CLINICAL PHARMACOLOGY REVIEW

NDA: 208032	Submission Date: 5/29/15
Submission Type; Code:	1S
Brand/Code Name:	Kovanaze™
Generic Name:	Tetracaine HCl 3%, Oxymetazoline HCl 0.05%
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Yun Xu, Ph.D.
OCP Division:	DCP 2
ORM Division:	Division of Anesthesia, Analgesia, and Addition Products
Sponsor:	St. Renatus
Relevant IND(s):	70868
Formulation; Strength(s):	Nasal spray; tetracaine HCl 3%, oxymetazoline HCl 0.05%
Proposed Indication:	Local anesthetic with a vasoconstrictor indicated for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J.
Proposed Dosage Regimen:	See table below

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)	

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 208032, for Kovanaze™, submitted on 5/29/15. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CPB Findings

St. Renatus, LLC, has submitted a New Drug Application (NDA) for Kovanaze™ Nasal Spray, 'Kovanaze' ('(b) (4) and (b) (4) notations were also used throughout the product development). Kovanaze is a fixed-combination product of a tetracaine HCl (3%), and oxymetazoline HCl, (0.05%) and is administered as a single-dose nasal spray during a dental procedure (e.g., drilling and restoring a decayed tooth), which is for (b) (4) regional anesthesia. Tetracaine and oxymetazoline are known to be an anesthetic and a vasoconstrictor, respectively. Historically tetracaine has been on the market since mid-1930's and utilized in the clinical setting for over more than 75 years. Additionally oxymetazoline has been used since mid-1960's, including for decades in multiple over-the-counter (OTC) drug products in the US, e.g., Afrin®, Visine LR®, Vicks Sinex®, etc. The Applicant is seeking approval for the use of Kovanaze in adult and pediatric (b) (4) dental patients. The proposed indication is for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J. The proposed dosing regimen in adults is 0.4 mL to 0.6 mL (2 to 3 sprayers), depending on the patient's response. The recommended dose in pediatric patients is (b) (4) 0.4 mL, based on the patient's weight (b) (4). Kovanaze is packaged as a single-use (b) (4) delivery system (sprayer). Each sprayer delivers a 0.2 mL that contains 6 mg of tetracaine HCl (3% w/v concentration) and 0.1 mg of oxymetazoline HCl (0.05% w/v concentration). The dose may be delivered as a single spray of 0.2 mL or as two divided sprays of 0.1 mL each.

The Applicant indicated that they have obtained a right of reference to Synera®, 'referred to as Synera' in this review, (lidocaine and tetracaine topical patch), N21623, in its entirety, in support of tetracaine component in Kovanaze. The Applicant also stated that they are also relying on reference to the OTC monograph for nasal decongestant products (21 CFR Part 341) as it applies

to the findings of nonclinical safety of oxymetazoline, as support for a 505(b)(2) application with respect to oxymetazoline hydrochloride component in Kovanaze. (b) (4) The discussions regarding references were conducted throughout the drug development phases, e.g., pre-NDA meeting, and deemed appropriate from the reviewing team.

The proposed indication for Kovanaze is for (b) (4) regional anesthesia. Tetracaine and oxymetazoline concentrations at the (b) (4), intranasal site, were not sampled and analyzed. There is no (b) (4) tetracaine exposure-success based on the completion of standard dental procedure without need for rescue by injection of local anesthetic-response relationship for this product. (b) (4) the critical clinical pharmacology aspect of this NDA was to focus on the systemic safety related to tetracaine and oxymetazoline systemic exposure delivered from Kovanaze.

The Applicant has submitted results from 3 pharmacokinetic studies: 1) SR 2-02, a preliminary pharmacokinetic (PK) study assessing 0.6 and 1.2 mL Kovanaze doses in adults; 2) SR 2-06, a PK study with 0.6 mL Kovanaze dose, highest Phase 3 adult dose, in adults; and 3) SR 2-07, a PK study with 0.1, 0.2 and 0.4 mL Kovanaze doses in pediatric subjects from 3.8 to 15.1 years of age stratified into 3 groups by weight. This review focused results from Studies SR 2-06 and SR 2-07. The results from the preliminary study SR 2-02 were briefly described. To-be-marketed product was used in all clinical studies. See below at the end of this section for summary findings from studies SR 2-06 and SR 2-07 and under Section 2.2 for additional discussion on PK studies.

For support of Kovanaze efficacy the Applicant relies upon the results from 3 clinical trials, 2 adults (SR 3-02 and SR 3-03) and 1 pediatric (SR 3-04) trials. To-be-marketed product was used in all clinical trials. The primary efficacy endpoint in Phase 3 trials was completion of standard dental procedure (e.g., drilling and restoring a decayed tooth) without the need for "rescue" by injection of local anesthetic (e.g., 4% articaine HCl with 1:200,000 epinephrine). In Study SR 3-02 (N=110) adult patients received three 0.2 mL intranasal sprays (0.6 mL total) of either Kovanaze (N=44), tetracaine alone (N=44), or placebo (N=22) ipsilateral to the target tooth over a period of 8 minutes. The Applicant stated that all subjects finished the trial. In Study SR 3-03 (N=150) adult patients received two to three 0.2 mL sprays (0.4 or 0.6 mL total) of either Kovanaze (N=100) or placebo (N=50) 4 minutes apart. An optional third spray was available if anesthesia was insufficient 15 minutes after the first dose. The Applicant stated that all subjects finished the trial except two subjects (one in each group). In Study SR 3-04 (N=90 age 3 through 17 years old inclusive) pediatric patients received one or two intranasal sprays of either Kovanaze (N=60) or placebo (N=30) based on body weight: 1) one 0.1 mL spray for patients weighing 10 kg to < 20 kg; 2) two 0.1 mL sprays for patients weighing 20 to < 40 kg; and 3) two 0.2 mL sprays for patients weighing ≥ 40 kg. In all Phase 3 trials the Applicant reported that success rates for the Kovanaze were 84% (27% placebo), 88% (28% placebo), and 77% (53% placebo) for SR 3-02, SR 3-03 and SR 3-04 trials, respectively. For a comprehensive overview regarding safety and effectiveness of Kovanaze, the reader is referred to reviews conducted by

medical officer and statistical reviewer for in depth discussion and assessment of the Phase 3 program.

Tetracaine and its major metabolite, para-aminobenzoic acid (PBBA) information in Synera Product Label

With respect to tetracaine, Synera Product Label indicated under Section 12.3 Clinical Pharmacology that 'plasma levels of tetracaine were below the limit of quantitation (<0.9 ng/mL) in all subjects tested (n = 12).' Synera Product Label does not provide PBBA exposure information (Note: Synera NDA clinical pharmacology review contains no PBBA exposure information). Similar findings for tetracaine were observed from Kovanaze administration. Of all samples analyzed for tetracaine, one quantifiable tetracaine concentration was observed in a single sample from one subject, which is barely above the LLOQ (0.05 ng/mL). As there were not enough samples in which tetracaine was quantifiable, tetracaine PK parameters were not obtained for Kovanaze.

Oxymetazoline nonclinical safety and OTC monograph for nasal decongestant (21 CFR Part 341)

Kovanaze is expected to be used as a one-time administration as a single-dose nasal spray during a dental procedure. As stated above the Applicant is relying on the OTC monograph for nasal decongestant products (21 CFR Part 341) to support the nonclinical safety of oxymetazoline in Kovanaze as support for a 505(b)(2) application. For products containing oxymetazoline hydrochloride identified in the OTC monograph for nasal decongestant, CFR 314.80(d)(2), the monograph states that: '(A) Nasal drops or sprays: (1) 0.05% aqueous solution. Adults and children 6 to <12 years of age: 2 or 3 drops or sprays in *each nostril* not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children <6 years of age: consult a doctor; (2) A 0.025% aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than *0.027 milligrams of oxymetazoline per three drops or three sprays*. Children 2 to <6 years of age: 2 or 3 drops or sprays in *each nostril* not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. Children <2 years of age: consult a doctor.' For a comprehensive overview regarding nonclinical safety of oxymetazoline, the reader is referred to review conducted by the Pharmacology/Toxicology reviewer. From a clinical pharmacology perspective, the Applicant has conducted adult and pediatric pharmacokinetic studies with Kovanaze to provide oxymetazoline exposure information, which will be described in the Kovanaze label.

Adults

Study SR-06 was conducted to evaluate the PKs of Kovanaze intranasal administration of 0.6 mL [18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl; at the maximum recommended dose (highest Phase 3 adult dose)] in healthy adult volunteers (N=24; 13/11 male/female, age 18.1 to 47.5 years old). Kovanaze 0.6 mL was administered as 3 sprays of 0.2 mL each, unilaterally in one nostril for a total dose of 0.6 mL (3 administrations of 1 X 0.2 mL). Each unilateral nasal spray (that is, to only one nostril) was separated from the previous one by a 4-min interval. The total dosing period was 8 minutes (0, 4, and 8 minutes). Tetracaine, PBBA and oxymetazoline

moieties were analyzed utilizing validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods.

After administration of Kovanaze, it appears that tetracaine was rapidly metabolized to PBBA. There were over 500 blood samples analyzed for tetracaine; the lower limit of quantitation (LLOQ) for tetracaine was 0.05 ng/mL. Of all samples analyzed one quantifiable tetracaine concentration was observed in a single sample from one subject (Subject 116, 0.08 h (5 min) sample, 0.0501 ng/mL), which is barely above the LLOQ. As there were not enough samples in which tetracaine was quantifiable, tetracaine PK parameters were not obtained. It is noted that similar findings were reported in Synera Product Label, which the Label indicated that 'plasma levels of tetracaine were below the limit of quantitation (<0.9 ng/mL) in all subjects tested (n = 12).'

Following Kovanaze intranasal administration of 0.6 mL, the observed mean oxymetazoline Cmax, AUC0-inf and T1/2 value were 1.78 ng/mL, 4.24 ng.h/mL and 5.23 h, respectively. The observed median Tmax was 5 minutes. The observed mean PBBA Cmax, AUC0-inf and T1/2 value were 465 ng/mL, 973 ng.h/mL and 2.6 h, respectively. The observed median Tmax was 20 minutes.

Pediatrics

Kovanaze development in pediatric population was discussed during end-of-phase 2 meeting and pre-NDA meeting, which included dose selection for pediatric patients, evaluation of safety and efficacy in patients down to the age of 3 years, plans for the initial pediatric trial to start with the older patients first, e.g., 12 to 17 years of age, followed by younger patients, etc. As previously stated the Applicant already assessed Kovanaze in pediatric patients 3 to 17 years of age (SR 3-04, a Phase 3 safety and efficacy trial, SR 2-03, a Phase 2 dose-ranging study, and SR 2-07, a Phase 1 pharmacokinetic study) prior to submitting the agreed initial Pediatric Study Plan.

Currently the Applicant is requesting approval of Kovanaze for adults and pediatric patients (b) (4) . Additionally the Applicant is requesting a waiver for patients 2 years old and younger.

Study SR 2-07 was an open-label, single-center, single-dose study to determine and evaluate the PK profiles and safety of tetracaine, PBBA, and oxymetazoline after intranasal administration of Kovanaze administered as the recommended weight-based Phase 3 dose (same dosing scheme was used in Phase 3 pediatric trial SR 3-04) in pediatric subjects, ages 3 to 17 years. Pediatric subjects were enrolled into 3 groups based on age: ages 3 to 6 years; ages 7 to 11 years; and ages 12 to 17 years, inclusive. Pediatric subjects weighing 1) 10 to < 20 kg received 1 0.1 mL spray, 2) 20 to < 40 kg received 2 unilateral 0.1 mL sprays (total dose 0.2 mL) dosed 4 minutes apart, 3) 40 kg or more received 2 unilateral 0.2 mL sprays (total dose 0.4 mL) dosed 4 minutes apart.

After Kovanaze administration, tetracaine was rapidly metabolized to PBBA. There were close to 200 blood samples analyzed for tetracaine; the lower limit of quantitation (LLOQ) for tetracaine was 0.05 ng/mL. Of all blood samples analyzed no quantifiable tetracaine concentrations was observed. Therefore tetracaine PK parameters were not determined. Tables

2 and 3 present oxymetazoline and PBBA pharmacokinetic parameters after 0.1 mL, 0.2 mL and 0.4 mL Kovanaze (0.05 mg, 0.1 mg, and 0.2 mg oxymetazoline dose, respectively).

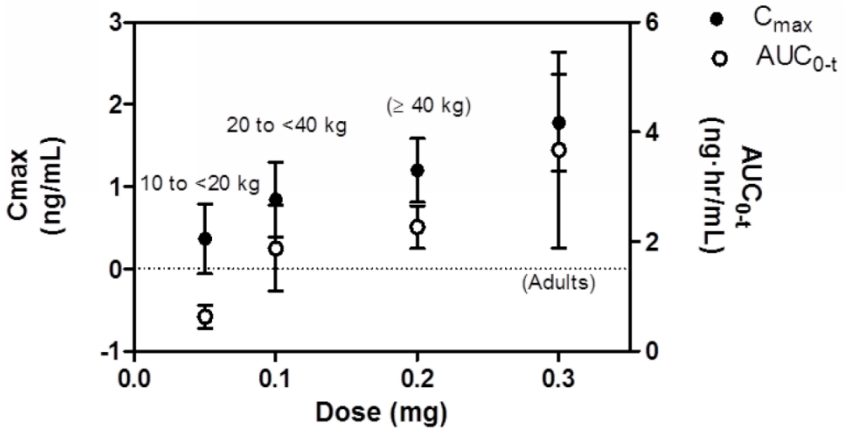
The observed oxymetazoline mean Cmax values were 0.37 ± 0.43, 0.85 ± 0.45, and 1.2 ± 0.38 ng/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean AUC0-inf values were 0.99 (N=1), 2.53 ± 1.08, and 2.64 ± 0.41 ng.h/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean T1/2 values were 1.57 h (n = 1), 4.32 h, and 3.49 h in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. Oxymetazoline Tmax (median) values were observed at 10 to 30 min post-dose.

The observed PBBA mean Cmax values were 166 ± 71, 345 ± 172, and 365 ± 30 ng/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean AUC0-inf values were 529 ± 222, 826 ± 606, and 665 ± 86 ng.h/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed PBBA Tmax (median) values were observed at 20 to 30 min post-dose. PBBA mean T1/2 values were 2.81 h, 2.18 h, and 1.57 h in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively.

Comparison between adults and pediatrics

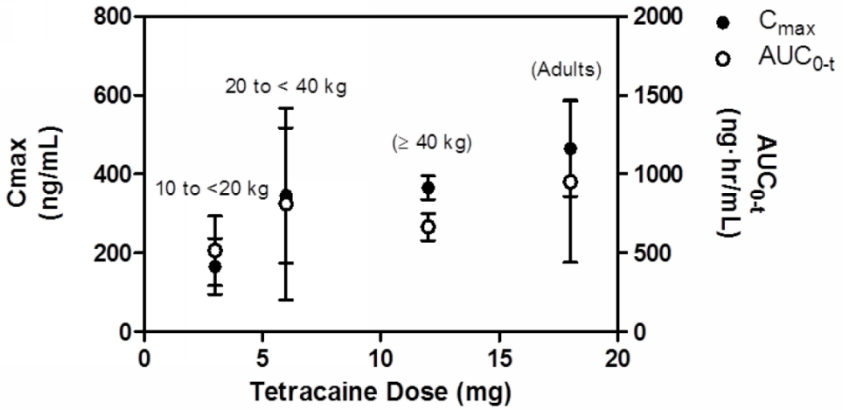
In Study SR 2-06 Kovanaze assessed dose in adults was 0.6 mL (0.3 mg oxymetazoline). In Study SR 2-07 Kovanaze assessed doses in pediatrics were 0.1, 0.2 and 0.4 mL (0.05, 0.1 and 0.2 mg oxymetazoline, respectively). As stated previously tetracaine concentrations were below the LLOQ for both studies. The following figures are to provide a quick snapshot of adult and pediatric Cmax and AUC values obtained from Studies SR 2-06 and SR 2-07. An increase in systemic oxymetazoline exposure, as indicated by mean Cmax and AUC0-t values, was observed with increasing mg-dose across the three pediatric groups. Additionally, this trend continued when mean values from adults (Study SR 2-06) were included (Figure 1). Similar findings were observed for PBBA with increasing tetracaine mg-dose (Figure 2). Accordingly the mean Cmax and AUC0-inf values are compared in Table 1 from Studies SR 2-06 and SR 2-07.

Figure 1 Mean (± SD) Oxymetazoline Cmax and AUC0-t in pediatric (Study SR 2-07) and adult (Study SR 2-06) subjects as a function of oxymetazoline mg-dose following Kovanaze administration.



Source data: Appendix 16 1 13, Table/Appendix 2 and Appendix 9, Table/Appendix 2 in Pharmacokinetic Analysis Report

Figure 2 Mean (± SD) PBBA Cmax and AUC0-t in pediatric (Study SR 2-07) and adult (Study SR 2-06) subjects as a function of tetracaine mg-dose following Kovanaze administration



Source data: Appendix 16 1 13, Table/Appendix 3 and Appendix 9, Table/Appendix 3 in PK Analysis Report

Table 1 Mean oxymetazoline and PBBA pharmacokinetic parameters in pediatric (0.1, 0.2 and 0.4 mL) and adult subjects (0.6 mL) after Kovanaze administration

		Dose mL	Cmax (ng/mL)	AUCinf (ng.h/mL)	T1/2 (h)
Group	Oxymetazoline				
Pediatric (SR 2-07)	10 to < 20 kg	0.1	0.367	0.992*	1.57*
	20 to < 40 kg	0.2	0.846	2.53	4.32
	≥ 40 kg	0.4	1.20	2.64	3.49
Adult (SR 2-06)		0.6	1.78	4.24	5.23
	PBBA				
Pediatric (SR 2-07)	10 to < 20 kg	0.1	166	529	2.81
	20 to < 40 kg	0.2	345	826	2.18
	≥ 40 kg	0.4	365	665	1.57
Adult (SR 2-06)		0.6	465	973	2.60

*N=1

Potential drug interaction for tetracaine and oxymetazoline

The pharmacokinetic interactions between tetracaine and oxymetazoline are not expected as tetracaine undergoes rapid hydrolysis by plasma esterases and oxymetazoline is thought to be metabolized by CYP enzymes according to the in vitro findings reported in the literature. In addition, the Applicant has measured the systemic exposure of both components when the combination product is administered.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What is Kovanaze?

Kovanaze, also notated throughout the drug development as 'Kovanaze' and '[redacted] is a fixed-combination product of a tetracaine HCl (3%), and oxymetazoline HCl, (0.05%), and is administered as a single-dose nasal spray during a dental procedure (e.g., drilling and restoring a decayed tooth), which is for [redacted] regional anesthesia. Tetracaine and oxymetazoline are known to be an anesthetic and a vasoconstrictor, respectively.

