CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	209963
Priority or Standard	Standard
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Division/Office	DAAAP/OND
Reviewer Name(s)	Renee Petit-Scott, M.D.
Review Completion Date	13 Dec 2017
Established Name	4% Cocaine HCl Topical Solution
(Proposed) Trade Name	Goprelto
Applicant	Genus Lifesciences, Incorporated
Formulation(s)	Topical solution
Dosing Regimen	Two pledgets, each containing 40 mg of cocaine hydrochloride, applied to each nasal cavity for a total dose of 160 mg
Applicant Proposed Indication(s)/Population(s)	For the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults.

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Cocaine hydrochloride topical solutions, hereinafter referred to as cocaine HCl, cocaine, or RX0041-002, are currently marketed unapproved drug products in the United States. The available formulations from Lannett Company, Inc. include 4% (40 mg/mL) and 10% (10 mg/mL) topical solutions. Genus Lifesciences, Inc. (GLS) is pursuing a 505(b)(2) pathway for approval of their manufactured 4% cocaine topical solution relying on published literature to support the safety of the drug product, as well as data collected from their own clinical trials. The proposed drug product is not a new molecular entity (NME).

Cocaine HCl, the active ingredient in the topical solutions, has the chemical name 3β-hydroxyl-1αH,5αH-tropane-2β-carboxylic acid methyl ester benzoate hydrochloride and is derived from the leaves of *Erythroxylon coca,* a plant grown primarily in South America. Cocaine HCl is classified as an ester-type local anesthetic, the properties for which the Applicant is seeking the approved indication, and also as a central nervous system stimulant. Cocaine HCl acts as a local anesthetic by reversibly inhibiting sodium conductance through voltage-gated ion channels, preventing the generation of the action potential and resulting in the loss of conduction of the nerve impulse throughout the nerve fiber. Cocaine HCl has no topical anesthetic action on intact skin but is readily absorbed from damaged skin or accessible mucous membranes. The vasoconstrictive properties of cocaine facilitate surgical visualization by decreasing surgical bleeding and congestion of the nasal mucous membranes. Cocaine HCl has a short time to onset (10-20 minutes) and a short duration of action (approximately 1 hour), making it a desirable drug product for use in the ambulatory surgical setting.

Genus Lifesciencs, Inc. (GLS) intends to manufacture and market cocaine as a 4% topical solution under the trade name of Goprelto. The proposed indication is as follows:

> *for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults*

The proposed dosing is two cotton (also referred to as cottonoid) pledgets, each containing 40 mg cocaine solution, applied to each nasal cavity for 20 minutes prior to surgery. The total proposed dose is 160 mg topical, intranasal administration.

Of note, (b) (4) was the company that originally met with the Division throughout the Investigational New Drug (IND) and pre-NDA phases of the drug development program. The IND (118527) was transferred (b) (4) On May 10, 2017, the Agency was notified of a company name change. Formerly (b) (4) is now Genus Lifesciences, Inc.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant's original submission received on November 23, 2016, contained incorrect, transposed data listings for the cocaine treatment arms, which resulted in incorrect initial results, conclusions, and summaries from the Phase 3, 2013011, study. This error required re-analysis of the correct treatment group data and resubmission of those key elements of the NDA application and required a second critical evaluation of the data submitted, resulting in different conclusions and clinical impressions of this drug product. Refer to section 6.1.1 Study Design, Data Quality and Integrity: Sponsor's Assurance, of this review for a more detailed discussion of the data transposition error.

