A. Arauz, L. M. Murillo-Bonilla, M. Lopez, and F. Barinagarrementeria. 2003. 'Stroke associated with sympathomimetics contained in over-the-counter cough and cold drugs', *Stroke*, 34: 1667-72.

Christie, J. L. 1976. 'Fatal consequences of local anesthesia: report of five cases and a review of the literature', *J Forensic Sci*, 21: 671-9.

Dorn, M., W. Hofmann, and E. Knick. 2003. '[Tolerance and effectiveness of oxymetazoline and xylometazoline in treatment of acute rhinitis]', *HNO*, 51: 794-9.

Doyle, E., J. Freeman, N. T. Im, and N. S. Morton. 1993. 'An evaluation of a new self-adhesive patch preparation of amethocaine for topical anaesthesia prior to venous cannulation in children', *Anaesthesia*, 48: 1050-2.

Duffin, R. M., and R. J. Olson. 1984. 'Tetracaine toxicity', *Ann Ophthalmol*, 16: 836, 38.

Duzman, E., A. Warman, and R. Warman. 1986. 'Efficacy and safety of topical oxymetazoline in treating allergic and environmental conjunctivitis', *Ann Ophthalmol*, 18: 28-31.

Escobar, J. I., and M. Karno. 1982. 'Chronic hallucinosis from nasal drops', *JAMA*, 247: 1859-60.

Fabi, M., R. Formigari, and F. M. Picchio. 2009. 'Are nasal decongestants safer than rhinitis? A case of oxymetazoline-induced syncope', *Cardiol Young*, 19: 633-4.

Ferguson, B. J., S. Paramaesvaran, and E. Rubinstein. 2001. 'A study of the effect of nasal steroid sprays in perennial allergic rhinitis patients with rhinitis medicamentosa', *Otolaryngol Head Neck Surg*, 125: 253-60.

Fivgas, G. D., and N. J. Newman. 1999. 'Anterior ischemic optic neuropathy following the use of a nasal decongestant', *Am J Ophthalmol*, 127: 104-6.

Garcia-Gavin, J., J. Alonso-Gonzalez, E. Gutierrez-Gonzalez, A. Alvarez-Perez, V. Fernandez-Redondo, and J. Toribio. 2011. 'Allergic contact dermatitis caused by tetracaine contained in otic drops', *Contact Dermatitis*, 65: 175-6.

Gaviola, G. C., V. Chen, and S. H. Chia. 2013. 'A prospective, randomized, double-blind study comparing the efficacy of topical anesthetics in nasal endoscopy', *Laryngoscope*, 123: 852-8.

Glazener, F., K. Blake, and M. Gradman. 1983. 'Bradycardia, hypotension, and near-syncope associated with Afrin (oxymetazoline) nasal spray', *N Engl J Med*, 309: 731.

Gobbels, M. J., C. Achten, and M. Spitznas. 1991. 'Effect of topically applied oxymetazoline on tear volume and tear flow in humans', *Graefes Arch Clin Exp Ophthalmol*, 229: 147-9.

Graf, P. 1997. 'Rhinitis medicamentosa: aspects of pathophysiology and treatment', *Allergy*, 52: 28-34.

Graf, P., H. Hallen, and J. E. Juto. 1995. 'The pathophysiology and treatment of rhinitis medicamentosa', *Clin Otolaryngol Allied Sci*, 20: 224-9.

Green, M. 1966. 'Double-blind study of nasal decongestion with oxymetazoline and phenylephrine in asthmatic children with rhinitis', *Rev Allergy*, 20: 863-8.

Greene, R. R. 2005. 'Clinical images: Afrin-induced central nervous system vasospasm and thunderclap headache', *Arthritis Rheum*, 52: 3314.

Hoffman, R. A., and C. L. Li. 2001. 'Tetracaine topical anesthesia for myringotomy', *Laryngoscope*, 111: 1636-8.

Holm, I. A., and S. K. Clarren. 1985. 'An unusual pattern of malformation associated with gestational exposure to nasal spray', *J Pediatr*, 106: 860-1.

Ireland, P. E., J. K. Ferguson, and E. J. Stark. 1951. 'The clinical and experimental comparison of cocaine and pontocaine as topical anesthetics in otolaryngological practice', *Laryngoscope*, 61: 767-77.