2.1.2 What is Kovanaze to-be-marketed formulation/product?

The composition of Kovanaze Nasal Spray is presented in Table 2, expressed as percent weight in volume and per spray unit basis for [redacted] spray volumes of 0.2 mL [redacted].

Table 2 Composition of Kovanaze Nasal Spray

Component	Function	Composition	Quantity per Spray
		% w/v	0.2 mL spray
Tetracaine hydrochloride, USP	Active	3.00	6.0 mg
Oxymetazoline hydrochloride, USP	Active	0.05	0.10 mg
Citric acid [redacted] USP	[redacted]		
Sodium citrate [redacted] USP			
[redacted]			
Benzyl alcohol, NF			
Hydroxyethylcellulose, NF			
Sodium hydroxide, NF	pH adjustment	as needed	as needed
Hydrochloric acid, NF	pH adjustment	as needed	as needed
[redacted] water, USP [1]	[redacted]	q.s. 100 mL	q.s. 0.2 mL

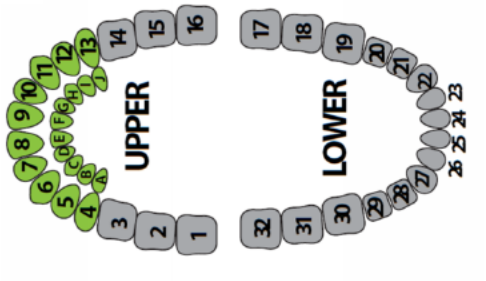
[1] [redacted]

Kovanaze is packaged as a single-use [redacted] delivery system (sprayer; by [redacted] the volume-fill is [redacted] mL, with [redacted] mL overfill which is [redacted]). Each sprayer delivers a 0.2 mL that contains 6 mg of tetracaine HCl (3% w/v concentration) and 0.1 mg of oxymetazoline HCl (0.05% w/v concentration). The dose may be delivered as a single spray of 0.2 mL [redacted]

2.1.3 What is the proposed indication?

The Applicant is seeking approval for the use of Kovanaze in adult and pediatric [redacted] dental patients. The proposed indication is for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J (Figure 4).

Figure 4 The notion for adult and deciduous teeth



2.1.4 What are the proposed dosage and route of administration?

Each sprayer delivers a 0.2 mL: 6 mg of tetracaine HCl (3% w/v concentration) and 0.1 mg of oxymetazoline HCl (0.05% w/v concentration. Generally, Kovanaze is administered in the nostril ipsilateral to the tooth or teeth targeted for treatment. Table 3 presents the proposed dosing regimen in adults and pediatric patients by the Applicant.

Table 3 The proposed dosing regimen in adults and pediatric patients

Age Group	Dose	Tetracaine total amount	Oxymetazoline total amount
Adults (≥ 18 years old)	2 sprays (0.2 mL per spray), 4-5 minutes apart	12 mg	0.2 mg
	1 additional spray (0.2 mL) if adequate anesthesia has not been achieved 10 minutes after the second spray	18 mg	0.3 mg
Children [redacted] weighing ≥ 40 kg)	2 sprays (0.2 mL per spray), 4 minutes apart	12 mg	0.2 mg

[redacted]

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials? What is the response endpoints used in Phase 3 trials?

For support of Kovanaze efficacy the Applicant relies upon the results from 3 clinical trials, 2 adults (SR 3-02 and SR 3-03) and 1 pediatric (SR 3-04) trials. To-be-marketed product was used in all clinical trials. All adult trials utilized multicenter, randomized, double-blind, placebo-controlled, parallel-groups study design. The pediatric trial was similar except that it was not a placebo-controlled. The primary efficacy endpoint in Phase 3 trials was completion of standard dental procedure (e.g., drilling and restoring a decayed tooth) without the need for "rescue" by injection of local anesthetic (e.g., 4% articaine HCl with 1:200,000 epinephrine).

In Study SR 3-02 (N=110) adult patients received three 0.2 mL intranasal sprays (0.6 mL total) of either Kovanaze (N=44), tetracaine alone (N=44), or placebo (N=22) ipsilateral to the target tooth over a period of 8 minutes. Kovanaze was compared to tetracaine alone and to placebo. All treatments were administered unilaterally on the same side as the target tooth/teeth. In Study SR 3-03 (N=150) adult patients received two to three 0.2 mL sprays (0.4 or 0.6 mL total) of either Kovanaze (N=100) or placebo (N=50) 4 minutes apart. An optional third spray was available if anesthesia was insufficient 15 minutes after the first dose. Kovanaze was compared to placebo. Again, unilateral administration was used for all treatments. In Study SR 3-04 (N=90 age 3 through 17 years old inclusive) pediatric patients received one or two intranasal sprays of either Kovanaze (N=60) or placebo (N=30) based on body weight: 1) one 0.1 mL spray for patients weighing 10 kg to < 20 kg; 2) two 0.1 mL sprays for patients weighing 20 to < 40 kg; and 3) two 0.2 mL sprays for patients weighing ≥ 40 kg. Kovanaze was compared to placebo. Again, unilateral administration was used for all treatments.

In all Phase 3 trials the Applicant reported that success rates for the Kovanaze were 84% (27% placebo), 88% (28% placebo), and 77% (53% placebo) for SR 3-02, SR 3-03 and SR 3-04 trials, respectively. For a comprehensive overview regarding safety and effectiveness of Kovanaze, the reader is referred to reviews conducted by medical officer and statistical reviewer for in depth discussion and assessment of the Phase 3 program.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to II. F, Analytical Section; if no, describe the reasons)

Yes, the active moieties, tetracaine, its metabolite, PBBA, and oxymetazoline have been identified and measured to assess pharmacokinetic parameters. See Analytical Section 2.6 for additional information regarding assay methodology employed.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

Kovanaze is administered intra-nasally [redacted]. Tetracaine and oxymetazoline concentrations at the [redacted] intranasal site, were not sampled and analyzed. Therefore, there is no [redacted] tetracaine exposure-success based on the completion of standard dental procedure without need for rescue by injection of local anesthetic-response relationship for this product. [redacted] the critical clinical pharmacology aspect of this NDA was to focus on the systemic safety related to tetracaine and oxymetazoline exposure delivered from Kovanaze.

2.2.3.2 Does this drug prolong the QT or QTc interval?

No information was submitted to characterize Kovanaze. The Applicant relies on the data in NDA N21623 (Synera) for tetracaine component and the monograph findings for oxymetazoline component.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

The following information has been obtained from Synera Labeling with respect to tetracaine. The systemic exposure information for oxymetazoline is virtually none existent in the literature; however, per 21 CFR Part 341, Final Monograph for over-the-counter (OTC) Nasal Decongestant Drug Products, oxymetazoline is generally recognized as safe and effective and not misbranded.

Mechanism of Action
Tetracaine is an ester-type local anesthetic agent. Tetracaine block sodium ion channels required for the initiation and conduction of neuronal impulses, resulting in local anesthesia.

Distribution
Volume of distribution and protein binding has not been determined for tetracaine due to rapid hydrolysis in plasma. [The reported tetracaine protein binding values range from 75% - 85% (Altman, 1985; McLure, 2005; Covino, 1984)].

Metabolism
Tetracaine undergoes rapid hydrolysis by plasma esterases. Primary metabolites of tetracaine include para-aminobenzoic acid (PBBA) and diethylaminoethanol, both of which have an unspecified activity.

Elimination
The half-life and clearance for tetracaine have not been established for humans, but hydrolysis in the plasma is rapid. (A description of the routes of excretion of tetracaine in humans was not described.)

The following information (from the literature) was submitted by the Applicant with respect to oxymetazoline.

Mechanism of Action
Oxymetazoline is believed to be a mixed α1/α2-adrenoceptor agonist (Haenisch 2010) and to exert its local decongestant effects in the nose by stimulating adrenergic receptors, eliciting vasoconstriction of dilated arterioles and reducing nasal blood flow.

Distribution
No information was available.

Metabolism
In vitro oxymetazoline metabolism evaluated in liver fractions (S9 fractions) suggested that oxymetazoline undergoes oxidative metabolism possibly via CYP2C19 isoform (Mahajan, Drug Metab and Disposition, Vol 39, No.4, 2011). Additionally in vitro oxymetazoline metabolism information suggested that oxymetazoline undergoes O-glucuronidation by UGT1A9 (Mahjan, J PHARM SCI, Vol. 100, No. 2, Feb 2011).

Elimination
No information was available.

2.2.4.1 What are the single dose PK parameters?

Study SR-06

Study SR-06 was conducted in healthy adult volunteers (N=24; 13/11 male/female, age 18.1 to 47.5 years old) to evaluate the pharmacokinetics of tetracaine, PBBA (a major metabolite of tetracaine) and oxymetazoline after Kovanaze intranasal administration of 0.6 mL [18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl; at the maximum recommended dose (highest Phase 3 adult dose)]. Kovanaze 0.6 mL was administered as 3 sprays of 0.2 mL each, unilaterally in one nostril for a total dose of 0.6 mL (3 administrations of 1 X 0.2 mL). Each unilateral nasal spray (that is, to only one nostril) was separated from the previous one by a 4-min interval. The total dosing period was 8 minutes (0, 4, and 8 minutes).

Blood samples were collected at pre-dose, at after the final nasal spray, at 5, 10, 15, 20, 25, 30, 40, and 50 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the final nasal spray. Tetracaine, PBBA and oxymetazoline were quantitated in plasma using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods with lower limits of quantitation (LLOQ) values of 0.0500 ng/mL for tetracaine and oxymetazoline, and 2.00 ng/mL for PBBA.

There were approx. equal number male and female subjects participated in the study (54% male and 46% female). The mean age was 28.7 ± 9.36 years (range 18 to 47 years). The majority of subjects were White (n = 19, 79.2%) as well as not of Hispanic or Latino ethnicity (n = 22, 91.7%). The subjects mean weight was 68.3 ± 10.85 kg (range 54 to 84 kg); mean height was 170.4 ± 9.45 cm (range 152 to 188 cm); mean BMI was 24.4 ± 3.60 kg/m2 (range 19 to 34 kg/m2).

After administration of Kovanaze, it appears that tetracaine was rapidly metabolized to PBBA. There were over 500 blood samples analyzed for tetracaine; the lower limit of quantitation

(LLOQ) for tetracaine was 0.05 ng/mL. Of all samples analyzed one quantifiable tetracaine concentration was observed in a single sample from one subject (Subject 116, 0.08 h (5 min) sample, 0.0501 ng/mL), which is barely above the LLOQ. As there were not enough samples in which tetracaine was quantifiable, tetracaine PK parameters were not obtained. It is noted that similar findings were reported in Synera Product Label, which the Label indicated that 'plasma levels of tetracaine were below the limit of quantitation (<0.9 ng/mL) in all subjects tested (n = 12).'

Mean (± SD) oxymetazoline and PBBA concentration vs time data are presented in Figure 5 and Figure 6, respectively.

Figure 5 Oxymetazoline Mean (sd) Plasma Concentration – Time Curves in Healthy Volunteers Administered (b) (4) (Tetracaine HCl 18 mg, Oxymetazoline HCl 0.3 mg)

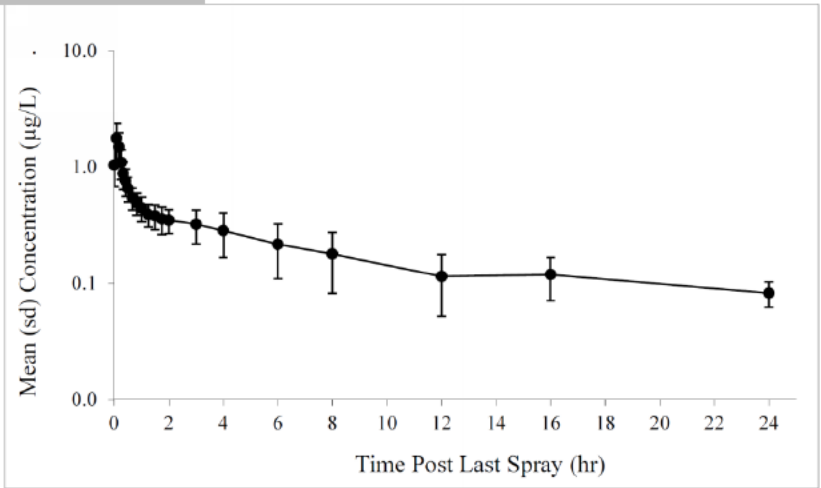
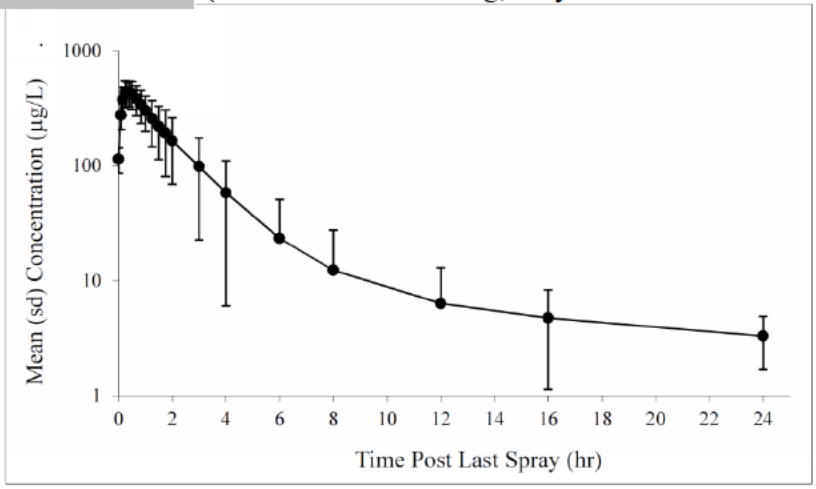


Figure 6 PBBA Mean (sd) Plasma Concentration – Time Curves in Healthy Volunteers Administered (b) (4) (Tetracaine HCl 18 mg, Oxymetazoline HCl 0.3 mg)



Oxymetazoline and PBBA PK parameters are summarized in Table 4.

Table 4 Mean Oxymetazoline and PBBA Plasma Pharmacokinetic Parameters* in Human Volunteers After the Intranasal Administration of [redacted] (b) (4) (Tetracaine HCL 18 mg, Oxymetazoline HCL 0.3 mg)

Compound	Parameter	C_{max} (µg/L)	T_{max} (min)	T_{last} (hr)	λz (hr-1)	$t_{1/2}$ (hr)	AUC_{0-t} (hr*µg/L)	$AUC_{0-\infty}$ (hr*µg/L)
Oxymetazoline	**Mean**	1.78	5.8	15	0.154	5.23	3.67	4.24
	sd	0.586	1.9	6.1	0.0575	2.20	1.79	2.09
	se	0.120	0.39	1.2	0.0117	0.449	0.366	0.426
	Minimum	0.841	5.0	8.0	0.0655	2.27	1.45	1.98
	Median	1.73	5.0	12	0.150	4.63	3.13	3.45
	Maximum	2.88	10.	24	0.306	10.6	7.00	8.39
	CV%	33	33	42	37	42	49	49
	Geo Mean	1.68	5.6	14	0.143	4.84	3.29	3.82
PBBA	**Mean**	465	21.6	14	0.346	2.6	960	973
	sd	122	6.6	3.7	0.184	1.23	509	513
	se	24.9	1.32	0.76	0.0376	0.252	104	105
	Minimum	208	15	8	0.149	0.887	383	389
	Median	448	19.8	12	0.252	2.78	817	826
	Maximum	663	40.2	24	0.781	4.65	2500	2530
	CV%	26	30	26	53	48	53	53
	Geo Mean	448	21	14	0.302	2.29	868	880

* N = 24

Source data: Pharmacokinetic Analysis Report

The observed mean oxymetazoline Cmax, AUC0-inf and T1/2 value were 1.78 ng/mL, 4.24 ng.h/mL and 5.23 h, respectively. The observed median Tmax was 5 minutes.

The observed mean PBBA Cmax, AUC0-inf and T1/2 value were 465 ng/mL, 973 ng.h/mL and 2.6 h, respectively. The observed median Tmax was 20 minutes.

Safety

A summary of TEAE incidence is provided in Tables 5. The most frequently reported TEAEs following administration of Kovanaze were respiratory, thoracic and mediastinal disorders (n = 22, 91.7%), gastrointestinal disorders (n = 17, 70.8%), and nervous system disorders (n = 16, 66.7%).

Table 5 Incidence (N, %) of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

SOC Preferred Term	N (%) (n = 24)
Gastrointestinal disorders	17 (70.8%)
Hypoaesthesia oral	9 (37.5%)
Hypoaesthesia teeth	7 (29.2%)
Nausea	3 (12.5%)
General disorders and administration site conditions	1 (4.2%)
Oedema peripheral	1 (4.2%)
Infections and infestations:	1 (4.2%)
Rhinitis	1 (4.2%)
Investigations	1 (4.2%)
Urine analysis abnormal	1 (4.2%)
Nervous system disorders	16 (66.7%)
Dizziness	1 (4.2%)
Headache	6 (25.0%)
Hypoaesthesia	11 (45.8%)
Paraesthesia	6 (25.0%)
Respiratory, thoracic and mediastinal disorders	22 (91.7%)
Epistaxis	3 (12.5%)
Increased viscosity of bronchial secretion	1 (4.2%)
Increased viscosity of nasal secretion	1 (4.2%)
Intranasal hypoaesthesia	1 (4.2%)
Nasal congestion	5 (20.8%)
Nasal discomfort	5 (20.8%)
Nasal inflammation	1 (4.2%)
Pharyngeal erythema	1 (4.2%)
Pharyngeal hypoaesthesia	7 (29.2%)
Rhinalgia	1 (4.2%)
Rhinorrhoea	11 (45.8%)
Throat irritation	5 (20.8%)

Source data: Table 14.3.1.2

2.2.4.2 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Study SR-02

Study SR-02 was a preliminary study conducted in healthy adult volunteers (N=12; 6/6 male/female, 25 to 47 years old) to evaluate the safety and to determine the pharmacokinetics of Kovanaze at the previously estimated maximum single dose of 0.6 mL (18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl) and 1.2 mL (36 mg tetracaine HCl and 0.6 mg oxymetazoline HCl). All subjects received 0.6 mL at the first treatment and 1.2 mL dose at least 1 week, but no more than 3 weeks, later as a second treatment. The first dose, 0.6 mL, was administered as 3 sprays in each nostril (0.1 mL/spray), for a total dose of 0.6 mL. The second dose, 1.2 mL, was administered as 6 sprays in each nostril for a total dose of 1.2 mL. Each set of bilateral nasal sprays (that is, one spray to each nostril for 2 sprays) was separated from the previous sprays by a 4-minute interval. The total dosing period was 8 minutes for the 0.6 mL (0, 4, and 8 minutes) and 20 minutes for the 1.2 mL (0, 4, 8, 12, 16, and 20 minutes). Blood samples were collected at pre-dose, followed by every 5 min following the beginning of dose administration through 30 min, every 10 min from 30 through 120 min. Tetracaine, PBBA (a major metabolite of tetracaine) and oxymetazoline were quantitated in plasma using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods with lower limits of quantitation (LLOQ) of 0.100 ng/mL for all analytes.