According to my review of the re-submitted, corrected clinical data in the application and review of articles in the published literature, I recommend approval of Goprelto with revisions to the proposed labeling as outlined in section 10 Labeling Recommendations. The revisions clarify the recommended surgical population, contraindicated concomitant medications, anticipated changes in measured hemodynamic parameters, adverse reactions, and the clinical study results.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

[Cocaine hydrochloride topical solution has been used for decades as an anesthetic and vasoconstrictive agent for surgeries involving the nasal mucosa, septum, and superficial sinuses. It has been marketed as an unapproved product for such use throughout the United States. Currently available concentrations include 4% and 10% topical solutions, however, additional concentrations have been used including 6% and 8%. In general, the more concentrated cocaine solutions result in improved efficacy (i.e., improved topical anesthesia and less surgical bleeding), but also result in a more notable cardiovascular responses such as hypertension and tachycardia. The Applicant conducted a Phase 3 study which evaluated 4% and 8% cocaine topical solutions versus placebo. There was no statistical analysis performed comparing the efficacy between the 4% and 8% treatment groups. Both experimental concentrations demonstrated adequate topical anesthesia for performance of the evaluated procedures and there was a slight dose response observed between the 4% and 8% cocaine topical solutions. Additionally, as expected, there were a larger number of subjects in the 8% treatment arm with increases in both heart rate and measured blood pressure parameters.

In office-based procedures involving conscious, unsedated patients, cocaine can provide predictable short-term topical anesthesia for minimally invasive, less painful procedures, such as nasal endoscopy, as demonstrated in the Applicant's Phase 3 study. Invasive procedures such as turbinate reduction, however, are likely to cause more discomfort and would require additional anesthesia beyond topical cocaine. Results from the Phase 3 study did not entirely support this conclusion for two reasons. First, there were only four subjects in the 4% cocaine treatment group who required additional anesthetic medication to complete the surgical procedure; two underwent nasal endoscopy, one underwent turbinate reduction, and one had no procedure listed. Second, the number of invasive procedures performed in the 4% treatment group was low compared to the number of nasal endoscopies; e.g., two turbinate reductions compared to 169 nasal endoscopies alone. Given these low numbers it is difficult to make definitive conclusions regarding the efficacy of cocaine as a sole anesthetic when performing more invasive procedures on or through the nasal mucosa and reliance on clinical experience may be necessary.

In my clinical experience, the true therapeutic benefit of cocaine topical solution administration during invasive surgical procedures on or through the mucous membranes of the nasal cavities is to minimize surgical bleeding, decrease nasal congestion, and improve surgical visualization. Fiberoptic nasal endoscopes are used to visualize the internal structures of the nasal cavities and sinuses during diagnostic or surgical procedures. These procedures become more challenging in the presence of active bleeding or mucosal swelling, potentially resulting in prolonged surgical/procedural time. During the performance of invasive procedures, cocaine is administered, in combination with either sedation, monitored anesthesia care (MAC), or general anesthesia, to minimize surgical bleeding. When used in this clinical situation, topical anesthesia is not necessary.

The risks of topical, intranasal cocaine administration are associated primarily with its sympathomimetic properties leading to increases in

measured hemodynamic parameters, including heart rate and systolic, diastolic, and mean arterial blood pressure. In the Applicant's Phase 3 study, approximately eight percent of subjects in the 4% cocaine treatment group had increases in heart rate equal to or greater than 30% above baseline measurements. The Applicant described these increases as expected due to cocaine's sympathomimetic actions and no adverse events of arrhythmia beyond sinus tachycardia were observed. The Applicant defined increases in systolic and diastolic blood pressure as being equal to or greater than 25% and 40% of baseline values. In clinical anesthesia practice, however, increases of 30% or greater of baseline measurements are considered significant and potentially require an intervention, such as increasing the depth of general anesthesia or administration of a beta blocking medication. Approximately three percent of subjects in the 4% cocaine treatment group had increases in systolic blood pressure and 18% had increases in diastolic blood pressure equal to or greater than 30% of baseline measurements.