Katz, R. I., A. R. Hovagim, H. S. Finkelstein, Y. Grinberg, R. V. Boccio, and P. J. Poppers. 1990. 'A comparison of cocaine, lidocaine with epinephrine, and oxymetazoline for prevention of epistaxis on nasotracheal intubation', *J Clin Anesth*, 2: 16-20.

Khan, A., and N. Dewhurst. 1997. 'Use of sympathomimetic nasal spray in association with cardiac fibroma: an unusual cause of ventricular tachycardia', *Br J Clin Pract*, 51: 192-3.

Latham, G. J., and D. S. Jardine. 2013. 'Oxymetazoline and hypertensive crisis in a child: can we prevent it?', *Paediatr Anaesth*, 23: 952-6.

Lavergne, S., M. Darmon, V. Levy, and E. Azoulay. 2006. 'Methemoglobinemia and acute hemolysis after tetracaine lozenge use', *J Crit Care*, 21: 112-4.

Lemyre, B., D. L. Hogan, I. Gaboury, R. Sherlock, C. Blanchard, and D. Moher. 2007. 'How effective is tetracaine 4% gel, before a venipuncture, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial', *BMC Pediatr*, 7: 7.

Lemyre, B., R. Sherlock, D. Hogan, I. Gaboury, C. Blanchard, and D. Moher. 2006. 'How effective is tetracaine 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial [ISRCTN75884221]', *BMC Med*, 4: 11.

Loewen, A. H., M. E. Hudon, and M. D. Hill. 2004. 'Thunderclap headache and reversible segmental cerebral vasoconstriction associated with use of oxymetazoline nasal spray', *CMAJ*, 171: 593-4.

Magargal, L. E., G. E. Sanborn, L. A. Donoso, and J. R. Gonder. 1985. 'Branch retinal artery occlusion after excessive use of nasal spray', *Ann Ophthalmol*, 17: 500-1.

Maulidi, H., C. McNair, N. Seller, J. Kirsh, T. J. Bradley, S. C. Greenway, and C. Tomlinson. 2012. 'Arrhythmia associated with tetracaine in an extremely low birth weight premature infant', *Pediatrics*, 130: e1704-7.

Mazumdar, B., A. A. Tomlinson, and G. C. Faulder. 1991. 'Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine', *Br J Anaesth*, 67: 432-6.

Montalban, J., L. Ibanez, C. Rodriguez, M. Lopez, J. Sumalla, and A. Codina. 1989. 'Cerebral infarction after excessive use of nasal decongestants', *J Neurol Neurosurg Psychiatry*, 52: 541-3.

O'Brien, L., A. Taddio, M. Ipp, M. Goldbach, and G. Koren. 2004. 'Topical 4% amethocaine gel reduces the pain of subcutaneous measles-mumps-rubella vaccination', *Pediatrics*, 114: e720-4.

Ogden, L., G. Love, and S. Basta. 2008. 'Systemic exposure to lidocaine and tetracaine is low after an application of a lidocaine 7%-tetracaine 7% peel in adults', *Int J Dermatol*, 47: 87-90.

Patel, D., S. Chopra, and M. D. Berman. 1989. 'Serious systemic toxicity resulting from use of tetracaine for pharyngeal anesthesia in upper endoscopic procedures', *Dig Dis Sci*, 34: 882-4.

Perelman, M., A. N. Fisher, A. Smith, and A. Knight. 2013. 'Impact of allergic rhinitis and its treatment on the pharmacokinetics of nasally administered fentanyl', *Int J Clin Pharmacol Ther*, 51: 349-56.

Rajpal, S., L. A. Morris, and N. I. Akkus. 2014. 'Non-ST-elevation myocardial infarction with the use of oxymetazoline nasal spray', *Rev Port Cardiol*, 33: 51 e1-4.

Rayburn, W. F., J. C. Anderson, C. V. Smith, L. L. Appel, and S. A. Davis. 1990. 'Uterine and fetal Doppler flow changes from a single dose of a long-acting intranasal decongestant', *Obstet Gynecol*, 76: 180-2.