Mean (±SD) oxymetazoline, tetracaine and PBBA concentration vs time data are presented in Figures 7, 8, and 9, respectively.

Figure 7 Oxymetazoline Mean (±SD) Plasma Concentration – Time Curves in Healthy Volunteers after Standard and High Dose Kovanaze Administration (Source data: Appendix 16.1.13; Table 2 in Pharmacokinetic Analysis Report)

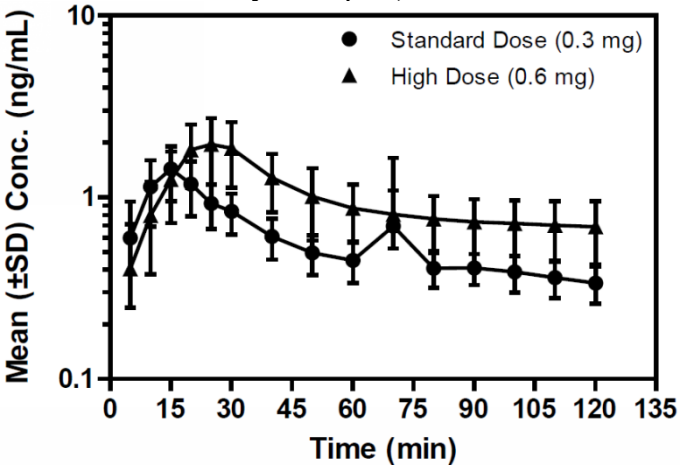


Figure 8 Tetracaine Mean (±SD) Plasma Concentration – Time Curves in Healthy Volunteers after Standard and High Dose Kovanaze Administration (Source data: Appendix 16.1.13; Table 3 in Pharmacokinetic Analysis Report)

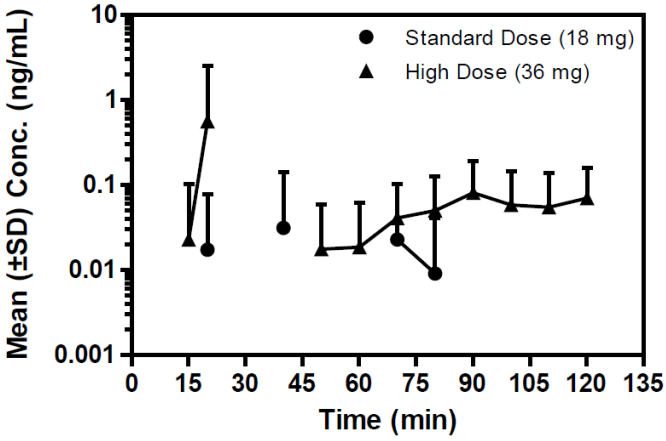
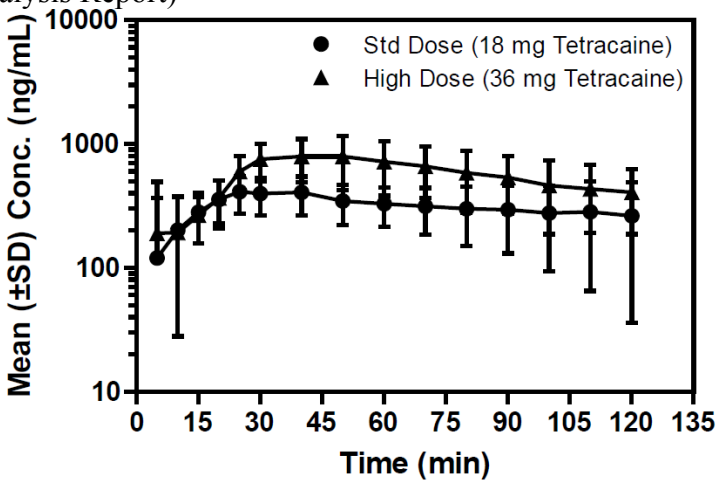


Figure 9 PBBA Mean (±SD) Plasma Concentration – Time Curves in Healthy Volunteers after Standard and High Dose Kovanaze Administration (Source data: Appendix 16.1.13; Table 4 in Pharmacokinetic Analysis Report)



Oxymetazoline, tetracaine, and PBBA PK parameters are summarized in Table 6.

Table 6 Oxymetazoline, Tetracaine, and PBBA PK Parameters

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]
		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 tmax, 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 Kovanaze 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 Kovanaze at Visit 2; NA = not applicable; ND = parameter could not be determined due to insufficient data; NR = not reported; PBBA = p-butylaminobenzoic acid.

The profiles indicated that 2 h collection interval may not be sufficient to adequately characterize Kovanaze after intranasal administration. Based on the 2 hour sampling scheme, AUC and T1/2 values cannot be considered definitive and should be interpreted with caution. If any information can be utilized from this data, observed Cmax and Tmax values for oxymetazoline and PBBA can be of some value. With a doubling of Kovanaze dose (0.6 to 1.2 mL), Cmax values increased approx. 41 and 80% for oxymetazoline and PBBA, respectively, showing less than dose proportional increase. One of the confounding factors for less than proportional increase may be due to the fact that there were 3 and 6 bilateral nasal sprays, for 0.6 and 1.2 mL, respectively, for administration durations of 8 to 20 minutes. As tetracaine was measurable only sporadically across subjects over the 2 h time course, tetracaine values, again, are not considered definitive and should be interpreted with caution.

2.3 Intrinsic Factors

2.3.1 What is the status of pediatric studies and/or any pediatric plan for study?

Kovanaze development in pediatric population was discussed during end-of-phase 2 meeting and pre-NDA meeting, which included dose selection for pediatric patients, evaluation of safety and efficacy in patients down to the age of 3 years, plans for the initial pediatric trial to start with the older patients first, e.g., 12 to 17 years of age, followed by younger patients, etc. Currently the Applicant is requesting approval of Kovanaze for adults and pediatric patients 3 to 17 years of age. Additionally the Applicant is requesting a waiver for patients 2 years old and younger. It is noted that the Applicant already assessed Kovanaze in pediatric patients (b) (4). They have conducted the pediatric studies, SR 3-04, a Phase 3 safety and efficacy trial, SR 2-03, a Phase 2 dose-ranging study, and SR 2-07, a Phase 1 pharmacokinetic study, prior to submitting the initial Pediatric Study Plan. A brief description of Phase 3 trial was presented in Section 2.2.1. The findings from Study SR 2-07 is presented below.

Study SR 2-07

Study SR 2-07 was an open-label, single-center, single-dose study to determine and evaluate the PK profiles and safety of tetracaine, its major metabolite (PBBA), and oxymetazoline after intranasal administration of Kovanaze [tetracaine HCl (3%) and oxymetazoline HCl (0.05%), which a single spray dose of 0.1 mL Kovanaze contains 3 mg tetracaine HCl and 0.05 mg oxymetazoline HCl] administered as the recommended weight-based Phase 3 dose in healthy pediatric subjects, ages 3 to 17 years. Pediatric subjects were enrolled into 3 groups based on age: ages 3 to 6 years; ages 7 to 11 years; and ages 12 to 17 years, inclusive. The Applicant made a statement in the study report that pediatric dosing established for Phase 3 was based on the results of the Phase 2 dose-ranging study SR 2-03 performed in subjects aged 3 to 17.

It is noted that the Applicant planned to initiate the pediatric program before NDA submission. With respect to this study protocol, the protocol was submitted to the Agency on September 3, 2013, initiated on September 24, 2013 and completed on November 1, 2013. By virtue of looking at the dates, this study was initiated quickly and completed rapidly after the protocol was submitted to the Agency. The Applicant stated that the study protocol, informed consent form (ICF), assent form, and Health Insurance Portability and Accountability Act (HIPAA) consent

form were approved by the (b) (4) Institutional Review Board (IRB) in conformance with regulations in 21 CFR (Code of Federal Regulations) Parts 50 and 56. After the NDA submission, there is an ongoing discussion with the enrollment of healthy pediatric subjects for this study with Good Clinical Practice Compliance Oversight Branch (GCPCOB), Division of Clinical Compliance Evaluation (DCCE), Office of Scientific Investigations (OSI), Office of Compliance (OC) and Office of Pediatric Therapeutics (OPT), Office of Special Medical Programs (OSMP), Office of the Commissioner (OC). The information obtained from this study may be needed in the Labeling if Kovanaze is approved for use in pediatric subjects (b) (4), although the current study was conducted in healthy population. Scientifically if one considers tetracaine and oxymetazoline exposure in healthy pediatric subjects to that of pediatric patients who are undergoing dental procedures ("otherwise healthy population"), there should be no differences in their metabolism profiles, which in turn will surmount to same if not very close tetracaine and oxymetazoline levels between the two populations.

Kovanaze was provided as pre-filled single use sprayers ((b) (4) Batch 200093 was used in this study, manufactured according to the proposed commercial formulation). Each sprayer contained 0.2 mL each, and can deliver either as a single 0.1 mL spray (with an aid of dose divider; dose divider was placed at the top of the plunger rod) or as two 0.1 mL sprays.

Pediatric subjects weighing 1) 10 to < 20 kg received 1 0.1 mL spray at Time 0 minute, 2) 20 to < 40 kg received 2 unilateral 0.1 mL sprays (total dose 0.2 mL) dosed 4 minutes apart at Times 0 and 4 (± 1) minutes, 3) 40 kg or more received 2 unilateral 0.2 mL sprays (total dose 0.4 mL) dosed 4 minutes apart at Times 0 and 4 (± 1) minutes (Table 7).

Table 7 Kovanaze administration based on subject weight

Subject Weight	Treatment Group: K305	Volume per Spray	Number of Sprays	K305 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 D_0

[b] Administered at D_0 and D_4 (4 min apart)

(Administration procedure: Spray 1 (all groups) – Approximately Horizontal: Position the sprayer tip approximately horizontal. Direct the sprayer toward the middle of the nasal cavity; Spray 2 (0.2 mL and 0.4 mL Groups) – 45 degrees: Position the sprayer tip approximately 45 degrees above the horizontal plane. Direct the sprayer toward the middle of the nasal cavity; push hard and fast on the plunger rod. Expel the spray in approximately ½ second or less)

Blood samples for PK analysis were collected at pre-dose, 0, 10, 30 min, 1, 3, 6, 8, 9, 12 and 24 hours post dosing. Plasma samples were analyzed using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) procedures for the three analytes, tetracaine, PBBA, and oxymetazoline. The following PK parameters were calculated using non-compartmental analysis: Cmax, Tmax, AUC0-t, AUC0-inf, elimination rate constant, and, T1/2. (Note: Time 0 refers to the sample drawn after administration of the last spray of study drug.)

Demographic characteristics of pediatric subjects receiving Kovanaze are summarized in Tables 8 through 10.

Table 8 Demographic Characteristics of Pediatric Volunteers Receiving Kovanaze

	Dose Level	Male	Female	Combined Gender
N	1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	1	2	3
	2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	6	3	9
	3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	2	4	6
Age[a] (years)	1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	4.	4.3 (0.7) 3.8 – 4.8	4.2 (0.5) 3.8 – 4.8
	2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	8.2 (2.2) 5.9 – 11.6	8.8 (3.1) 5.4 – 11.6	8.4 (2.3) 5.4 – 11.6
	3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	14.3 (1.1) 13.5 – 15.1	13.1 (0.5) 12.4 – 13.5	13.5 (0.9) 12.4 – 15.1
Weight[a] (kg)	1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	17.0	17.6 (1.3) 16.6 – 18.5	17.4 (1.0) 16.6 – 18.5
	2 20 to < 40 kg Oxymetazoline: 0.1 mg Tetracaine: 6 mg	28.0 (6.7) 20.3 – 35.4	28.5 (10.0) 20.4 – 39.6	28.2 (7.3) 20.3 – 39.6
	3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	63.4 (17.5) 51.0 – 75.8	63.4 (9.6) 55.1 – 76.2	63.4 (10.8) 51.0 – 76.2

[a]: Age and weight reported as mean (sd) and range

Table 9 Pediatric subjects according to the age group

Age category (y)	Male (N)	Female (N)
0 – 2	0	0
2 -> 6	2	3
6 – 12	5	2
> 12	2	4

Table 10 Pediatric gender range in years (y)

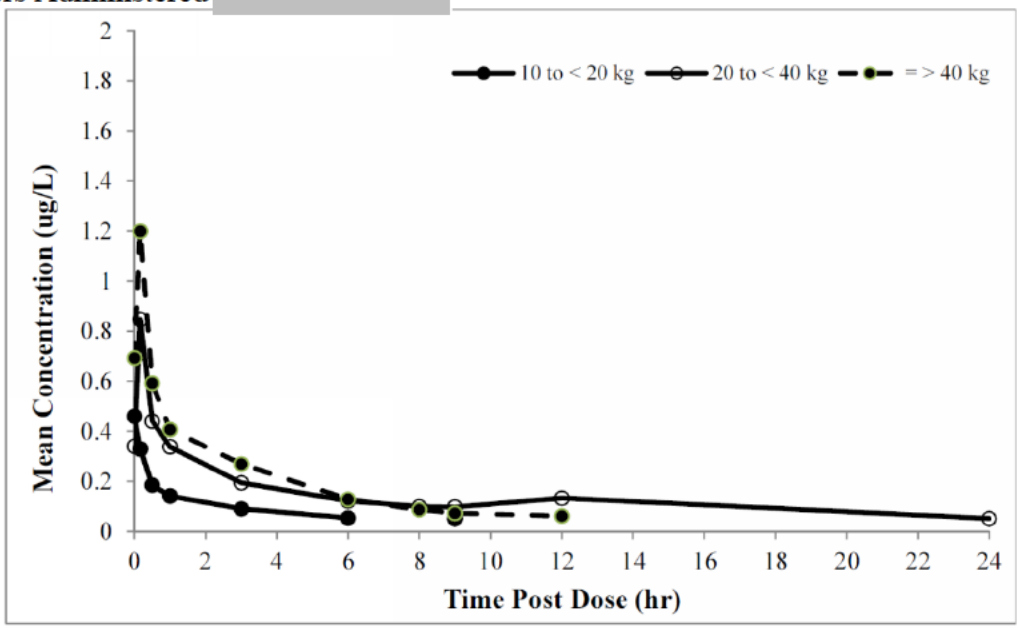
Male Age range (y)	Female Age range (y)
4.1	3.8
5.9	4.8
6	5.4
8.2	9.4
8.2	11.6
9.4	12.4
11.6	13.3
13.5	13.3
15.1	13.5

The age of the study population ranged between 3.8 to 15.1 years old. Mean body mass index (BMI) for the 3 dose groups was as follows: 15.2 ± 0.70 kg/m2 (range 15 to 16 kg/m2) for the 0.1 mL group, 16.4 ± 1.29 kg/m2 (range 15 to 19 kg/m2) for the 0.2 mL group, and 23.2 ± 3.83 kg/m2 (range 19 to 29 kg/m2) for the 0.4 mL group.

After Kovanaze administration, tetracaine was rapidly metabolized to PBBA. There were close to 200 blood samples analyzed for tetracaine; the lower limit of quantitation (LLOQ) for tetracaine was 0.05 ng/mL. Of all blood samples analyzed no quantifiable tetracaine concentrations was observed. Therefore tetracaine PK parameters were not determined. Tables 2 and 3 present oxymetazoline and PBBA pharmacokinetic parameters after 0.1 mL, 0.2 mL and 0.4 mL Kovanaze (0.05 mg, 0.1 mg, and 0.2 mg oxymetazoline dose, respectively).

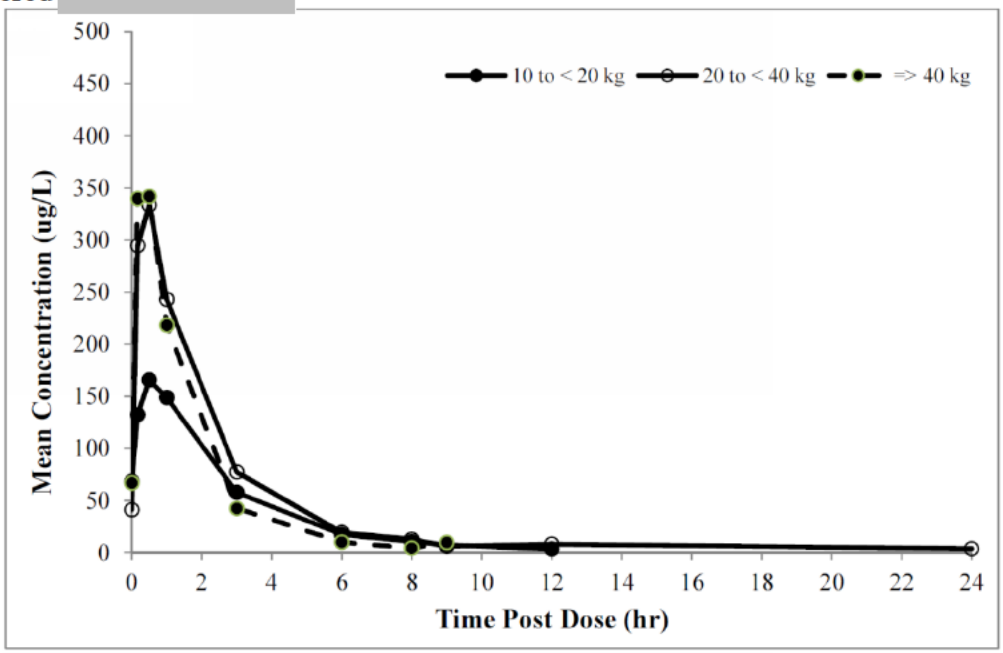
Mean (±SD) oxymetazoline and PBBA concentration vs time data are presented in Figure 10 and Figure 11, respectively.