There were no reported adverse events related to these hemodynamic changes in the Applicant's Phase 3 study. While these findings are reassuring, they do not entirely support the conclusion that there is no risk for the development of a cardiovascular-related adverse event for four reasons. First, there have been case reports of patients developing ventricular arrhythmias, myocardial ischemia, myocardial infarction, and cardiogenic shock associated with intranasal cocaine administration (Lormans *et al,* 1992; Lenders *et al,* 2013). Second, not all patients who receive intranasal cocaine may tolerate increases in heart rate and blood pressure of 30% above baseline values. Third, cocaine can cause vasoconstriction of the coronary arteries (Lange *et al*, 1989) and patients with a history of coronary artery disease may be at increased risk of developing myocardial ischemia and infarction. And lastly, because cocaine is a marketed unapproved drug product, most of the safety information has come from a limited number of controlled clinical studies, published case reports, and anecdotal clinical experiences, none of which are adequate substitutes for a large post-marketing safety database.

Additional risks related to intranasal cocaine topical solution include nasal mucosal irritation and alterations in smell. The results of the Applicant's Phase 3 study did not observe these findings and are reassuring, but as discussed later in this review, three of the excipients in the proposed marketed formulation have not been previously characterized for intranasal administration.

In summary, the Applicant's Phase 3 study did demonstrate that 4% cocaine topical solution is an efficacious topical anesthetic in the setting of minimally invasive surgical procedures on or through the mucous membranes of the nasal cavities in adults. When used during the performance of more invasive procedures, additional anesthetics are often needed and cocaine's primary therapeutic benefit is in reducing surgical bleeding, an endpoint not evaluated in this study. The cardiovascular risks associated with the administration of cocaine topical solution can be mitigated by careful patient selection, requiring a thorough history and physical exam, and with continuous hemodynamic monitoring during the entire treatment period and post-operatively.]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diagnostic and surgical procedures on or through the mucous membranes of the nasal cavities in adults require use of an anesthetic. The following are anesthetic options: – Topical – Sedation – MAC – General – Combination of the above four • These procedures are typically performed with a vasoconstrictor agent to minimize bleeding and improve visualization. Invasive surgical procedures rely more on the vasoconstriction versus the anesthetic properties of cocaine.	**While exposure to cocaine topical solution may be low in the general population, those subjects requiring nasal surgery have a high likelihood of receiving cocaine. Furthermore, those subjects requiring repeat or additional nasal diagnostic procedures may receive subsequent doses of cocaine topical solution.**
Current Treatment Options	• Cocaine topical solution is currently available from another manufacturer in the United States and is used for nasal diagnostic and surgical procedures. It is most commonly available for clinical use as 4% (40 mg/mL) and 10% (100 mg/mL) solutions, but other concentrations have been used in clinical practice. • Nasal mucosal injections of local anesthetics with a vasoconstrictor agent are commonly used during nasal surgeries. Examples include lidocaine (typically 2% or 4%) or tetracaine with either epinephrine or phenylephrine. • Aerosolized local anesthetics with a vasoconstrictor agent are also commonly administered prior to nasal surgery. • Other agents commonly administered include benzocaine nasal spray, the decongestant oxymetazoline (as a nasal spray), and topical silver nitrate for chemical cauterization of small areas of bleeding. • MAC or general anesthesia are used for invasive or painful procedures	**4% cocaine topical solution will be the only approved topical anesthetic for use during nasal diagnostic procedures. It has the advantage of being topically administered versus injected into the nasal mucosa, the route of administration for many of the other commonly used local anesthetics. Cocaine and other short-acting local anesthetics allow nasal procedures to be performed on an outpatient basis, thus potentially reducing medical costs and risks associated with hospital procedures.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that cannot be successfully completed in the office under topical anesthesia.	