Riegle, E. V., J. B. Gunter, R. P. Lusk, H. R. Muntz, and K. L. Weiss. 1992. 'Comparison of vasoconstrictors for functional endoscopic sinus surgery in children', *Laryngoscope*, 102: 820-3.

Saadah, H. A. 1987. 'A case of panic disorder precipitated by oxymetazoline withdrawal', *J Clin Psychiatry*, 48: 293.

Schatz, M., R. S. Zeiger, K. Harden, C. C. Hoffman, L. Chilingar, and D. Petitti. 1997. 'The safety of asthma and allergy medications during pregnancy', *J Allergy Clin Immunol*, 100: 301-6.

Shah, V. S., A. Taddio, R. Hancock, P. Shah, and A. Ohlsson. 2008. 'Topical amethocaine gel 4% for intramuscular injection in term neonates: a double-blind, placebo-controlled, randomized trial', *Clin Ther*, 30: 166-74.

Soderman, P., D. Sahlberg, and B. E. Wiholm. 1984. 'CNS reactions to nose drops in small children', *Lancet*, 1: 573.

Speirs, A. F., K. H. Taylor, D. N. Joanes, and N. M. Girdler. 2001. 'A randomised, double-blind, placebo-controlled, comparative study of topical skin analgesics and the anxiety and discomfort associated with venous cannulation', *Br Dent J*, 190: 444-9.

Taddio, A., C. Lee, A. Yip, B. Parvez, P. J. McNamara, and V. Shah. 2006. 'Intravenous morphine and topical tetracaine for treatment of pain in [corrected] neonates undergoing central line placement', *JAMA*, 295: 793-800.

Thrush, D. N. 1995. 'Cardiac arrest after oxymetazoline nasal spray', *J Clin Anesth*, 7: 512-4.

Ticoll, B., and G. Shugar. 1994. 'Paranoid psychosis induced by oxymetazoline nasal spray', *CMAJ*, 150: 375-6.

Torfs, C. P., E. A. Katz, T. F. Bateson, P. K. Lam, and C. J. Curry. 1996. 'Maternal medications and environmental exposures as risk factors for gastroschisis', *Teratology*, 54: 84-92.

Tucker, H. M., and S. al Haddad. 1991. 'Topical anesthesia for peroral endoscopy', *Ear Nose Throat J*, 70: 494-6.

Wang, R., N. F. Souza, J. A. Fortes, G. J. Santos, J. R. Faria Neto, and L. Zytinski. 2009. 'Apical ballooning syndrome secondary to nasal decongestant abuse', *Arq Bras Cardiol*, 93: e75-8.

Warshaw, E. M., S. E. Schram, D. V. Belsito, V. A. DeLeo, J. F. Fowler, Jr., H. I. Maibach, J. G. Marks, Jr., C. G. Mathias, M. D. Pratt, R. L. Rietschel, D. Sasseville, F. J. Storrs, J. S. Taylor, and K. A. Zug. 2008. 'Patch-test reactions to topical anesthetics: retrospective analysis of cross-sectional data, 2001 to 2004', *Dermatitis*, 19: 81-5.

Watanabe, H., T. H. Foo, B. Djazaeri, P. Duncombe, I. S. Mackay, and S. R. Durham. 2003. 'Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis', *Rhinology*, 41: 167-74.

Whited, C., and S. M. Cohen. 2012. 'Nasal tetracaine spray-induced methemoglobinemia', *Otolaryngol Head Neck Surg*, 146: 678-9.

Wongprasartsuk, P., and B. J. Main. 1998. 'Adverse local reactions to amethocaine cream--audit and case reports', *Anaesth Intensive Care*, 26: 312-4.

Woolfson, A. D., D. F. McCafferty, and V. Boston. 1990. 'Clinical experiences with a novel percutaneous amethocaine preparation: prevention of pain due to venepuncture in children', *Br J Clin Pharmacol*, 30: 273-9.

Zhijun, C., Z. Fugao, Z. Niankai, and C. Jingjing. 2008. 'Therapeutic experience from 1428 patients with pediatric tracheobronchial foreign body', *J Pediatr Surg*, 43: 718-21.

---

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

---

/s/

---

MARY A LUCKETT
06/28/2016

RIGOBERTO A ROCA
06/28/2016