Figure 10 Oxymetazoline Mean Plasma Concentration – Time Curves in Healthy Pediatric Volunteers Administered [redacted] (b) (4)



1) 10 to < 20 kg: one 0.1 mL spray at Time 0 min
2) 20 to < 40 kg: two unilateral 0.1 mL sprays (total dose 0.2 mL) dosed 4 min apart at Times 0 and 4 (± 1) min
3) >40 kg or more: two unilateral 0.2 mL sprays (total dose 0.4 mL) dosed 4 min apart at Times 0 and 4 (± 1) min

Figure 11 PBBA Mean Plasma Concentration – Time Curves in Healthy Pediatric Volunteers Administered [redacted] (b) (4)



1) 10 to < 20 kg: one 0.1 mL spray at Time 0 min
2) 20 to < 40 kg: two unilateral 0.1 mL sprays (total dose 0.2 mL) dosed 4 min apart at Times 0 and 4 (± 1) min
3) >40 kg or more: two unilateral 0.2 mL sprays (total dose 0.4 mL) dosed 4 min apart at Times 0 and 4 (± 1) min

All subjects had measurable plasma oxymetazoline concentrations through 6 h post dose, with quantifiable concentrations observed in a total of 7 subjects through 9 h and in a total of 2 subjects through 12 h; one subject in the 0.2 mL dose group had a measurable concentration near the LLOQ at 24 h. All subjects had measurable PBBA concentrations. All subjects had measurable PBBA plasma concentrations through at least 8 h post dose, with measureable concentrations observed in a total of 11 subjects through 9 h and in a total of 5 subjects through 12 h; one subject in the 0.2 mL dose group had measurable PBBA concentrations through 24 h.

Oxymetazoline and PBBA PK parameters are summarized in Table 11 and Table 12, respectively.

Table 11 Plasma Pharmacokinetic Parameters for Oxymetazoline after Intranasal Administration of Kovanaze 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	NA	0.211	NA
	CV (%)	116	138	50	NA	33	NA
	Minimum	0.082	0	3.0	1.57	0.387	0.992
	Median	0.162	30	6.0	1.57	0.750	0.992
	Maximum	0.857	180	9.0	1.57	0.754	0.992
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
	SD	0.454	0	5.6	2.24	0.780	1.08
	CV (%)	54	0	57	52	42	43
	Minimum	0.361	10	6.0	2.63	0.970	1.22
	Median	0.733	10	9.0	3.30	1.74	2.15
	Maximum	1.73	10	24	8.41	3.14	4.39
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
	Minimum	0.816	10	6.0	2.69	1.70	2.11
	Median	1.02	10	9.0	3.14	2.25	2.67
	Maximum	1.73	10	12	4.59	2.83	3.22

Source data: Appendix 16.1.13, Table/Appendix 2 in Pharmacokinetic Analysis Report
NA: not applicable
1) 10 to < 20 kg: one 0.1 mL spray at Time 0 min
2) 20 to < 40 kg: two unilateral 0.1 mL sprays (total dose 0.2 mL) dosed 4 min apart at Times 0 and 4 (± 1) min
3) >40 kg or more: two unilateral 0.2 mL sprays (total dose 0.4 mL) dosed 4 min apart at Times 0 and 4 (± 1) min

The observed oxymetazoline mean Cmax values were 0.37 ± 0.43, 0.85 ± 0.45, and 1.2 ± 0.38 ng/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean AUC0-inf values were 0.99 (N=1), 2.53 ± 1.08, and 2.64 ± 0.41 ng.h/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively.

Oxymetazoline mean T1/2 values were 1.57 h (n = 1), 4.32 h, and 3.49 h in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. Oxymetazoline Tmax (median) values were observed at 10 to 30 min post-dose.

Table 12 Plasma Pharmacokinetic Parameters for PBBA after Intranasal Administration of Kovanaze 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
	Minimum	124	30	12	2.40	366	376
	Median	126	30	12	2.87	411	427
	Maximum	247	30	12	3.16	768	783
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
	Minimum	164	10	9.0	1.04	289	305
	Median	294	30	9.0	2.16	637	648
	Maximum	705	30	24	3.60	2230	2240
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
	Minimum	322	10	8.0	1.31	571	577
	Median	373	20	9.0	1.47	640	644
	Maximum	400	30	9.0	2.08	731	807

Source data: Appendix 16.1.13, Table/Appendix 3 in Pharmacokinetic Analysis Report

[a] Dose of tetracaine

1) 10 to < 20 kg: one 0.1 mL spray at Time 0 min
2) 20 to < 40 kg: two unilateral 0.1 mL sprays (total dose 0.2 mL) dosed 4 min apart at Times 0 and 4 (± 1) min
3) >40 kg or more: two unilateral 0.2 mL sprays (total dose 0.4 mL) dosed 4 min apart at Times 0 and 4 (± 1) min

The observed PBBA mean Cmax values were 166 ± 71, 345 ± 172, and 365 ± 30 ng/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean AUC0-inf values were 529 ± 222, 826 ± 606, and 665 ± 86 ng.h/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively.

PBBA Tmax (median) values were observed at 20 to 30 min post-dose. PBBA mean T1/2 values were 2.81 h, 2.18 h, and 1.57 h in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively.

Table 13 presents a summary of the number and subjects with Treatment Emergent AEs (TEAEs) in each treatment group.

Table 13 Summary of Treatment Emergent Adverse Events

Category	0.1 mL (n = 3)	0.2 mL (n = 9)	0.4 mL (n = 6)
Number of AEs Reported	0	0	4
Subjects with AEs	0	0	3 (50.0%)
Subjects with Study Medication Related AE[a]	0	0	3 (50.0%)
Subjects with Serious AE	0	0	0
Subjects Discontinued From Study Due to AE	0	0	0
Deaths	0	0	0
Treatment Emergent Adverse Events by System Organ Class and Preferred Term			
Nervous System Disorders:	0	0	3 (50.0%)
Dizziness[b]	0	0	1 (16.7%)
Headache[b]	0	0	3 (50.0%)

Source data: Table 14.3.1.1, Table 14.3.1.2 and Table 14.3.1.3

[a] Study Medication Related AE = Remotely, Possibly and Probably Related

[b] All AEs (1 event dizziness and 3 events headache) in all 3 subjects receiving the 0.4 mL dose were mild

The Applicant stated that a total of 4 TEAEs were reported by 3 subjects (50%) in the 0.4 mL dose group. All TEAEs were from a single SOC (nervous system disorders). The most frequently reported TEAE on the PT level was headache (in 3 subjects, 50.0%) followed by dizziness (1 subject, 16.7%). There were no reports of TEAEs in the 0.1 or 0.2 mL dose groups.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

The pharmacokinetic interactions between tetracaine and oxymetazoline are not expected as tetracaine undergoes rapid hydrolysis by plasma esterases and oxymetazoline is thought to be metabolized by CYP enzymes according to the in vitro findings reported in the literature.

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

TMB formulation/ (b) (4) was used in all clinical studies.

2.6 Analytical Section

2.6.1 Which metabolites have been selected for analysis and why? What bioanalytical methods are used to assess concentrations?

Tetracaine, its major metabolite, PBBA, and oxymetazoline moieties were measured and analyzed from plasma samples. A high-performance liquid chromatography method with mass spectrometric detection (LC-MS/MS) methodology was use (b) (4) . Oxymetazoline-d4, tetracaine-d6, and PBBA-d7 were used as the respective internal standards. Human plasma in K2EDTA was utilized and contained 1 mg/mL neostigmine bromide as a stabilizing agent. The extract was analyzed by using a Waters X-Bridge C18, 50×2.1 mm, 3.5 µm column. Oxymetazoline, tetracaine, PBBA, and their respective internal standards were monitored on an Applied Biosystems API-4000, or equivalent, mass spectrometric system with turbo-ion spray ionization (electrospray) in positive ion mode and multiple reaction monitoring (MRM) detection.

Sensitivity: The lower limit of quantification (LLOQ) was 0.050 ng/mL for oxymetazoline and tetracaine, and 2.00 ng/mL for PBBA. Calibration curves ranged from 0.050 to 10.0 ng/mL for oxymetazoline and tetracaine, and 2.00 to 1000 ng/mL for PBBA. Dilution integrity was demonstrated at 4-fold and 20-fold dilutions for all three analytes.

Precision: For plasma oxymetazoline, tetracaine, and PBBA, precision of the quality control (QC) samples %CV ranged from 5.8% to 9.2%, 4.9% to 8.0%, and 4.4% to 9.5%, respectively.

Accuracy: For plasma oxymetazoline, tetracaine, and PBBA, accuracy of the QC samples bias ranged from -4.1% to 1.5%, -3.4% to -3.2%, and -5.5% to -2.7%, respectively.

Linearity: Linearity during sample analysis was reflected by r (correlation coefficient) of the standard curves. For plasma oxymetazoline, tetracaine, and PBBA, these ranged from 0.9973 to 0.9984, 0.9985 to 0.9994, and 0.9983 to 0.9991, respectively.

Specificity: There were no significant chromatographic peaks detected at mass transitions and expected retention times of the analytes or their internal standards that would interfere with quantitation.

Stability: Oxymetazoline, tetracaine, and PBBA were stable in human plasma at room temperature for 9 h (oxymetazoline and tetracaine) and 18 h (PBBA), and all three analytes were stable for at least 769 days at -80ºC. The analytes were stable during 4 freeze-thaw cycles for oxymetazoline and tetracaine, and 6 freeze-thaw cycles for PBBA. All three analytes were stable in processed samples at 4°C for at least 4 days.

A typical set of values for quality control samples for oxymetazoline, tetracaine and PBBA presented below (Tables 14, 15, and 16, respectively):

Table 14 Performance of Quality Control Samples Analyzed Concurrently with Study Samples Oxymetazoline

		Nominal Concentration of Oxymetazoline						
		QC-L		QC-M		QC-H		
		0.0600 ng/mL		0.400 ng/mL		8.00 ng/mL		
File Name	Replicate	Measured Conc. ng/mL	Acc.	Measured Conc. ng/mL	Acc.	Measured Conc. ng/mL	Acc.	Acceptance Ratio[a]
R 80469 Reinjection 21NOV2013	1							10/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		3/4		3/4		
R 80469 22NOV2013 B1	1							12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		
P 80469 30APR2014	1							12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		

[a] Acceptance Ratio = Acceptable QC samples / Total QC samples.

[b] Value is outside the acceptance criteria of ± (b) (4)% Acc of the nominal concentration.

Acceptance criteria = (b) (4) of QCs pass overall and (b) (4)% at each concentration

Table 15 Performance of Quality Control Samples Analyzed Concurrently with Study Samples Tetracaine

		Nominal Concentration of Tetracaine						
		QC-L		QC-M		QC-H		
		0.0600 ng/mL		0.400 ng/mL		8.00 ng/mL		
File Name	Replicate	Measured Conc. ng/mL	Acc.	Measured Conc. ng/mL	Acc.	Measured Conc. ng/mL	Acc.	Acceptance Ratio[a]
R 80469 Reinjection 21NOV2013	1							12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		
R 80469 22NOV2013 B1	1							11/12
	2							
	3							
	4							
Acceptance Ratio[a]		3/4		4/4		4/4		
P 80469 30APR2014	1							12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		

[a] Acceptance Ratio = Acceptable QC samples / Total QC samples.

[b] Value is outside the acceptance criteria of ± (b) (4)% Acc of the nominal concentration.

Acceptance criteria = (b) (4) of QCs pass overall and (b) (4)% at each concentration

Table 17 Performance of Quality Control Samples Analyzed Concurrently with Study Samples PBBA

		Nominal Concentration of PBBA						
		QC-L		QC-M		QC-H		
		6.00 ng/mL		40.0 ng/mL		800 ng/mL		
File Name	Replicate	Measured Conc. ng/mL	Acc.	Measured Conc. ng/mL	Acc.	Measured Conc. ng/mL	Acc.	Acceptance Ratio[a]
R 80469 Reinjection 21NOV2013	1						(b) (4)	11/12
	2							
	3							
	4							
Acceptance Ratio[a]		3/4		4/4		4/4		
R 80469 22NOV2013 B1	1						(b) (4)	12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		
R Bioanalysis 22NOV2013 B2	1						(b) (4)	12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		
P 80469 30APR2014	1						(b) (4)	12/12
	2							
	3							
	4							
Acceptance Ratio[a]		4/4		4/4		4/4		

[a] Acceptance Ratio = Acceptable QC samples / Total QC samples.
[b] Value is outside the acceptance criteria of ± (b) (4)% Acc of the nominal concentration.
Acceptance criteria = (b) (4) of QCs pass overall and (b) (4)% at each concentration

3 Detailed Labeling Recommendations

The following labeling wording is recommended for Kovanaze Label. Some of the proposed wording by the Applicant has been relocated, numerical values updated and new additional wording is proposed to enhance the overall description of the overall findings presented in the application.

12.2 Pharmacokinetics

Absorption: Following Kovanaze nasal administration of 0.6 mL in adult subjects (n=24), oxymetazoline attained maximum concentrations within approximately 10 minutes following the end of dosing; the observed mean oxymetazoline Cmax and AUC0-inf value were 1.78 ng/mL and 4.24 ng.h/mL, respectively (b) (4) the observed median Tmax was 5 minutes.

Plasma concentrations of tetracaine in all subjects were at or below the limit of assay quantification (0.05 ng/mL). The primary metabolite of tetracaine, p butylaminobenzoic acid (PBBA) achieved peak concentrations within approximately 25 minutes following the end of Kovanaze dosing. The observed mean PBBA Cmax and AUC0-inf value were 465 ng/mL and 973 ng.h/mL, respectively. The observed median Tmax was 20 minutes.

Distribution: Protein binding and distribution of oxymetazoline, (b) (4) and PBBA have not been determined. Plasma protein binding of tetracaine has been reported to be 75% to 85%.

Elimination: The terminal half-life of oxymetazoline in plasma following nasal administration of Kovanaze to adult subjects is approximately 5.2 hours.
The elimination half-life and apparent clearance of tetracaine could not be determined after Kovanaze administration because it is rapidly and thoroughly hydrolyzed in plasma. The plasma half-life of PBBA is approximately 2.6 hours in adult subjects.

Metabolism: Oxymetazoline is converted to a glucuronide conjugate in vitro by UGT1A9. Tetracaine is rapidly and thoroughly cleaved by esterases in plasma and other tissues to PBBA and dimethylaminoethanol. These metabolites (b) (4) have an (b) (4) activity.

Excretion: The apparent clearance of oxymetazoline after nasal administration of Kovanaze has not been determined. It is thought that the primary route of oxymetazoline elimination at clinically relevant concentrations is by renal excretion. PBBA clearance cannot be determined after administration of tetracaine.

Special Populations
Pediatrics:
In subjects 4-15 years of age (n=18) that received Kovanaze doses of 0.1 mL (10 to < 20 kg body weight), 0.2 mL (20 to < 40 kg), or 0.4 mL (≥ 40 kg), oxymetazoline and PBBA attained maximum concentrations within approximately 10 minutes to 30 minutes (median time) following the end of dosing. The observed oxymetazoline mean Cmax values were 0.37 ± 0.43, 0.85 ± 0.45, and 1.2 ± 0.3 (b) (4) ng/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean AUC0-inf values were 0.99 (N=1), 2.53 ± 1.08, and 2.64 ± 0.41 ng.h/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. Mean elimination half-life values for oxymetazoline were approximately 1.6 to 4.3 hours across pediatric dose groups.

Plasma concentrations of tetracaine were below the limit of assay quantification (0.05 ng/mL) in all subjects. PBBA attained maximum concentrations within approximately 20 minutes to 30 minutes (median time) following the end of dosing. The observed PBBA mean Cmax values were 166 ± 71, 345 ± 172, and 365 ± 30 ng/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. The observed oxymetazoline mean AUC0-inf values were 529 ± 222, 826 ± 606, and 665 ± 86 ng.h/mL in the 0.1 mL, 0.2 mL, and 0.4 mL dose groups, respectively. Mean elimination half-life values for PBBA were approximately 1.6 (b) (4) to 2.8 (b) (4) hours across pediatric dose groups.

Specific population
Elderly: The pharmacokinetics of Kovanaze were not evaluated in subjects greater than 50 years of age.

Renal or Hepatic Impairment: The pharmacokinetics of oxymetazoline, tetracaine, and PBBA were not evaluated after nasal administration of Kovanaze in subjects with renal or hepatic impairment.

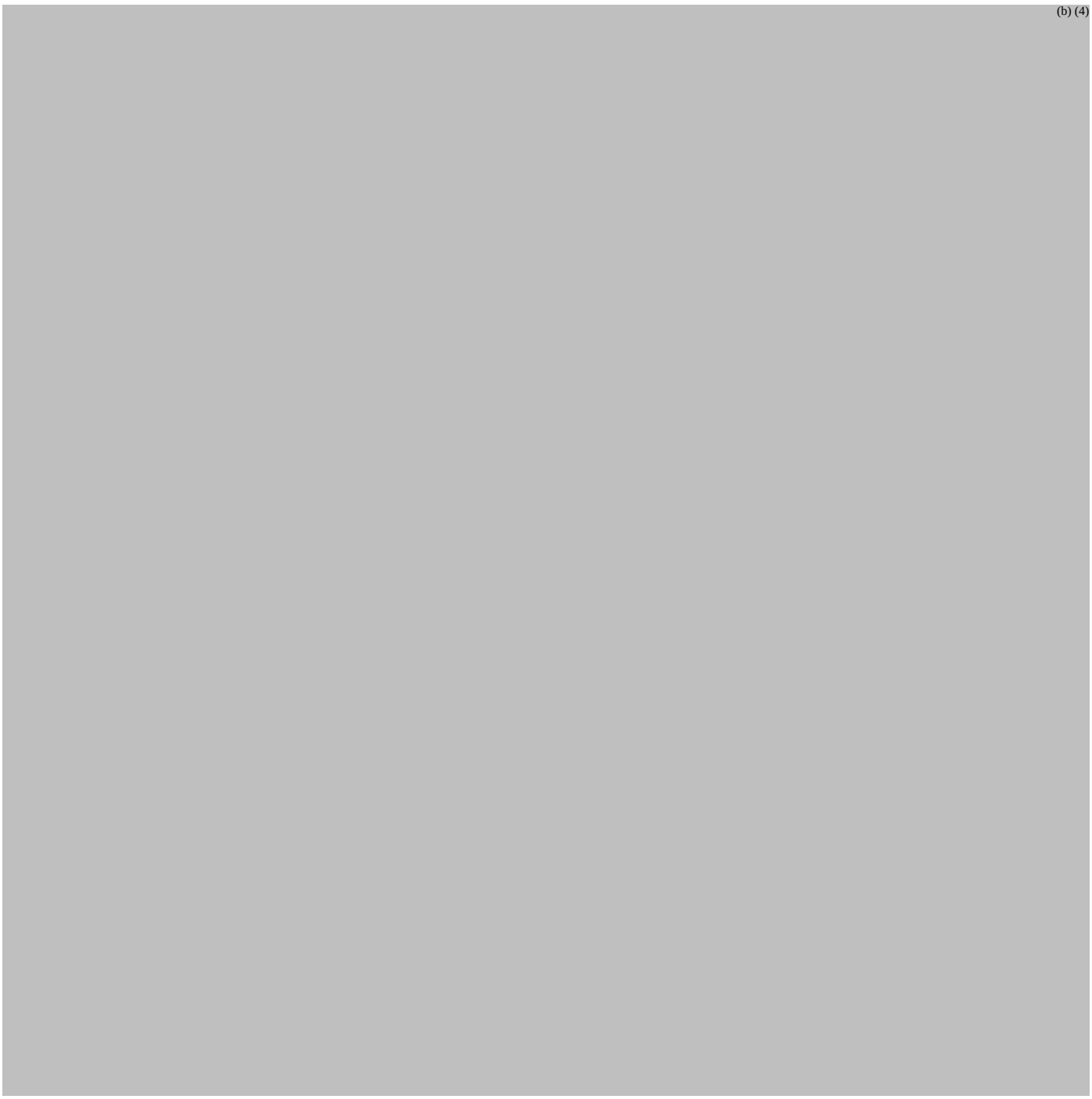
Race: There were insufficient data to evaluate the effect of race on oxymetazoline, tetracaine, and PBBA pharmacokinetics after nasal administration of Kovanaze.