Benefit	• The results from the Applicant's Phase 3 study found that 4% cocaine topical solution administered via four cottonoid pledgets, two per nostril, did result in adequate anesthesia for successful completion of nasal endoscopy, nasal laryngoscopy, nasopharyngeal laryngoscopy, and nasal debridement. When compared to placebo responses during von Frey Filament testing (6.1, 100 gm filament), the 4% cocaine topical solution was statistically more efficacious, resulting in fewer subjects reporting pain scores above zero on the Visual Numeric Rating Scale (VNRS). • The ability to minimize surgical bleeding with use of topical cocaine administered to the nasal mucosa, albeit difficult to accurately quantify and not evaluated in the Applicant's Phase 3 study, is a benefit of this medication. The presence of bleeding can obscure the surgical view and result in increased surgical times. Topically administered local anesthetics commonly contain a vasoconstrictor agent such as epinephrine or phenylephrine. Because of cocaine's inherent sympathomimetic properties, no additional vasoconstrictor medication may be needed. Additionally, the topical route of administration of cocaine results in fewer submucosal injections of other vasoconstrictor agents and potentially less trauma to the nasal mucosa. • Because cocaine topical solution has been used clinically for many years as a topical anesthetic and vasoconstrictor agent during nasal procedures, there is information in the published literature	**4% cocaine topical solution is the first drug product to be approved for use as an intranasal anesthetic during procedures on or through the mucous membranes. It provides rapid, predictable, and reversible nerve blockade.** **Topical anesthesia of the mucous membranes of the nasal cavities allows for the successful completion of surgical procedures without the need for general anesthesia. This permits minimally invasive diagnostic and surgical procedures to be conducted in an office-based setting, as opposed to the Operating Room, resulting in more efficient use of time, decreased healthcare costs, less inconvenience and time lost from work or school for the patient, and a lower incidence of adverse events observed in patients undergoing general anesthesia, including post-operative nausea and vomiting.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	supporting its safe use in concentrations ranging from 4% to 10%. • The vast majority of adverse events and serious adverse events attributed to cocaine have been described in cases of illicit use, where the administered doses are in excess of those recommended for clinical use. Additionally, in situations of cocaine abuse there is often repeat administration(s) and co-administration of other illicit substances, which contribute to the observed adverse outcomes.	
Risk	• The observed increases in measured hemodynamic parameters in the Applicant's Phase 3 study exceeded 40% above baseline values in a small group of treated subjects. These increases were observed on average 15-30 minutes post-pledget removal and persisted for 60-70 minutes post-pledget removal. Those subjects who experienced such increases did not appear to have an increased number of adverse events. • Several prospective, randomized controlled clinical studies have demonstrated a decrease in coronary blood flow, diseased arteries more affected than non-diseased, and an increase in myocardial oxygen demand after administration of cocaine topical solutions or pastes, doses ranging from 2-3 mg/kg. Despite these findings, however, subjects were asymptomatic and there were no observed ECG changes demonstrating either ischemia or infarction and no observed arrhythmias beyond sinus tachycardia and bradycardia. The degree of coronary vasoconstriction in subjects with a known history of coronary artery disease and cigarette smoking was increased. • There are case reports of myocardial ischemia and infarction with and without cardiogenic shock associated with topical intranasal cocaine. In some cases, the patients had an underlying history of cardiovascular disease. In other cases, an additional vasoconstrictive	**Despite the wealth of information in the published literature and the results from the Applicant's Phase 3 study, the increases in hemodynamic parameters appear to be well-tolerated in the majority of treated patients. In controlled clinical studies, documented decreases in coronary artery cross-sectional area of 22±7% in non-diseased arteries and 45±18% in diseased arteries did not result in myocardial ischemia, myocardial infarction, or arrhythmias.** **There are documented cases in the literature of hypertension, myocardial ischemia and infarction, and ventricular arrhythmias. While some of these cases may involve patients with underlying cardiovascular disease or some who received an additional vasoconstrictive agent during the procedure, there is a risk of an adverse cardiac event during the administration of cocaine topical**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	agent such as epinephrine was administered, potentially increasing the degree of coronary vasoconstriction and the risk of adverse cardiac events. There are also case reports of tachycardia and ventricular arrhythmias associated with topical intranasal cocaine. A single case report documents acute angle closure glaucoma 24 hours post-operatively in a subject with a known history of repeated subacute attacks of glaucoma. • Patients with a history of ester local anesthetic allergy or sensitivity, including plasma cholinesterase deficiency should not receive cocaine topical solution. Additionally, plasma cholinesterase activity may be diminished by certain medications, including oral contraceptives and irreversible plasma cholinesterase inhibitors. The risk of increased plasma levels, prolonged duration of action, and occurrence of adverse events is possible. • Patients receiving amphetamines, MAOIs, SSRIs, SNRIs, or other medications that act to either inhibit the reuptake of catecholamines or inhibit their metabolism should not receive cocaine topical solution. There is the risk of clinically relevant increases in blood pressure and heart rate and potentially serious adverse events related to those increases (e.g., myocardial ischemia). • Because cocaine is a Schedule II drug per the Controlled Substances Act, misuse, abuse, or diversion by office staff is a concern. Careful documentation, including waste of residual volume, is required.	**solution and all patients will need adequate clinical monitoring.** **The majority of serious adverse events, including death, occurred as a result of illicit use. The dose of cocaine ingested under circumstances of abuse is difficult to quantify but doses ranging from 10-120 mg per "line" snorted have been documented, and daily doses as high as 5 g have been reported. Unlike situations of abuse, the clinical administration of cocaine involves a single topical application, and the maximum dose is 160 mg.** **Caution should be exercised in patients receiving medications that increase the concentration of catecholamines in the synaptic cleft, including MAOIs, TCAs, amphetamines, SSRIs, and SNRIs. The concurrent use of these medications can increase measured hemodynamic parameters beyond those observed with cocaine administration in isolation. These increases have the potential to become clinically significant and increase the incidence of adverse events, such as hypertension and myocardial ischemia.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• All patients receiving cocaine topical solution need close and constant monitoring of hemodynamic parameters and ECG. • All facilities administering cocaine topical solution need to have immediate access to ACLS medications and cardiopulmonary rescue equipment. • All facilities administering cocaine topical solution need to employ strict documentation and inventory procedures to minimize risk of misuse, abuse, or diversion. • Careful review of a patient's current medications is required.	**An emphasis on adequate and prolonged hemodynamic monitoring will facilitate early detection and intervention in the case of an adverse event related to the administration of cocaine topical solution.**