4 Appendices

4.1 Proposed Package Insert (Original and Annotated)

Proposed by the Applicant:

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



4.2 Individual Study Review

Study SR 2-02 Study Synopsis provided by the Applicant

The Applicant stated that there is one publication based on this clinical study: Giannakopoulos H, Levin LM, Chou JC, Cacek AT, Hutcheson M, Secreto SA, Moore PA, Hersh EV. The cardiovascular effects and pharmacokinetics of intranasal tetracaine plus oxymetazoline: Preliminary findings. J Am Dent Assoc 143(8):872-880, 2012.

Name of Sponsor: St. Renatus, LLC 1000 Centre Avenue Fort Collins, CO 80526	**Name of Finished Product:** (b) (4)	**Name of Active Ingredient(s):** Tetracaine hydrochloride and oxymetazoline hydrochloride in fixed combination

Revised Title: Phase I, Open-Label, Dose-Escalation, Safety and Pharmacokinetic Study of K305 in Healthy Volunteers

Original Title: Cardiovascular Changes and Tetracaine Pharmacokinetics Following Intranasal Administration of Standard and High Doses of Kovacaine Mist (Tetracaine Hydrochloride with Oxymetazoline Hydrochloride) in Healthy Volunteers

Investigator(s) and Study Center(s):

Elliot V Hersh, DMD, MS, PhD, Hospital of University of Pennsylvania, Department of Oral and Maxillofacial Surgery and Hospital Dentistry, 5-White, 3400 Spruce Street, Philadelphia, PA 19104, USA

University of Pennsylvania School of Dental Medicine Department of Oral and Maxillofacial Surgery, 240 South 40th Street, Philadelphia, PA 19104-6030, USA

Publication (reference):
Giannakopoulos H, Levin LM, Chou JC, Cacek AT, Hutcheson M, Secreto SA, Moore PA, Hersh EV. The cardiovascular effects and pharmacokinetics of intranasal tetracaine plus oxymetazoline: preliminary findings. J Am Dent Assoc. 2012 Aug;143(8):872-80

Study Period: First subject, first visit: 22-Sep-2010 Last subject, last visit: 16-Nov-2010	**Clinical Phase:** 1

Objectives:
Primary Objectives:

- to determine if (b) (4) (formerly (b) (4)) significantly changes pulse rate (PR), blood pressure ([BP] systolic [SBP] and diastolic [DBP]) or oxygen saturation (SpO_2) levels from Baseline pretreatment values after administration of 2 different doses

- to determine the safety profile of (b) (4) after administration of 2 different doses

Secondary Objective:

- to establish the pharmacokinetics (PK) of oxymetazoline, tetracaine, and the major metabolite of tetracaine, *p*-butylaminobenzoic acid (PBBA), following the intranasal administration of both the estimated maximum single dose ("standard") and 2 times the estimated maximum single dose ("high") of (b) (4)

Endpoints:
The study endpoints were:

- the mean maximum changes in PR, SBP, DBP, and SpO_2 compared to Baseline for both doses
- a comparison of the incidence of spontaneously reported or observed adverse events (AE) between the doses
- PK profile of tetracaine (and PBBA) and oxymetazoline in plasma following both doses levels

Methodology:
This was an open-label, within-subject dose escalation study in healthy volunteers in which all subjects were to receive the standard dose of (b) (4) at the first treatment visit and 2 times the standard dose at least 1 week (and no more than 3 weeks) later, at the second treatment visit.

Number of Subjects (planned and analyzed):
Planned: 14 (to obtain 12 completed)

Analyzed: 12 subjects completed the study and were included in the analyses. The PK population comprised 12 subjects. No subjects were excluded from the PK population, although PK parameters could not be determined in all individuals for all analytes.

Diagnosis and Criteria for Inclusion:
Healthy volunteers were enrolled in this study. The inclusion criteria were as follows:

1. male or female between 18 and 65 years of age
2. body mass index (BMI) between 19 and 29 kg/m^2
3. sufficiently healthy as determined by the Investigator to receive the test medications and undergo the scheduled study procedure
4. able to breathe through both nostrils
5. females of child-bearing potential had to have a negative urine pregnancy test and had to have been using adequate means of birth control (abstinence, oral contraceptive steroids, intrauterine device, etc.) for at least 1 month prior to study entry and during the study
6. screening BP (systolic/diastolic) $\leq$ 140/90 mmHg
7. screening level of saturation of peripheral oxygen (SpO_2) $\geq$ 96%
8. able to understand and sign the informed consent document, to communicate with the Investigator, and to understand and comply with the requirements of the protocol

Test Product, Dose, Mode of Administration and Lot Number:
Dose 1 (standard dose) of [redacted] (3% tetracaine HCl and 0.05% oxymetazoline HCl) consisted of 6 sprays of 0.1 mL, administered bilaterally as 1 spray each in the left and right nostrils at each of 3 intervals. Time between the 3 sets of sprays was specified as 4 min, for a total dosing period of 8 min. The total drug content of the 0.6 mL dose was 18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl.

Dose 2 (high dose) of [redacted] consisted of 12 sprays of 0.1 mL, administered bilaterally as 1 spray each in the left and right nostrils at each of 6 intervals. Time between the 6 sets of sprays was specified as 4 min, for a total dosing period of 20 min. The total drug content of the 1.2 mL dose was 36 mg tetracaine HCl and 0.6 mg oxymetazoline HCl.

The individual sprayers delivered a 0.1 mL volume of solution. Six sprayers were used for the standard dose and 12 sprayers for the high dose.

Lot number: Drug Lot 004011 was used in the study.

Duration of Treatment:
2 doses were administered to each subject, with an interval of at least 1 week and no more than 3 weeks between doses.

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable to this study.

Criteria for Evaluation:
Assessment of pharmacodynamic (PD) effect of standard and high doses of [redacted] on PR, SBP, DBP and SpO_2. Safety was evaluated based on incidence rates for AEs.

PK was assessed for the two doses of [redacted] with blood sampling to follow PR, SBP, DBP and SpO_2 measurements at the following times: prior to administration of study drug (T_0) and every 5 min through 30 min, then every 10 min until 120 min (ie, at T_0, T_5, T_{10}, T_{15}, T_{20}, T_{25}, T_{30}, T_{40}, T_{50}, T_{60}, T_{70}, T_{80}, T_{90}, T_{100}, T_{110}, and T_{120} min) following initiation of the first intranasal spray.

Statistical Methods:
Maximum changes in PR, SBP, DBP, and SpO_2 were compared to the corresponding Baseline for each subject. For each vital sign variable, a 2-sided paired-difference t-test was used for each treatment separately (2 primary hypotheses) as well as to evaluate differences between the 2 treatments (1 secondary hypothesis). A 5% level of significance was used. In addition, changes from Baseline at each time point for these variables were evaluated similarly. Criteria for defining clinically significant (CS) changes from Baseline for vital sign assessments were established.

Descriptive statistics were used to summarize PK parameters for tetracaine, PBBA, and oxymetazoline. Mean, median, standard deviation (SD), standard error of the mean (SEM) and coefficients of variation were provided for the individual concentrations and PK parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, λ_z, and $t_{1/2}$). No formal statistical tests were used. Graphs and summary tables of mean plasma concentrations versus time were generated to visualize the difference between the 2 treatments.

If the assumptions of normality were not met based on the Shapiro-Wilk test (at a 5% level of significance), a nonparametric test was used. Where vital sign measures could have violated the assumptions of normality, the Wilcoxon signed-rank test was used in place of the paired-difference t-test.

Summary of Results and Conclusions:

Pharmacodynamic Results:

A statistically significant (*P*-value ≤ 0.05) within-dose difference in vital signs with respect to maximum change from Baseline was detected in all cases except maximum increase from Baseline SpO_2 following the high dose, and also maximum decrease from Baseline SpO_2 following the standard dose. These changes were not considered to be of clinical significance however, and potentially contributing factors for such differences are discussed below.

A between-dose difference was largely not apparent; assessment of a significant difference between the standard and high doses for this endpoint showed that there was no difference in maximum change from Baseline for PR, SBP or DBP. Only the increase from Baseline SpO_2 showed statistical significance between doses, with a mean increase from Baseline in percentage SpO_2 for the standard dose of $0.9 \pm 0.90\%$ (range 0.0 to 3.0%) compared to $0.3 \pm 0.65\%$ (range 0.0 to 2.0%) for the high dose (*P*-value = 0.0156). This increase in SpO_2 was also not considered to be clinically significant. The comparable vital sign response between standard and high doses, in combination with the safety analysis, suggests that dosing at the higher level was well tolerated and did not appear to result in any adverse clinical effects.

Examination of the mean change from Baseline measurements for vital signs at individual sampling times post standard and high dose also found few instances of a statistically significant difference. Following application of Bonferroni's correction, statistical significance was observed at only 3 sampling times post-dose: PR at 50 min following the standard dose (-7.5 ± 5.49 bpm, range -13.0 to 2.0, *P*-value = 0.0020), PR at 40 min following the high dose (-6.2 ± 5.54 bpm, range -13.0 to 5.0, *P*-value = 0.0027), and DBP at 90 min following the high dose (6.5 ± 6.64 mmHg, range 1.0 to 24.0, *P*-value = 0.0010). At all other time points post dose there was no difference detected.

The vital sign variability that was observed in this study, both in terms of the within-dose vital sign comparison and to a lesser degree in mean vital sign measurements at discrete time points, did not appear to have a clinical impact in this study. AEs related to vital sign response were few in number and were mild in severity.

Pharmacokinetic Results:

Oxymetazoline was rapidly absorbed into the systemic circulation after nasal administration of (b) (4) Maximum plasma concentrations were attained within 5 to 7 min after the end of dosing, regardless of dose administered, and measurable oxymetazoline plasma concentrations persist for at least 120 min. Doubling the (b) (4) dose resulted in a 35 to 50% increase in oxymetazoline systemic exposure.

Tetracaine was rapidly and extensively converted to PBBA. Tetracaine plasma concentrations were low after administration of either a standard or high dose of (b) (4) Systemic tetracaine exposure increased with dose; however, the reported tetracaine PK parameter values should be viewed cautiously in view of the low and sporadic plasma concentrations observed.

Maximum PBBA plasma concentrations were attained within 25 to 27 min after the end of (b) (4) administration, regardless of dose, and measurable PBBA plasma concentrations persist for at least 120 min. Doubling the (b) (4) dose resulted in a proportional increase in PBBA systemic exposure.

A 120-min sample collection interval was insufficient to adequately characterize oxymetazoline and PBBA PK after nasal administration of (b) (4)

Safety Results:

The full study cohort (12 subjects) received a single dose of the standard dose (0.6 mL) of (b) (4) at treatment Visit 1. There were no subjects who experienced a decrease in SpO_2 to below 91% or an increase in BP of above 165/100 mmHg following administration of the standard dose of (b) (4) (0.6 mL). All subjects were therefore escalated to the high dose (1.2 mL) and received this dose at treatment Visit 2. Stopping rules for subject dosing were not met following treatment at either of the dosing levels.

Incidence rates of TEAEs following administration of the standard dose were lower than following administration of the high dose: 7 subjects (58.3%) experienced TEAEs after the standard dose compared with 12 subjects (100%) following the high dose. The TEAEs reported in this study were of mild or moderate intensity only; there were no reports of severe TEAEs and also no reports of SAEs. In addition, there were no discontinuations from the study due to AE.

A comparison of the incidence of spontaneously reported or observed AEs between the dose levels demonstrated that both standard and high dose [(b) (4)] appeared to be well tolerated in this subject population. Serious AEs did not occur and there were no subjects who discontinued the study due to an AE. Although a higher number of subjects experienced treatment-related TEAEs following administration of the high dose compared to the standard dose, the nature of these events and their mild to moderate severity was not identified as a safety signal in this study.

Vital sign variability following administration at both dosing levels was observed but was not marked. In addition, where a change from Baseline occurred of sufficient magnitude to meet the definition of a potential clinical significance (in 2 subjects only), the AEs arising from the change (2 AEs in 1 subject only) were not considered serious and were managed to resolution without the need for intervention.

PK analysis of oxymetazoline, tetracaine and the major metabolite of tetracaine (PBBA) following administration of standard and high doses of [(b) (4)] showed that:

- Oxymetazoline was rapidly absorbed into the systemic circulation after nasal administration of [(b) (4)] Doubling the [(b) (4)] dose resulted in a 35 to 50% increase in oxymetazoline systemic exposure.
- Tetracaine was rapidly and extensively converted to PBBA. Low and sporadic tetracaine plasma concentrations were observed after the standard and high [(b) (4)] dose.
- Maximum PBBA plasma concentrations were attained less than 30 min after the end of [(b) (4)] administration. Doubling the [(b) (4)] dose resulted in a proportional increase in PBBA systemic exposure.
- A 120 min sample collection interval was insufficient to adequately characterize oxymetazoline and PBBA PK after nasal administration of [(b) (4)].

In conclusion, intranasal administration of 2 different doses of [(b) (4)] in this within-subject dose escalation study demonstrated that both standard and high doses were safe and well tolerated, producing a comparable between-dose vital sign response and no apparent clinical impact as a result of some within-dose vital sign variability. AEs that occurred during the study were mild to moderate in severity, non-serious and did not result in study discontinuation. PK analysis of the components and major metabolite of [(b) (4)] showed that doubling the dose resulted in an increase in systemic exposure that was in the range of 35 to 50% for oxymetazoline and was proportional for PBBA, while tetracaine was observed in low and sporadic plasma concentrations after both standard and high [(b) (4)] doses.

Date of the Report: Final 09-Jan-2015

Study SR 2-06 Study Synopsis provided by the Applicant

Name of Company: St. Renatus, LLC 1000 Centre Avenue Fort Collins, CO 80526, USA	**Name of Finished Product:** (b) (4)	**Name of Active Ingredient(s):** Tetracaine hydrochloride and oxymetazoline hydrochloride in fixed combination
Title of Study: Single-Center, Open-Label, Single-Dose Study of the Pharmacokinetics and Safety of Intranasally Administered (b) (4) in Healthy Volunteers **Original Title:** The Pharmacokinetics of Tetracaine, Para-Butylaminobenzoic Acid, and Oxymetazoline after Intranasal Administration of the Highest Phase 3 Dose of Kovacaine Mist (tetracaine hydrochloride with oxymetazoline hydrochloride) to Healthy Volunteers		
Investigator and Study Center: Derek Muse, MD, Jean Brown Research Center, 1045 E. 3900 S. Suite 100, Salt Lake City, Utah 84124		
Publication (reference): None		
Study Period: First subject, first visit: 14-Mar-2013 Last subject, last visit: 28-Mar-2013	**Clinical Phase:** 1	
Objectives: **Primary objective:** • to characterize the pharmacokinetics (PK) of tetracaine, the major metabolite of tetracaine [*p*-butylaminobenzoic acid (PBBA)], and oxymetazoline after intranasal administration of the highest Phase 3 adult dose of (b) (4) (18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl). **Secondary objective:** • to assess the safety of the highest Phase 3 dose of (b) (4) (18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl) — blood pressure (BP) readings, pulse rate (PR), temperature, and oxygen saturation (SpO_2) levels — and overall safety profile after intranasal administration to healthy volunteers.		
Endpoints: • the PK profiles of tetracaine, PBBA, and oxymetazoline • the mean changes in pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and SpO_2 compared to Baseline • the incidence of spontaneously reported or observed adverse events (AEs)		

Methodology:
This was a single-center, open-label, single-dose study in healthy volunteers in which all subjects received [redacted] (18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl) on one occasion. No randomization was necessary for this study.

Number of Subjects (planned and analyzed):
Planned: 24 (to obtain 20 completed)

Analyzed: 24 subjects were treated and included in the analyses (Safety population). The PK population comprised all 24 subjects.

Diagnosis and Criteria for Inclusion:

Inclusion Criteria:

1. male or non-pregnant, non-breast-feeding female subjects between the ages of 18 and 75 years (inclusive)
2. could understand and sign the informed consent document, could communicate with the investigator, and could understand and comply with the requirements of the protocol
3. body mass index (BMI) between 18 and 35 kg/m^2
4. sufficiently healthy as determined by the investigator to receive the test medications and undergo the scheduled study procedure
5. could breathe through both nostrils
6. screening BP $\leq$ 140/90 mmHg

Exclusion Criteria:

1. history of clinically significant respiratory, gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, including cardiac arrhythmia, narrow angle glaucoma and benign prostatic hypertrophy (in men), uncontrolled thyroid disease (including Hashimoto's thyroiditis and lymphocytic thyroiditis), uncontrolled diabetes mellitus or any other condition which, in the opinion of the Principal Investigator, would have jeopardized the safety of the subject or impact the validity of the study results
2. had clinically significant abnormal findings on the physical examination, medical history, electrocardiogram (ECG), or clinical laboratory evaluation during screening. This includes current upper respiratory infections
3. currently experiencing seasonal or perennial allergic rhinitis, recurrent nose-bleeds or asthma, or has a significant history of these conditions, in the opinion of the Investigator
4. current, including the last 30 days, sinusitis or other upper respiratory infections
5. nasal polyps, significant nasal or sinus surgery or other abnormality that might have interfered with the dose administration
6. history of allergic or adverse responses to tetracaine, other ester local anesthetics, PBBA,

oxymetazoline and its preservatives, or *p*-aminobenzoic acid as found in PABA containing sunscreens or any comparable or similar product
7. donation of blood or plasma within 30 days of the first dose of study drug
8. participation in a clinical trial within 30 days prior to the first dose of study drug
9. use of any new over-the-counter (OTC) medication, including topical anesthetic creams or gels, vitamins, within 7 days prior to the first dose of the study drug or during the study unless approved by the Principal Investigator
10. any prescription medication, whose dose is not stable at the time of screening, as determined by the Principal Investigator
11. treatment with any known enzyme altering drugs such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study drug or during the study
12. smoking or use of tobacco products within 6 months prior to the first dose of study drug or during the study
13. female trying to conceive, is pregnant, suspected of being pregnant, or is lactating. (Females of child-bearing potential were required to take a serum pregnancy test at screening [up to 21 days prior to the start of the study, including the day of the study], as well as a urine pregnancy test at check-in to rule out pregnancy)
14. positive serum pregnancy test at screening or urine pregnancy test at check-in for all women of childbearing potential
15. positive blood screen for HIV, hepatitis B surface antigen (HbSAg), or hepatitis C, or a positive urine screen for alcohol, drugs of abuse, or cotinine
16. had a history of pseudocholinesterase deficiency or previous prolonged paralysis with succinylcholine or difficulty waking up from general anesthesia
17. had a history of alcoholism and/or drug abuse
18. had taken a monoamine oxidase inhibitor or vasopressor drug within the past 3 weeks

Test Product, Dose, Mode of Administration and Lot Number:
Each subject was to receive a single dose (3 nasal sprays) of (b) (4) on Day 1 (dosing day). Each spray constituted a volume of 0.2 mL of the investigational product, giving a total of 0.6 mL (containing a total of 18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl). The 3 sprays were administered at 4-min intervals, for a total dosing period of 8 min.