2 Therapeutic Context

2.1. Analysis of Condition

Cocaine has been used for decades as a topical anesthetic and a vasoconstrictor for a variety of diagnostic and surgical procedures performed on or through the nasal cavities, the oral cavity, and the respiratory tract (refer to Table 1 for examples of such procedures). For relatively benign, noninvasive diagnostic or surgical procedures, cocaine topical solution can be used as the sole anesthetic agent. For more invasive surgical procedures, however, cocaine does not offer the degree of anesthesia necessary for acceptable patient comfort and is often used in combination with sedation, MAC, or general anesthesia. In this setting, topical cocaine is used for its vasoconstrictive properties to decrease surgical bleeding.

Table 1: Diagnostic or Surgical Procedures that Use Cocaine as a Topical Anesthetic

Nasal procedures	Polypectomy, septal surgery, biopsy, foreign body removal, transnasal antral irrigation, cauterization, control of bleeding sites
Oral cavity procedures	Cleft palate evaluation, biopsy, and local tonsillectomy
Respiratory tract procedures	Indirect and direct laryngoscopy, laryngography, tracheoscopy, bronchoscopy, bronchography

Source: Verlander and Johns, 1981.

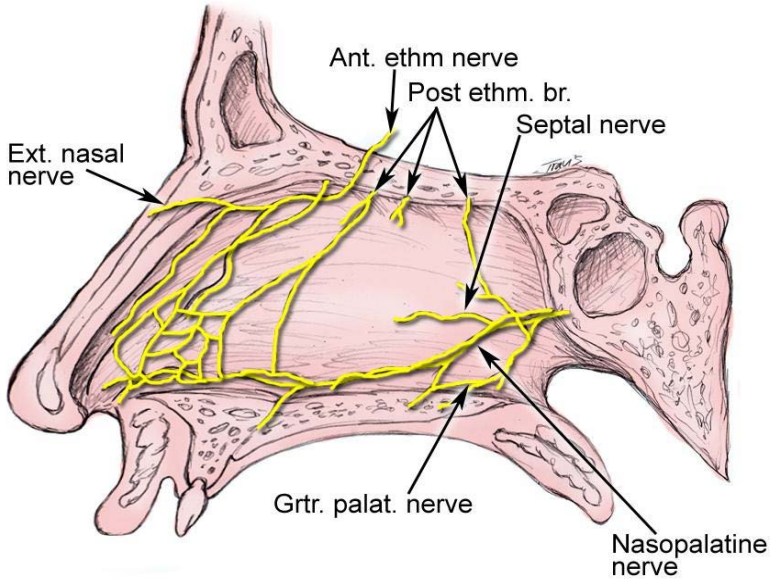
2.2. Analysis of Current Treatment Options

Anesthesia of the nasal mucosa, including the septum, is most commonly obtained via a combination of topical administration (including soaked pledgets and aerosols) and submucosal infiltration of a local anesthetic, with and without a vasoconstrictor agent. A current dilemma in the delivery of controlled and measurable anesthesia for the performance of nasal and sinus surgical procedures is that there are currently no FDA-approved products labeled for this use. Therefore, clinicians are administering a variety of local anesthetics, in varying concentrations, via differing routes based on preference and clinical experience. The use of such a wide variety of medications is problematic for two reasons. First, it leads to inconsistency amongst clinicians and no universally agreed upon protocols to induce adequate topical anesthesia for surgical procedures on or through the nasal mucous membranes. Second, tracking specific safety and efficacy outcomes is challenging when there is no agreed upon medication or route of administration.

In general, an ideal topical anesthetic has a rapid onset of action, predictable duration of action, and minimal systemic exposure. Topical application of local anesthetic-soaked pledgets is one route of administration that appears to be widely used. Placement of these pledgets in the

nasal cavities results in blockade of the anterior and posterior ethmoid, sphenopalatine, and nasopalatine nerves (refer to Figure 1 for nasal cavity innervation). After pledget removal, submucosal injections of local anesthetics can be performed to ensure adequate anesthesia of the nasal septum, lateral walls and floor of the nasal cavity. More invasive nasal or sinus surgery may require the administration of sedation, MAC, or general anesthesia for patient comfort. Local anesthetics with the addition of a vasoconstrictor are often used under these circumstances, not for topical anesthesia but to minimize bleeding and improve surgical visualization.

Figure 1: Innervation of Nasal Cavity and Mucosa



Source: Lai, D., Gnagi, SH., Nose Anesthesia. May, 2017.

Lidocaine in differing concentrations with and without a vasoconstrictor is the most commonly administered local anesthetic for use during nasal surgery. It can be administered via soaked cottonoid pledgets, aerosolized, or submucosal injections. It can be nebulized for use during endotracheal intubation, however systemic absorption is higher due to absorption from the lower respiratory tract. It has a very rapid onset of action, predictable duration of action, and has less toxicity associated with its use than other local anesthetics, making it an ideal anesthetic for use during ambulatory nasal surgical procedures. Benzocaine sprays had been commonly used in the past with mixed results, however, the increasing concern regarding the development of methemoglobinemia has caused its use to decline in the recent past.

Decongestants, such as oxymetazoline, are also commonly administered to patients undergoing diagnostic or surgical procedures of the nasal cavities to decrease nasal congestion. Similar to the majority of drug products used during nasal surgery, they are not approved for this use. Refer to Table 2 for a summary of current anesthetics and vasoconstrictors used during nasal

surgery.