(b) (4) nasal spray was supplied in pre-filled single-use sprayers (b) (4) (b) (4) Each sprayer delivered a single spray of 0.2 mL. Three sprayers were used to produce the total dose specified in the protocol.

Lot No. 006775

Duration of Treatment:
Each subject was to receive a single dose of [redacted] (b) (4) (administered as 3 sprays in 8 min)

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable; this was a single dose, single arm study.

Criteria for Evaluation:

Pharmacokinetics:

PK was assessed for [redacted] (b) (4) with blood sampling to follow BP, HR, body temperature, and SpO_2 measurements at the following times: prior to administration of study drug and at T_0, T_5, T_{10}, T_{15}, T_{20}, T_{25}, T_{30}, T_{40}, and T_{50} min and T_1, $T_{1.25}$, $T_{1.5}$, $T_{1.75}$, T_2, T_3, T_4, T_6, T_8, T_{12}, T_{16} and T_{24} h after dosing, where T_0 was the time of completion of administration of the last dose of nasal spray.

Safety:

Vital signs (SBP, DBP, PR, body temperature, and SpO_2). Vital signs were measured predose and before each PK measurement; vital signs were also measured at Discharge/Day 2. Treatment emergent AEs (TEAEs) and safety laboratory parameters were evaluated.

Statistical Methods:
PK parameters were calculated using non compartmental analysis. Descriptive statistics were used to summarize plasma concentrations and PK parameters by analyte. Mean, median, standard deviation (SD), standard error of the mean, and coefficients of variation were provided. Geometric means could be used if deemed appropriate.

Changes in PR, SBP, DBP, body temperature, and SpO_2 were compared to the corresponding Baseline for each subject. Paired t-test or Wilcoxon signed rank were used to test within-group differences. If Shapiro Wilk $P \leq 0.05$, the null hypothesis of normality was rejected, and Wilcoxon signed rank was the appropriate test. I f Shapiro Wilk $P > 0.05$ the null hypothesis of normality was accepted, and paired t-test was the appropriate test. The Bonferroni correction was used to address the issue of multiplicity arising from the number of change from Baseline results being tested for significance (ie, to control the false positive rate). As the original level of significance was $P \leq 0.05$, each change from Baseline was tested for significance at $P \leq 0.0023$ (ie, $P \leq 0.05/22$, where 22 was the number of individual hypotheses). Criteria for defining clinically significant changes from Baseline for vital sign assessments were established. Descriptive statistics were used to summarize other safety data.

Date of the Report: Final 04-Feb-2015

Prepared in: Microsoft Word 2010

Subject demography data are summarized in Tables 1 and 2.

Table 1 Summary of Demography

Parameter	Category	Statistics	Screening Visit (n = 24)
Gender	Male	N (%)	13 (54.2%)
	Female	N (%)	11 (45.8%)
Race	White	N (%)	19 (79.2%)
	Asian	N (%)	1 (4.2%)
	Other [a]	N (%)	4 (16.7%)
Ethnicity	Hispanic or Latino	N (%)	2 (8.3%)
	Not Hispanic or Latino	N (%)	22 (91.7%)
Age (years)		n	24
		Mean	28.7
		SD	9.36
		Median	25.2
		(Min, Max)	(18,47)
Weight (kg)		n	24
		Mean	71.2
		SD	13.03
		Median	69.9
		(Min, Max)	(46,96)
Height (cm)		n	24
		Mean	170.4
		SD	9.45
		Median	170.0
		(Min, Max)	(152,188)
BMI (kg/m^2)		n	24
		Mean	24.4
		SD	3.60
		Median	24.4
		(Min, Max)	(19,34)

Source data: Table 14.1.4, Table 14.1.6; Listing 16.2.4.1
a White/Asian (n = 3) or White/native Hawaiian or other Pacific Islander (n = 1)

Table 2 Demographic Characteristics* of Normal Adult Volunteers Receiving Kovanaze (b) (4) (Tetracaine 18 mg, Oxymetazoline 0.3 mg)

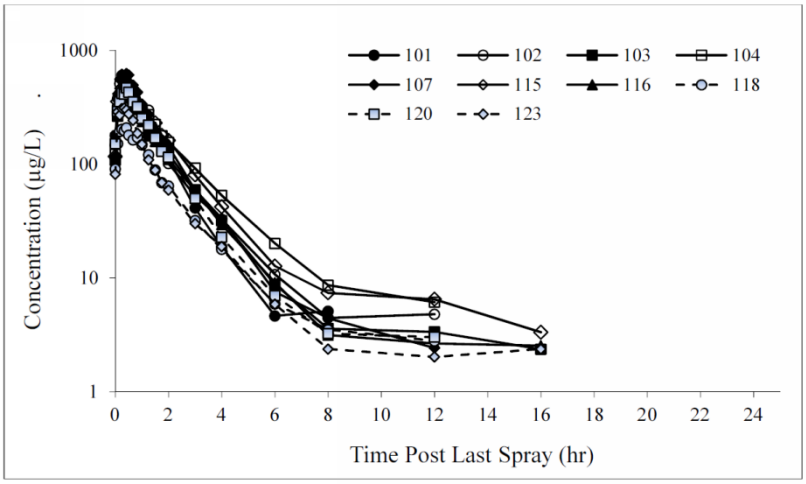
	Male	Female	Combined Gender
N	13	11	24
Age (years)	24.9 (8.1) (18.1 – 47.4)	33.2 (9.0) (21.8 – 46.7)	28.7 (9.4)
Height (cm)	176.6 (6.7) (166.5 – 188.0)	163.1(6.6) (152.0 – 172.7)	170.4 (9.5)
Weight (kg)	74.9 (11.9) (51.7 – 94.3)	66.8 (13.5) (46.4 – 96.2)	71.2 (13.0)
BMI	24.0 (3.4) (18.5 – 29.9)	25.0 (3.9) (19.2 – 34.1)	24.4 (3.6)

* mean (sd), (range)

After administration of Kovanaze, tetracaine was rapidly and thoroughly metabolized to PBBA. The lower limit of quantification for tetracaine was reported as 0.05 ng/mL (LLOQ = 0.05 ng/mL).

Individual profiles of PBBA are presented in Figure 1.

Figure 1 PBBA Plasma Concentration – Time Curves in Healthy Volunteers With PBBA Concentrations that Increased in the Terminal Phase



Oxymetazoline and PBBA PK parameters are summarized in Table 3. There were no notable differences in PK parameters between males and females for either oxymetazoline or PBBA. Therefore, combined-sex data are provided.

Table 3: Mean Oxymetazoline and PBBA Plasma Pharmacokinetic Parameters* in Human Volunteers After the Intranasal Administration of [redacted] (b) (4) (Tetracaine HCL 18 mg, Oxymetazoline HCL 0.3 mg)

Analyte	Statistic	Pharmacokinetic Parameters					
		C_{max} (ng/mL)	t_{max} (min)	λ_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

Safety

A summary of TEAE incidence is provided in Table 4.

Table 4 Incidence (N, %) of Treatment Emergent Adverse Events by System Organ

Class and Preferred Term

SOC Preferred Term	N (%) (n = 24)
Gastrointestinal disorders	17 (70.8%)
Hypoaesthesia oral	9 (37.5%)
Hypoaesthesia teeth	7 (29.2%)
Nausea	3 (12.5%)
General disorders and administration site conditions	1 (4.2%)
Oedema peripheral	1 (4.2%)
Infections and infestations:	1 (4.2%)
Rhinitis	1 (4.2%)
Investigations	1 (4.2%)
Urine analysis abnormal	1 (4.2%)
Nervous system disorders	16 (66.7%)
Dizziness	1 (4.2%)
Headache	6 (25.0%)
Hypoaesthesia	11 (45.8%)
Paraesthesia	6 (25.0%)
Respiratory, thoracic and mediastinal disorders	22 (91.7%)
Epistaxis	3 (12.5%)
Increased viscosity of bronchial secretion	1 (4.2%)
Increased viscosity of nasal secretion	1 (4.2%)
Intranasal hypoaesthesia	1 (4.2%)
Nasal congestion	5 (20.8%)
Nasal discomfort	5 (20.8%)
Nasal inflammation	1 (4.2%)
Pharyngeal erythema	1 (4.2%)
Pharyngeal hypoaesthesia	7 (29.2%)
Rhinalgia	1 (4.2%)
Rhinorrhoea	11 (45.8%)
Throat irritation	5 (20.8%)

Source data: Table 14.3.1.2

Appendix

Table 1: Mean Oxymetazoline and PBBA Plasma Pharmacokinetic Parameters* in Human Volunteers After the Intranasal Administration of [redacted] (b) (4) (Tetracaine HCL 18 mg, Oxymetazoline HCL 0.3 mg)

Compound	Parameter	C_{max} (µg/L)	T_{max} (min)	T_{last} (hr)	λZ (hr-1)	$t_{1/2}$ (hr)	AUC_{0-t} (hr*µg/L)	$AUC_{0-\infty}$ (hr*µg/L)
Oxymetazoline	**Mean**	1.78	5.8	15	0.154	5.23	3.67	4.24
	sd	0.586	1.9	6.1	0.0575	2.20	1.79	2.09
	se	0.120	0.39	1.2	0.0117	0.449	0.366	0.426
	Minimum	0.841	5.0	8.0	0.0655	2.27	1.45	1.98
	Median	1.73	5.0	12	0.150	4.63	3.13	3.45
	Maximum	2.88	10.	24	0.306	10.6	7.00	8.39
	CV%	33	33	42	37	42	49	49
	Geo Mean	1.68	5.6	14	0.143	4.84	3.29	3.82
PBBA	**Mean**	465	21.6	14	0.346	2.6	960	973
	sd	122	6.6	3.7	0.184	1.23	509	513
	se	24.9	1.32	0.76	0.0376	0.252	104	105
	Minimum	208	15	8	0.149	0.887	383	389
	Median	448	19.8	12	0.252	2.78	817	826
	Maximum	663	40.2	24	0.781	4.65	2500	2530
	CV%	26	30	26	53	48	53	53
	Geo Mean	448	21	14	0.302	2.29	868	880

* N = 24

Table 2 Individual and Mean Oxymetazoline Plasma Pharmacokinetic Parameters in Human Volunteers After the Intranasal Administration of [redacted] (b) (4) (Tetracaine HCl 18 mg, Oxymetazoline HCl 0.3 mg) (additional information on gender)

Gender	Subject	C_{max} (µg/L)	T_{max} (min)	T_{last} (hr)	λZ (hr-1)	$t_{1/2}$ (hr)	AUC_{0-t} (hr*µg/L)	$AUC_{0-\infty}$ (hr*µg/L)
Male	100	1.52	5.0	8.0	0.193	3.60	1.91	2.34
	102	1.86	5.0	24	0.0871	7.96	6.48	7.34
	103	1.33	5.0	24	0.0941	7.37	5.58	6.20
	104	1.63	5.0	16	0.131	5.28	4.26	4.86
	110	0.859	5.0	8.0	0.186	3.72	1.56	2.15
	112	1.62	10	8.0	0.177	3.92	2.04	2.55
	117	1.45	5.0	12	0.135	5.13	2.15	2.59
	118	0.923	10	8.0	0.148	4.69	1.45	1.98
	119	1.32	5.0	12	0.152	4.56	2.32	2.69
	120	2.26	5.0	12	0.166	4.18	3.11	3.48
	121	2.88	5.0	12	0.204	3.41	3.18	3.42
	122	1.38	5.0	24	0.0655	10.6	6.65	8.39
	123	1.69	5.0	16	0.144	4.81	3.72	4.16
Female	101	1.76	10	8.0	0.306	2.27	2.55	2.88
	105	2.19	5.0	24	0.0822	8.43	5.52	6.36
	106	2.02	5.0	12	0.184	3.77	2.89	3.21
	107	2.85	5.0	12	0.175	3.96	3.17	3.52
	108	2.05	5.0	24	0.0876	7.92	7.00	7.90
	109	0.841	5.0	16	0.143	4.83	3.16	3.51
	111	1.97	5.0	8.0	0.255	2.72	2.15	2.41
	113	2.47	5.0	24	0.0737	9.40	6.96	8.31
	114	1.07	10	12	0.190	3.64	2.59	2.85
	115	2.51	5.0	12	0.183	3.78	2.88	3.16
	116	2.22	5.0	16	0.127	5.48	4.83	5.57
Mean		1.78	5.8	15	0.154	5.23	3.67	4.24
sd		0.586	1.9	6.1	0.0575	2.20	1.79	2.09
se		0.120	0.39	1.2	0.0117	0.449	0.366	0.426
CV%		33	33	42	37	42	49	49

Table 3 Individual and Mean PBBA Plasma Pharmacokinetic Parameters in Human Volunteers After the Intranasal Administration of [redacted] (b) (4) (Tetracaine HCl 18 mg, Oxymetazoline HCl 0.3 mg)

Gender	Subject	C_{max} (µg/L)	T_{max} (min)	T_{last} (hr)	λZ (hr-1)	$t_{1/2}$ (hr)	AUC_{0-t} (hr*µg/L)	$AUC_{0-\infty}$ (hr*µg/L)
Male	100	426	15	12	0.277	2.5	766	782
	102	576	15	12	0.506	1.37	794	803
	103	441	20	16	0.559	1.24	745	749
	104	399	15	12	0.444	1.56	882	896
	110	323	40	16	0.227	3.06	840	849
	112	373	25	12	0.175	3.96	688	712
	117	401	20	16	0.185	3.75	1430	1470
	118	208	25	12	0.483	1.43	383	389
	119	415	30	16	0.185	3.75	872	886
	120	468	25	12	0.565	1.23	692	697
	121	612	15	24	0.189	3.67	2220	2240
	122	614	25	16	0.15	4.62	1170	1200
	123	312	20	16	0.517	1.34	452	456
Female	101	604	15	8	0.781	0.887	718	725
	105	663	30	24	0.149	4.65	2500	2530
	106	564	30	16	0.224	3.1	1580	1590
	107	627	25	12	0.549	1.26	907	912
	108	605	25	12	0.2	3.47	1030	1050
	109	294	20	12	0.218	3.18	647	664
	111	425	15	12	0.174	3.99	639	654
	113	522	20	12	0.28	2.48	864	872
	114	376	25	12	0.217	3.19	644	655
	115	464	15	16	0.505	1.37	866	873
	116	454	15	16	0.548	1.26	697	702
Mean		465	21.6	14	0.346	2.6	960	973
sd		122	6.6	3.7	0.184	1.23	509	513
se		24.9	1.32	0.76	0.0376	0.252	104	105
CV%		26	30	26	53	48	53	53

Table 4 Individual and Summary Plasma Tetracaine Concentrations After A Single Dose of (b) (4)

		Predose	0	0.08	0.17	0.25	0.33	0.42	0.5	0.67	0.83	1
Compound	Subject	Concentration (µg/L)										
Tetracaine	100	(b) (4)										
	101											
	102											
	103											
	104											
	105											
	106											
	107											
	108											
	109											
	110											
	111											
	112											
	113											
	114											
	115											
	116											
	117											
	118											
	119											
	120											
	121											
	122											
	123											
	N	0	0	1	0	0	0	0	0	0	0	0
	Mean			0.0501								
	sd											
	Min			0.0501								
	Median			0.0501								
	Max			0.0501								
	CV%											

a: not provided by analytical laboratory, Missing: not included in PK analysis – LLOQ/BQL as reported by analytical laboratory

		1.25	1.5	1.75	2	3	4	6	8	12	16	24
Compound	Subject	Concentration (ng/L)										
Tetracaine	100	(b) (4)										
	101											
	102											
	103											
	104											
	105											
	106											
	107											
	108											
	109											
	110											
	111											
	112											
	113											
	114											
	115											
	116											
	117											
	118											
	119											
	120											
	121											
	122											
	123											
	N	0	0	0	0	0	0	0	0	0	0	0
	Mean											
	sd											
	Min											
	Median											
	Max											
	CV%											

a: not provided by analytical laboratory, Missing: not included in PK analysis – LLOQ/BQL as reported by analytical laboratory

Table 5 Individual and Summary Plasma Oxymetazoline Concentrations After A Single Dose of (b) (4)

		0	0.08	0.17	0.25	0.33	0.42	0.5	0.67	0.83	1
Compound	**Subject**	**Concentration (µg/L)**									
Oxymetazoline	100	(b) (4)									
	101										
	102										
	103										
	104										
	105										
	106										
	107										
	108										
	109										
	110										
	111										
	112										
	113										
	114										
	115										
	116										
	117										
	118										
	119										
	120										
	121										
	122										
	123										
	N	24	23	23	24	24	24	24	23	24	24
	Mean	**1.04**	**1.77**	**1.49**	**1.10**	**0.879**	**0.759**	**0.659**	**0.544**	**0.492**	**0.445**
	sd	**0.356**	**0.604**	**0.493**	**0.315**	**0.232**	**0.199**	**0.159**	**0.117**	**0.105**	**0.105**
	Min	**0.505**	**0.841**	**0.695**	**0.629**	**0.465**	**0.354**	**0.357**	**0.330**	**0.317**	**0.267**
	Median	**0.935**	**1.69**	**1.40**	**1.10**	**0.865**	**0.776**	**0.661**	**0.525**	**0.499**	**0.437**
	Max	**1.65**	**2.88**	**2.49**	**1.74**	**1.31**	**1.20**	**0.899**	**0.772**	**0.684**	**0.622**
	CV%	**34**	**34**	**33**	**29**	**26**	**26**	**24**	**22**	**21**	**24**

a: not provided by analytical laboratory, Missing: not included in PK analysis – LLOQ/BQL as reported by analytical laboratory

		1.25	1.5	1.75	2	3	4	6	8	12	16	24
Compound	**Subject**	**Concentration (µg/L)**										
Oxymetazoline	100	(b) (4)										
	101											
	102											
	103											
	104											
	105											
	106											
	107											
	108											
	109											
	110											
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	116											
	117											
	118											
	119											
	120											
	121											
	122											
	123											
	N	24	24	24	24	24	24	24	24	18	10	6
	Mean	**0.391**	**0.381**	**0.359**	**0.350**	**0.323**	**0.285**	**0.217**	**0.179**	**0.115**	**0.119**	**0.0826**
	sd	**0.0861**	**0.0915**	**0.0957**	**0.0817**	**0.104**	**0.118**	**0.107**	**0.0964**	**0.0625**	**0.0477**	**0.0204**
	Min	**0.221**	**0.205**	**0.184**	**0.188**	**0.151**	**0.146**	**0.0964**	**0.0684**	**0.050**	**0.0512**	**0.0586**
	Median	**0.392**	**0.394**	**0.360**	**0.351**	**0.315**	**0.238**	**0.170**	**0.126**	**0.0999**	**0.114**	**0.0771**
	Max	**0.536**	**0.551**	**0.510**	**0.476**	**0.513**	**0.550**	**0.454**	**0.372**	**0.227**	**0.175**	**0.114**
	CV%	**22**	**24**	**27**	**23**	**32**	**41**	**49**	**54**	**54**	**40**	**25**

a: not provided by analytical laboratory, Missing: not included in PK analysis – LLOQ/BQL as reported by analytical laboratory

Table 6 Individual and Summary Plasma PBBA Concentrations After A Single Dose of (b) (4)

		0	0.08	0.17	0.25	0.33	0.42	0.5	0.67	0.83	1
Compound	Subject	Concentration (µg/L)									
PBBA	100	(b) (4)									
	101										
	102										
	103										
	104										
	105										
	106										
	107										
	108										
	109										
	110										
	111										
	112										
	113										
	114										
	115										
	116										
	117										
	118										
	119										
	120										
	121										
	122										
	123										
	N	24	23	23	24	24	24	24	23	24	24
	Mean	115	277	377	435	428	435	425	384	342	302
	sd	28.7	69.6	103	114	102	111	116	112	109	102
	Min	73.8	151	194	203	197	208	180	163	171	148
	Median	116	288	372	426	412	413	403	363	318	280
	Max	179	379	560	617	592	627	663	629	637	545
	CV%	25	25	27	26	24	25	27	29	32	34

a: not provided by analytical laboratory, Missing: not included in PK analysis – LLOQ/BQL as reported by analytical laboratory,

		1.25	1.5	1.75	2	3	4	6	8	12	16	24
Compound	Subject	Concentration (µg/L)										
PBBA	100	(b) (4)										
	101											
	102											
	103											
	104											
	105											
	106											
	107											
	108											
	109											
	110											
	111											
	112											
	113											
	114											
	115											
	116											
	117											
	118											
	119											
	120											
	121											
	122											
	123											
	N	24	24	24	24	24	24	24	24	23	11	2
	Mean	257	221	193	165	98.7	58.4	23.4	12.4	6.35	4.75	3.31
	sd	111	108	113	96.2	76.0	52.4	27.5	15.1	6.68	3.61	1.61
	Min	109	88.4	68.6	59.1	30.0	17.8	4.63	2.37	2.02	2.14	2.17
	Median	225	189	156	137	71.3	39.8	13.3	7.28	4.19	3.33	3.31
	Max	579	514	526	435	307	206	111	64.6	28.3	13.8	4.44
	CV%	43	49	58	58	77	90	118	122	105	76	49

a: not provided by analytical laboratory, Missing: not included in PK analysis – LLOQ/BQL as reported by analytical laboratory, b:excluded from determination of λz

Study SR 2-07 Study Synopsis provided by the Applicant

Name of Company: St. Renatus, LLC 1000 Centre Avenue, Suite 120 Fort Collins, CO 80526	**Name of Finished Product:** (b) (4)	**Name of Active Ingredient(s):** Tetracaine hydrochloride and oxymetazoline hydrochloride in fixed combination
Title of Study: A Single-Center Study Evaluating The Pharmacokinetics Of Tetracaine, Para-Butylaminobenzoic Acid, And Oxymetazoline After Intranasal Administration Of (b) (4) (Tetracaine Hydrochloride With Oxymetazoline Hydrochloride) To Healthy Pediatric Subjects		
Investigator(s) and Study Center(s): Lydie Hazan, MD AXIS Clinical Trials Research Center 5800 Wilshire Blvd Los Angeles CA 90036 Tel: (323) 648-4105		
Publication (reference): None.		
Study Period: First subject, first visit: 24-Sep-2013 Last subject, last visit: 01-Nov-2013	**Clinical Phase:** Phase 1	
Objectives: Primary Objective: To characterize the PK of tetracaine, its metabolite PBBA, and oxymetazoline in pediatric subjects, ages 3-17 years, after intranasal administration of the recommended, weight-based Phase 3 pediatric dose of (b) (4) Secondary Objective: To assess the safety of the recommended, weight-based Phase 3 pediatric dose of (b) (4) on systolic and diastolic blood pressure (SBP and DBP, respectively) readings, pulse rate (PR), temperature, and oxygen saturation (SpO_2) levels and on the overall safety profile after intranasal administration to healthy pediatric subjects.		
Endpoints: • the pharmacokinetic profile of tetracaine, PBBA, and oxymetazoline • the mean changes in PR, SDP, DBP, and SpO_2 compared to Baseline • a comparison of the incidence of spontaneously reported or observed adverse events (AEs)		

Methodology:
Open-label, single-center, single-dose study in healthy pediatric subjects.

Number of Subjects (planned and analyzed):
Planned: 18 pediatric subjects aged 3 to 17 years.

Analyzed: 18 subjects were analyzed in the PK and safety populations.

Diagnosis and Criteria for Inclusion:

1. male or female 3-17 years of age inclusive
2. sufficiently healthy as determined by the Investigator to receive the test medications
3. accompanied and/or represented by a parent or guardian able to comprehend and sign the informed consent document
4. subject able to understand and provide assent to an age-appropriate subject assent form (as defined by local practice or regulation)
5. subject or parent/guardian able to communicate with the investigator and comply with the requirements of the protocol
6. within the 10^{th} and 90^{th} percentiles for weight by age
7. able to breathe through both nostrils
8. body mass index (BMI) from 14 and 30 kg/m^2 inclusive

Test Product, Dose, Mode of Administration and Lot Number:
(b) (4) Batch # 200093

- subjects weighing 10 to < 20 kg, 1 intranasal spray of 0.1 mL of (b) (4)
- subjects weighing 20 to < 40 kg, 2 intranasal sprays of 0.1 mL of (b) (4) given 4 min apart
- subjects weighing ≥ 40 kg, 2 intranasal sprays of 0.2 mL of (b) (4) given 4 min apart

Duration of Treatment: 1 day

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable.

Criteria for Evaluation:

Pharmacokinetics (PK):
Evaluation of plasma PK for oxymetazoline, tetracaine, and PBBA. Blood samples were collected at the following times relative to dosing: pre-dose and T_0, T_{10} min, and $T_{0.5}$, T_1, T_3, T_6, T_8, T_9, T_{12}, and T_{24} h after completion of all dosing.

Noncompartmental PK parameters for each analyte included: maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), elimination rate constant (λz), elimination half-life ($t_{½}$), area under the plasma concentration vs. time curve from 0 to the time of the last detectable analyte concentration (AUC_{0-t}) and AUC from time 0 extrapolated to infinity (AUC_{0-inf}).

Safety:
Sitting vital signs (VS - PR, SBP, DBP, temperature, and SpO_2) before PK sample collection at each time point; physical examination, hematology, clinical chemistry, and urinalysis at Screening, at Baseline, and at the end-of-study visit (2 weeks after dosing).

- sitting VS (HR, SBP, DBP, temperature, and SpO_2) at follow-up visits (24 h and 1 week after dosing), and at the end-of-study visit (2 weeks after dosing)
- recording of AEs

Statistical Methods:
Descriptive statistics (number of subjects, mean, standard deviation (SD), % coefficient of variation, median, minimum, and maximum) were to be used to summarize plasma concentrations of tetracaine, PBBA, and oxymetazoline at each sampling time point.

Descriptive statistics were also to be used to summarize PK parameters by analyte. Geometric means may have been used if deemed appropriate. Subjects were to be grouped by age and by weight for statistical analyses (ages 3-5 years, 6-11 years, and 12-17 years; body weights 10 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg). The effects of various demographic parameters (eg, age, weight, body surface area, gender) on tetracaine, its metabolite PBBA, and oxymetazoline PK may also have been evaluated.

Incidence rates for all AEs and serious adverse events (SAEs) along with Investigator-assessed severity and relationship to study drug for individual events were to be reported for all treatments. Results for safety were to be tabulated by weight group. Mean changes from Baseline for VS (SBP, DBP, PR, temperature, and SpO_2) were to be summarized by weight group using descriptive statistics.

Blood samples for PK analysis were collected at pre-dose, 0, 10, 30 min, 1, 3, 6, 8, 9, 12 and 24 hours post dosing. Plasma samples were analyzed using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) procedures for the three analytes, tetracaine, PBBA, and oxymetazoline. The following PK parameters were calculated using non-compartmental analysis: Cmax, Tmax, AUC0-t, AUC0-inf, elimination rate constant, and, T1/2. (Note: Time 0 refers to the sample drawn after administration of the last spray of study drug.)

Demographics

Table 1 Summary of Demography (Safety Population)

Parameter	Category / Statistics	(b) (4) 0.1 mL (n = 3)	(b) (4) 0.2 mL (n = 9)	(b) (4) 0.4 mL (n = 6)
Gender, n (%)	Male	1 (33.3%)	6 (66.7%)	2 (33.3%)
	Female	2 (66.7%)	3 (33.3%)	4 (66.7%)
Race, n (%)	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
	Alaskan Native	0	0	0
	Other	0	0	0
Ethnicity, n (%)	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)	Mean	4.3	8.4	13.5
	SD	0.49	2.31	0.86
	Median	4.1	8.2	13.4
	(Min, Max)	(4,5)	(5,12)	(12,15)
Weight (kg)	Mean	17.4	28.2	63.4
	SD	1.00	7.28	10.81
	Median	17.0	26.6	61.2
	(Min, Max)	(17,19)	(20,40)	(51,76)
Height (cm)	Mean	107.0	130.0	164.9
	SD	1.00	16.20	4.60
	Median	107.0	128.0	165.5
	(Min, Max)	(106,108)	(112,156)	(160,170)
BMI (kg/m^2)	Mean	15.2	16.4	23.3
	SD	0.70	1.29	3.83
	Median	15.1	16.3	22.7
	(Min, Max)	(15,16)	(15,19)	(19,29)
Age and Weight Percentile (%)	Mean	73.0	53.9	78.3
	SD	3.46	21.18	27.14
	Median	75.0	50.0	90.0
	(Min, Max)	(69,75)	(25,85)	(25,95)

Source data: Table 14.1.4 and Table 14.1.6.

Table 2: Demographic Characteristics of Pediatric Volunteers Receiving (b) (4)

	Dose Level	Male	Female	Combined Gender
N	1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	1	2	3
	2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	6	3	9
	3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	2	4	6
Age[a] (years)	1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	4.	4.3 (0.7) 3.8 – 4.8	4.2 (0.5) 3.8 – 4.8
	2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	8.2 (2.2) 5.9 – 11.6	8.8 (3.1) 5.4 – 11.6	8.4 (2.3) 5.4 – 11.6
	3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	14.3 (1.1) 13.5 – 15.1	13.1 (0.5) 12.4 – 13.5	13.5 (0.9) 12.4 – 15.1
Weight[a] (kg)	1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	17.0	17.6 (1.3) 16.6 – 18.5	17.4 (1.0) 16.6 – 18.5
	2 20 to < 40 kg Oxymetazoline: 0.1 mg Tetracaine: 6 mg	28.0 (6.7) 20.3 – 35.4	28.5 (10.0) 20.4 – 39.6	28.2 (7.3) 20.3 – 39.6
	3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	63.4 (17.5) 51.0 – 75.8	63.4 (9.6) 55.1 – 76.2	63.4 (10.8) 51.0 – 76.2

[a]: Age and weight reported as mean (sd) and range

Table 3 Pediatric subjects according to the age group

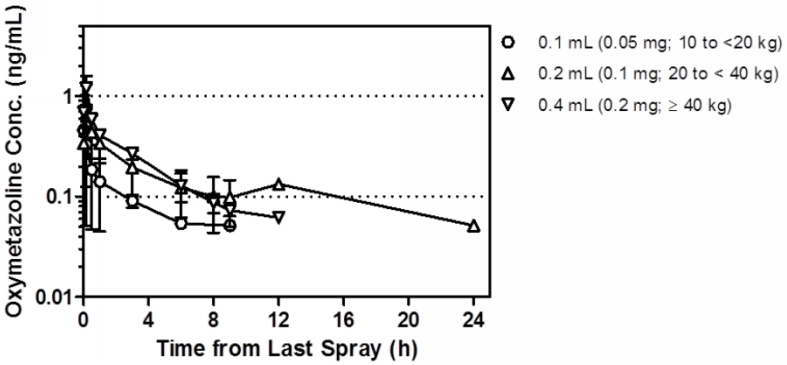
Age category (y)	Male (N)	Female (N)
0 – 2	0	0
2 -> 6	2	3
6 – 12	5	2
> 12	2	4

Table 4 Pediatric gender range in years (y)

Male Age range (y)	Female Age range (y)
4.1	3.8
5.9	4.8
6	5.4
8.2	9.4
8.2	11.6
9.4	12.4
11.6	13.3
13.5	13.3
15.1	13.5

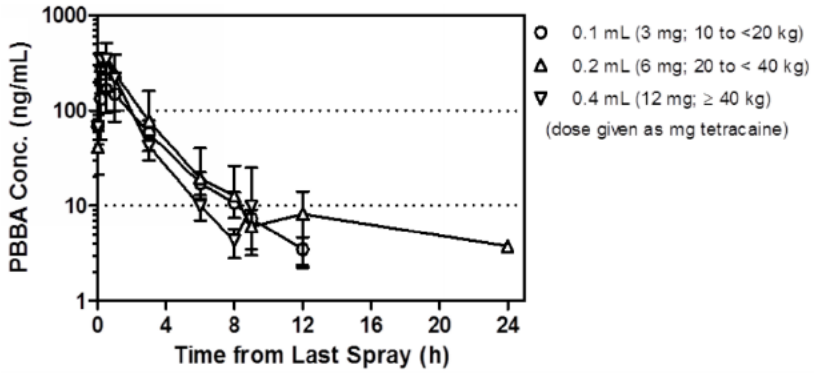
PK information

Figure 1 Mean (± SD) Plasma Concentration-Time Profiles for Oxymetazoline after Intranasal Administration of Kovanaze to Healthy Pediatric Subjects by Group (NOTE: same figure as in the main body; another data presentation style)



Source Data: Appendix 16.1.13, Table/Appendix 6 in Pharmacokinetic Analysis Report

Figure 2 Mean (± SD) Plasma Concentration-Time Profile for PBBA after Intranasal Administration of Kovanaze to Healthy Pediatric Subjects by Group (NOTE: same figure as in the main body; another data presentation style)



Source Data: Appendix 16.1.13, Table/Appendix 7 in Pharmacokinetic Analysis Report

Appendix

1. Demographics

St. Renatus, LLC
Protocol: SR 2-07

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Listing 16.2.4.1
Demographics

Dose Cohort (ul)	Subject ID	Date of Birth	Age (years)	Sex	Race	Ethnicity	Height	Weight	Body Mass Index	Age & Weight Percentile
100	8-001	(b) (6)	4.8	Female	Black or African American	Not Hispanic or Latino	108.0	18.5	15.9	69
	8-003		4.1	Male	White	Hispanic or Latino	106.0	17.0	15.1	75
	8-018		3.8	Female	Black or African American	Not Hispanic or Latino	107.0	16.6	14.5	75
200	8-002		5.9	Male	White	Hispanic or Latino	115.5	20.3	15.2	50
	8-004		11.6	Female	White	Hispanic or Latino	156.0	39.6	16.3	50
	8-010		11.6	Male	Black or African American	Not Hispanic or Latino	153.0	35.4	15.1	25
	8-011		8.2	Male	Black or African American	Not Hispanic or Latino	124.0	26.6	17.3	50
	8-012		8.2	Male	White	Hispanic or Latino	128.0	30.5	18.6	75
	8-014		9.4	Male	White	Hispanic or Latino	138.5	34.8	18.1	85
	8-016		5.4	Female	Black or African American	Not Hispanic or Latino	112.0	20.4	16.3	75
	8-017		6.0	Male	Black or African American	Not Hispanic or Latino	114.3	20.5	15.7	50
	8-019		9.4	Female	White	Hispanic or Latino	129.0	25.4	15.3	25

SF = Screen Failure

Dataset Status: September 25, 2014 as received from Rho
U:\SASCPPGM\PROJECTS\Renatus\SR-2-07\DEVELOP\PGM\TABLES\l 16 2 04 1 dem.sas (24FEB2015:11:42:01.6)

St. Renatus, LLC
Protocol: SR 2-07

Listing 16.2.4.1
Demographics

Dose Cohort (ul)	Subject ID	Date of Birth	Age (years)	Sex	Race	Ethnicity	Height	Weight	Body Mass Index	Age & Weight Percentile
400	8-005	(b) (6)	15.1	Male	White	Hispanic or Latino	160.0	51.0	19.9	25
	8-006		13.3	Female	White	Hispanic or Latino	170.0	55.1	19.1	75
	8-007		13.3	Female	White	Hispanic or Latino	168.5	65.3	23.0	90
	8-013		13.5	Male	White	Hispanic or Latino	168.5	75.8	26.7	95
	8-015		12.4	Female	Black or African American	Not Hispanic or Latino	160.0	57.0	22.3	90
	8-020		13.5	Female	White	Hispanic or Latino	162.5	76.2	28.9	95
SF	8-008		8.5	Female	White	Not Hispanic or Latino	136.0	30.6	16.5	75
	8-009		13.7	Male	White	Not Hispanic or Latino	170.0	58.8	20.3	82
	8-021		15.1	Female	Black or African American	Not Hispanic or Latino	167.0	73.5	26.4	93
	8-SF01		3.6	Female	White	Hispanic or Latino	108.0	15.0	12.9	52
	8-SF02		8.2	Male	Black or African American	Not Hispanic or Latino	124.0	20.4	13.3	3
	8-SF03		5.5	Female	Black or African American	Not Hispanic or Latino	114.0	20.5	15.8	80