Table 2: Summary of Topical Anesthetics and Vasoconstrictors Used During Surgical Procedures on or Through the Nose

Product (s) Name	Relevant Indication	Year of Approval	Route of Administration	Efficacy Information	Important Safety and Tolerability
Afrin (oxymetazoline) nasal spray	For nasal decongestion while performing diagnostic or surgical procedures on or through the nose	OTC mongraph Not approved for use during nasal surgery	Intranasal	Temporarily relieves nasal congestion; shrinks swollen nasal membranes	Not recommended for use in patients with poorly controlled hypertension, active thyroid disease, or frequent (≥5 per month) nose bleeds
2% lidocaine with and without epinephrine or phenylephrine	For topical anesthesia (and vasoconstriction) while performing diagnostic or surgical procedures on or through the nose	Not approved for intranasal use during surgical procedures	Submucosal infiltration	Predictable topical anesthesia	Caution in patients with history of severe coronary disease, hypertension, or cardiac dysrhythmias. Caution with concurrent administration of monoamine oxidase inhibitors or tricyclic antidepressants when used in combination with a vasoconstrictor Max dose 4.5 mg/kg (7 mg/kg with epinephrine)
4% lidocaine with and without epinephrine or phenylephrine	For topical anesthesia (and vasoconstriction) while performing diagnostic or surgical procedures on or through the nose	Not approved for intranasal use during surgical procedures	Topical via soaked pledgets or aerosolized	Predictable topical anesthesia	Extreme caution in patients with traumatized mucosa Max dose 4.5 mg/kg (7 mg/kg with epinephrine)
5% lidocaine with phenylephrine	For topical anesthesia (and vasoconstriction) while performing diagnostic or surgical procedures on or through the nose	Not approved for intranasal use during surgical procedures	Topical, aerosolized	For use in nasal surgery or endoscopy, including foreign body removal	Contraindicated in patients with hypertension, acute ischemic heart disease, complete heart block, thyrotoxicosis, glaucoma, urinary retention Max dose 8 sprays total
0.5%, 2%, or 4% tetracaine with and without oxymetazoline	For topical anesthesia while performing diagnostic or surgical procedures on or through the nose	Not approved for intranasal use during surgical procedures	Topical via soaked pledgets or aerosolized	Longer duration of action	Lower threshold for CNS toxicity when compared to lidocaine Tetracaine – prolonged duration of action Oxymetazoline – not recommended for use in patients with poorly controlled hypertension, active thyroid disease, or frequent (≥5 per month) nose bleeds Max dose 1.5 mg/kg (2.5 mg/kg with epinephrine)
Hurricaine® spray (20% benzocaine	For topical anesthesia while performing	Not approved for intranasal use during	Topical, intranasal	Less efficacious that lidocaine for nasal surgery	Methemoglobinemia A 2 sec spray can cause a statistically significant but

Product (s) Name	Relevant Indication	Year of Approval	Route of Administration	Efficacy Information	Important Safety and Tolerability
spray)	diagnostic or surgical procedures on or through the nose	surgical procedures			clinically insignificant increase in methemoglobin levels up 60 min post-administration
Cetacaine® spray (14% benzocaine, 2% tetracaine, 2% butamben combination)	For topical anesthesia while performing diagnostic or surgical procedures on or through the nose	Not approved for intranasal use during surgical procedures	Topical, Intranasal	Less efficacious than lidocaine for nasal surgery	Methemoglobinemia Toxicity can be associated with recommended doses