SF = Screen Failure

Dataset Status: September 25, 2014 as received from Rho
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2. Study drug administration

St. Renatus, LLC
Protocol: SR 2-07

Listing 16.2.5
Stady Drug Administration

Dose Cohort (ul)	Subject ID	Birthdate	Administration naris (nostril)	Ade Cohort	Weight Cohort	Visit Date	Actual Time Administered: Spray 1 (0 minutes)	Actual Time Administered: Spray 2 (4 minutes +/-1)	Actual Time Administered: Spray 2 Not Done	Date Signed
		(b) (6)								
100	8-001		Right	3 to 6 years	10 kg to <20 kg	30SEP2013	8:57	.	Not Done	30SEP2013
	8-003		Right	3 to 6 years	10 kg to <20 kg	10OCT2013	9:06	.	Not Done	10OCT2013
	8-018		Left	3 to 6 years	10 kg to <20 kg	16OCT2013	10:14	.	Not Done	16OCT2013
200	8-002		Left	3 to 6 years	20 kg to <40 kg	10OCT2013	9:16	9:20		10OCT2013
	8-004		Right	7 to 12 years	20 kg to <40 kg	10OCT2013	9:26	9:30		10OCT2013
	8-010		Left	7 to 12 years	20 kg to <40 kg	08OCT2013	8:56	9:00		29OCT2013
	8-011		Right	7 to 12 years	20 kg to <40 kg	08OCT2013	9:21	9:25		22OCT2013
	8-012		Left	7 to 12 years	20 kg to <40 kg	02OCT2013	11:38	11:42		02OCT2013
	8-014		Left	7 to 12 years	20 kg to <40 kg	09OCT2013	9:57	10:01		09OCT2013
	8-016		Left	3 to 6 years	20 kg to <40 kg	01OCT2013	9:47	9:51		02OCT2013
	8-017		Right	3 to 6 years	20 kg to <40 kg	01OCT2013	10:00	10:04		21OCT2013
	8-019		Left	7 to 12 years	20 kg to <40 kg	15OCT2013	9:34	9:38		15OCT2013
400	8-005		Left	13 to 17 years	40 kg or more	10OCT2013	10:06	10:10		10OCT2013
	8-006		Right	13 to 17 years	40 kg or more	10OCT2013	9:46	9:50		10OCT2013
	8-007		Right	13 to 17 years	40 kg or more	02OCT2013	11:50	11:54		02OCT2013
	8-013		Right	13 to 17 years	40 kg or more	09OCT2013	9:38	9:42		09OCT2013
	8-015		Left	7 to 12 years	40 kg or more	01OCT2013	9:35	9:39		02OCT2013
	8-020		Right	13 to 17 years	40 kg or more	15OCT2013	10:18	10:22		15OCT2013

3. Individual and Summary Plasma Tetracaine Concentrations After A Single Dose of (b) (4)

		Time (hr)									
		0	0.17	0.5	1	3	6	8	9	12	24
Dose Level	ID	Concentration (µg/L)									
1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	1	(b) (4)									
	3										
	18										
	Mean	-	-	-	-	-	-	-	-	-	-
	sd	-	-	-	-	-	-	-	-	-	-
	Min	-	-	-	-	-	-	-	-	-	-
	Median	-	-	-	-	-	-	-	-	-	-
	Max	-	-	-	-	-	-	-	-	-	-
2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	2	(b) (4)									
	4										
	10										
	11										
	12										
	14										
	16										
	17										
	19										
	Mean	-	-	-	-	-	-	-	-	-	-
	sd	-	-	-	-	-	-	-	-	-	-
	Min	-	-	-	-	-	-	-	-	-	-
	Median	-	-	-	-	-	-	-	-	-	-
	Max	-	-	-	-	-	-	-	-	-	-
Dose Level	ID	Concentration (µg/L)									
3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	5	(b) (4)									
	6										
	7										
	13										
	15										
	20										
	Mean	-	-	-	-	-	-	-	-	-	-
	sd	-	-	-	-	-	-	-	-	-	-
	Min	-	-	-	-	-	-	-	-	-	-
	Median	-	-	-	-	-	-	-	-	-	-
	Max	-	-	-	-	-	-	-	-	-	-

BQL: omitted for PK modeling data set – LLOQ/BQL as reported by analytical laboratory
-: Insufficient data to determine, a:excluded from determination of λz

4. Oxymetazoline Plasma Pharmacokinetic Parameters in Pediatric Volunteers After the Administration of (b) (4)

Dose Level	Subject	C_{max} (µg/L)	T_{max} (min)	T_{last} (hr)	$t_{1/2}$ (hr)	AUC_{0-t} (hr*µg/L)	$AUC_{0-\infty}$ (hr*µg/L)	Vz/F (L)	Cl/F (L/hr)
1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	1	(b) (4)							
	3								
	18								
	Mean	**0.367**	**70**	**6.0**	**1.57**	**0.630**	**0.992**	**100**	**44.4**
	sd	**0.426**	**96**	**3.0**	**-**	**0.211**	**-**	**-**	**-**
	se	**0.246**	**56**	**1.7**	**-**	**0.122**	**-**	**-**	**-**
	CV%	**116**	**138**	**50**	**-**	**33**	**-**	**-**	**-**
2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	2	(b) (4)							
	4								
	10								
	11								
	12								
	14								
	16								
	17								
	19								
	Mean	**0.846**	**10**	**9.9**	**4.32**	**1.88**	**2.53**	**240**	**40.6**
	sd	**0.454**	**0.0**	**5.6**	**2.24**	**0.780**	**1.08**	**147**	**17.5**
	se	**0.151**	**0.0**	**1.9**	**0.85**	**0.260**	**0.408**	**55.4**	**6.62**
	CV%	**54**	**0**	**57**	**52**	**42**	**43**	**61**	**43**
3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	5	(b) (4)							
	6								
	7								
	13								
	15								
	20								
	Mean	**1.20**	**10**	**9.0**	**3.49**	**2.27**	**2.64**	**334**	**68.0**
	sd	**0.387**	**0.0**	**1.9**	**0.81**	**0.39**	**0.405**	**45.3**	**10.6**
	se	**0.158**	**0.0**	**0.77**	**0.33**	**0.159**	**0.165**	**18.5**	**4.31**
	CV%	**32**	**0**	**21**	**23**	**17**	**15**	**14**	**16**

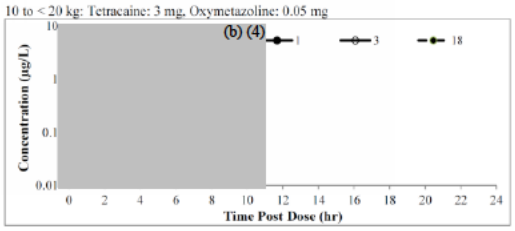
-: Insufficient data to determine

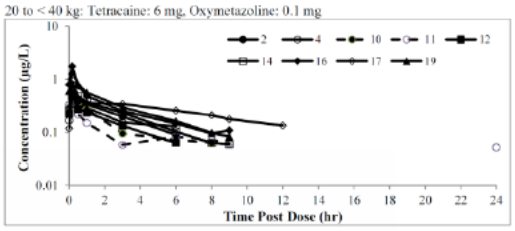
5. PBBA Plasma Pharmacokinetic Parameters in Pediatric Volunteers After the Administration of (b) (4) ® Mist

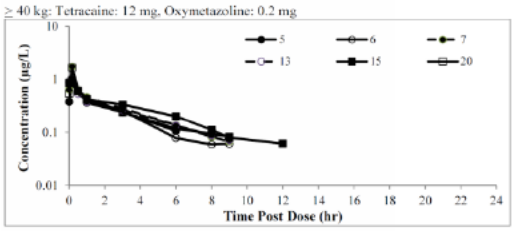
Dose Level	Subject	C_{max} (µg/L)	T_{max} (min)	T_{last} (hr)	$t_{1/2}$ (hr)	AUC_{0-t} (hr*µg/L)	$AUC_{0-\infty}$ (hr*µg/L)	Vz/F (L)	Cl/F (L/hr)
1 10 to < 20 kg Tetracaine: 3 mg Oxymetazoline: 0.05 mg	1	247	30	12	2.40	768	783	7.46	2.15
	3	124	30	12	2.87	366	376	18.6	4.49
	18	126	30	12	3.16	411	427	18.0	3.95
	Mean	**166**	**30**	**12**	**2.81**	**515**	**529**	**14.7**	**3.53**
	sd	**70.5**	**0.0**	**0.0**	**0.38**	**220**	**222**	**6.26**	**1.22**
	se	**40.7**	**0.0**	**0.0**	**0.22**	**127**	**128**	**3.62**	**0.706**
	CV%	**43**	**0**	**0**	**14**	**43**	**42**	**43**	**35**
2 20 to < 40 kg Tetracaine: 6 mg Oxymetazoline: 0.1 mg	2	294	30	9.0	1.61	637	648	12.1	5.21
	4	225	30	9.0	2.13	531	544	19.1	6.20
	10	264	10	9.0	3.60	417	443	39.6	7.62
	11	164	10	9.0	2.16	289	305	34.5	11.1
	12	184	10	9.0	1.20	371	379	15.5	8.91
	14	363	30	9.0	1.04	641	649	7.81	5.20
	16	705	30	24	2.47	2225	2238	5.36	1.51
	17	444	10	12	3.05	1180	1210	12.3	2.79
	19	466	30	12	2.31	1010	1020	11.0	3.31
	Mean	**345**	**21**	**11**	**2.18**	**811**	**826**	**17.5**	**5.76**
	sd	**172**	**11**	**4.9**	**0.83**	**606**	**606**	**11.8**	**3.06**
	se	**57.3**	**3.5**	**1.6**	**0.28**	**202**	**202**	**3.95**	**1.02**
	CV%	**50**	**50**	**43**	**38**	**75**	**73**	**68**	**53**
3 ≥ 40 kg Tetracaine: 12 mg Oxymetazoline: 0.2 mg	5	322	30	9.0	1.40	595	600	22.8	11.2
	6	366	30	9.0	1.31	661	665	19.3	10.2
	7	400	10	9.0	1.69	571	577	28.5	11.7
	13	380	10	8.0	1.54	618	623	24.1	10.8
	15	338	30	9.0	1.40	731	807	16.9	8.36
	20	387	10	9.0	2.08	705	719	28.1	9.39
	Mean	**365**	**20**	**8.8**	**1.57**	**647**	**665**	**23.3**	**10.3**
	sd	**29.9**	**11**	**0.41**	**0.28**	**63.2**	**85.7**	**4.66**	**1.24**
	se	**12.2**	**4.5**	**0.17**	**0.11**	**25.8**	**35.0**	**1.9**	**0.507**
	CV%	**8**	**55**	**5**	**18**	**10**	**13**	**20**	**12**

-: Insufficient data to determine

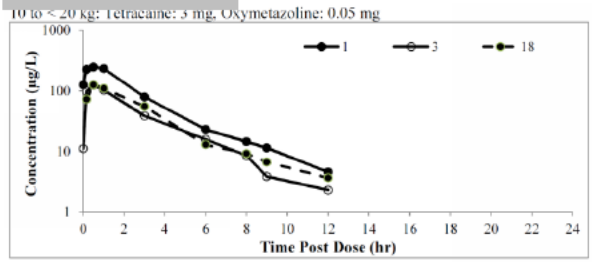
6. Oxymetazoline Plasma Concentration – Time Curves in Healthy Pediatric Volunteers Administered (b) (4)

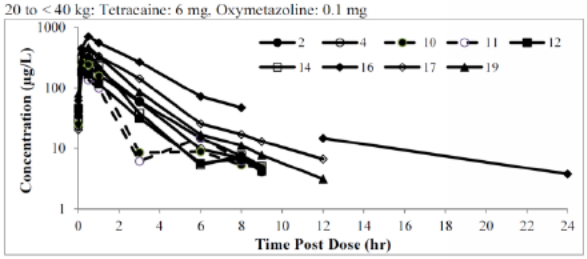


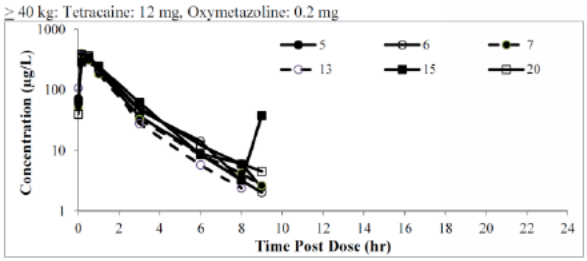




7. PBBA Plasma Concentration – Time Curves in Healthy Pediatric Volunteers Administered (b) (4)







8. Safety Summary of Treatment Emergent Adverse Events (Safety Population)

Category	(b) (4) 0.1 mL (n = 3)	(b) (4) 0.2 mL (n = 9)	(b) (4) .4 mL (n = 6)
Number of AEs Reported	0	0	4
Subjects with AEs	0	0	3 (50.0%)
Subjects with Study Medication Related AE[a]	0	0	3 (50.0%)
Subjects with Serious AE	0	0	0
Subjects Discontinued From Study Due to AE	0	0	0
Deaths	0	0	0
Treatment Emergent Adverse Events by System Organ Class and Preferred Term			
Nervous System Disorders:	0	0	3 (50.0%)
Dizziness[b]	0	0	1 (16.7%)
Headache[b]	0	0	3 (50.0%)

Source data: Table 14.3.1.1, Table 14.3.1.2 and Table 14.3.1.3

[a] Study Medication Related AE = Remotely, Possibly and Probably Related

[b] All AEs (1 event dizziness and 3 events headache) in all 3 subjects receiving the 0.4 mL dose were mild

The Applicant stated that a total of 4 TEAEs were reported by 3 subjects (50%) in the 0.4 mL dose group. All TEAEs were from a single SOC (nervous system disorders). The most frequently reported TEAE on the PT level was headache (in 3 subjects, 50.0%) followed by dizziness (1 subject, 16.7%). There were no reports of TEAEs in the 0.1 or 0.2 mL dose groups.

4.3 Consult Review (including Pharmacometric Reivews) – Not Applicable

4.4 Cover Sheet and OCPB Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208032; 505(b)(2)	**SDN 000**	
Applicant	St. Renatus	**Submission Date**	5/29/15
Generic Name	3% tetracaine HCl and 0.05% Oxymetazoline HCl solution	**Brand Name**	Kovanaze™
Drug Class	Anesthesia		
Current Indication	Regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J		
Dosage Regimen	Single administration during dental procedure ☐ Adults: 0.4 to 0.6 mL (2 to 3 sprays), depending on the patient's response. ☐ Pediatrics (b) (4) 0.4 mL, based on the patient's weight (b) (4)		
Dosage Form	Solution spray	**Route of Administration**	Intranasal
OCP Division	DCP 2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	David Lee	Yun Xu	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	7/28/15	**74-Day Letter Date**	8/11/15
Review Due Date	2/23/16	**PDUFA Goal Date**	3/29/16

Application Fileability
Is the Clinical Pharmacology section of the application fileable? ☑Yes ☐ No If no list reason(s)
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? ☐ Yes ☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	2	
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			

☐ Geriatrics		
☑ Pediatrics	1	
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	3
Total Number of Studies to be Reviewed				3

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505 b)(2) application?	☐Yes ☐No ☑N/A	The Applicant obtained a right of reference to NDA 21623 for Synera® (lidocaine and tetracaine topical patch). The Applicant is relying on the OTC monograph for nasal decongestant products (21

		CFR Part 341). Available literature was also reviewed on the clinical pharmacology, and safety of tetracaine, oxymetazoline, and metabolites.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the	☑Yes ☐No	

appropriate format (e.g., CDISC)?	☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☑Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

The Applicant has submitted a fixed-combination drug product, Kovanaze™, as a 505(b)(2) submission. Kovanaze™ is a formulation of two ingredients, 3% tetracaine hydrochloride (HCl) and 0.05% oxymetazoline HCl, to achieve regional anesthesia when sprayed into the respiratory region of the nasal cavity. The product is provided in single-use, prefilled nasal spray systems that deliver 0.2 mL (containing 6 mg tetracaine HCl and 0.1 mg Oxymetazoline HCl).

As support for a 505(b)(2) application, with respect to tetracaine hydrochloride, the Applicant obtained a right of reference to NDA 21623 for Synera® (lidocaine and tetracaine topical patch). With respect to oxymetazoline hydrochloride, the Applicant is relying on the OTC monograph for nasal decongestant products (21 CFR Part 341) as it applies to the findings of nonclinical

safety of oxymetazoline. Available literature was also reviewed on the clinical pharmacology, and safety of tetracaine, oxymetazoline, and metabolites.

In addition, the Applicant submitted information from three pharmacokinetic studies as follows (an excerpt from Clinical-Overview, page 7, Section 2.25):

- SR 2-02 was a preliminary cross-over study conducted in 12 healthy adult subjects to investigate the PK of intranasally administered (b) (4) at the estimated maximum single dose (standard dose) of 0.6 mL (18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl) and twice the estimated maximum single dose (high dose) of 1.2 mL (36 mg tetracaine HCl and 0.6 mg oxymetazoline HCl), and to determine the PK of oxymetazoline, tetracaine, and the major tetracaine metabolite (*p*-butylaminobenzoic acid [PBBA]) after delivery of both doses. (b) (4) was administered bilaterally as 3 sprays of 0.1 mL in each nostril for the standard dose and 6 sprays of 0.1 mL in each nostril for the high dose.
- SR 2-06 was a definitive study conducted in 24 healthy adults to evaluate the PK of oxymetazoline, tetracaine, and PBBA after intranasal administration of (b) (4) at the maximum recommended dose (highest Phase 3 adult dose) of 0.6 mL (18 mg tetracaine HCl and 0.3 mg oxymetazoline HCl). (b) (4) was administered unilaterally as 3 sprays of 0.2 mL in 1 nostril, with the sequential sprays separated by an interval of approximately 4-min. The determination of the 4 minute interval between sprays was initially based on the understanding of the mechanism of action for oxymetazoline (AHFS Drug Information®, 2006; Haenisch, 2010) which was subsequently observed to be efficacious in Sponsored clinical trials.
- SR 2-07 was a definitive study conducted in 18 healthy pediatric subjects (age 4 to 15 years) to evaluate the PK of oxymetazoline, tetracaine, and PBBA after intranasal administration of (b) (4) Subjects were stratified into 3 groups by weight and (b) (4) was administered based on body weight: 1 spray of 0.1 mL in subjects 10 to < 20 kg, 2 sprays of 0.1 mL in subjects 20 to < 40 kg, and 2 sprays of 0.2 mL in subjects ≥ 40 kg. Dosing was administered unilaterally, and for those who received 2 sprays, delivery was separated by a 4-min intervals.

No filing deficiencies are identified for the 74-day letter from the clinical pharmacology perspective.

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

/s/

DAVID J LEE
02/22/2016

YUN XU
02/22/2016