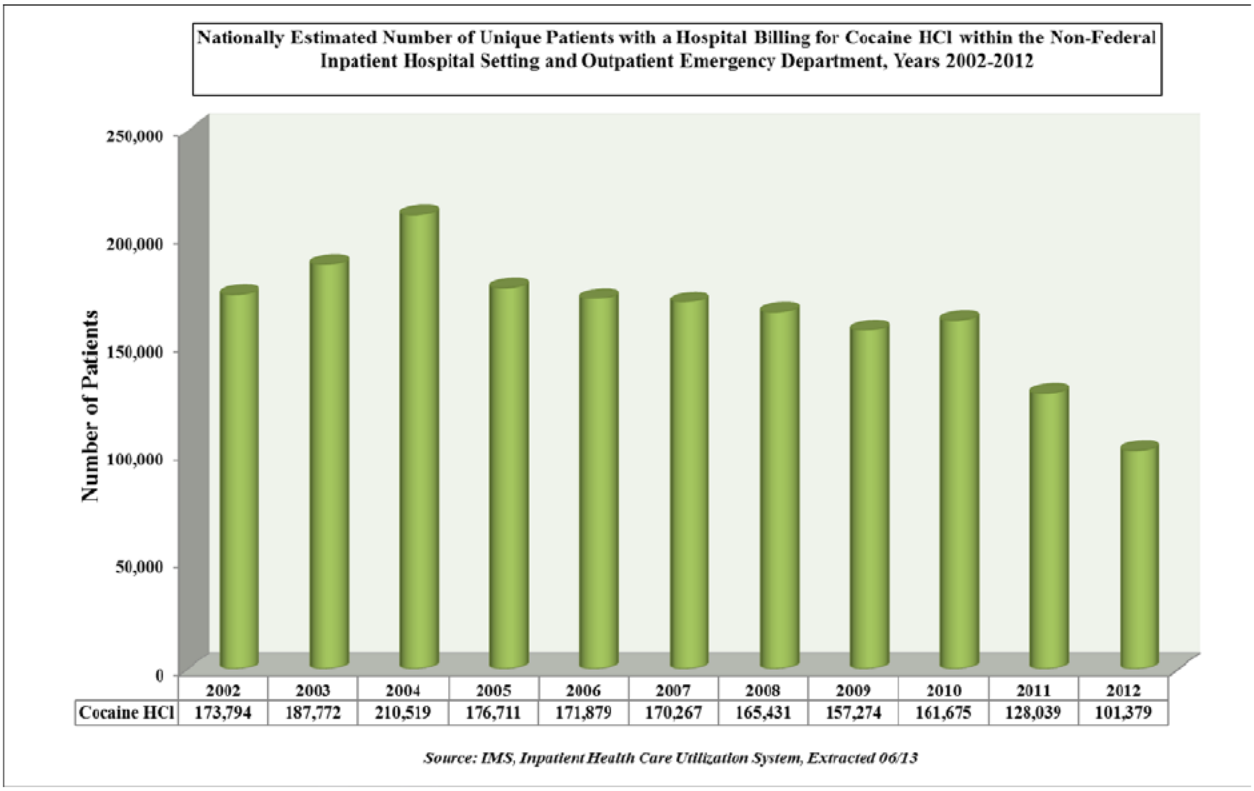
3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Four (and ten) percent cocaine topical solutions are marketed unapproved products in the United States. GLS, however, does not currently market these drug products. There is recent data to suggest that the clinical use of cocaine for nasal and sinus surgical procedures is declining. This decline is most likely due to two reasons. First, cocaine's Schedule II classification under the Controlled Substances Act, requires strict documentation of administration, waste, and overall inventory, which can be time-consuming in the office setting of rapid patient turnover. Second, cocaine has a high abuse potential, making diversion in the office setting a concern.

In 2013, the Applicant initiated communication, as a pre-IND meeting, with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) regarding their planned Phase 3 protocol submission under IND 118527. During that time, DAAAP had become aware of the results of a survey of Ear, Nose, and Throat (ENT) surgeons that suggested the clinical use of cocaine topical solutions had declined over the past decade. DAAAP consulted with the Office of Surveillance and Epidemiology, Division of Epidemiology II (DEPI-II) for evaluation of drug utilization patterns for cocaine topical solution in the setting of ENT diagnostic and surgical procedures. The consult review, completed by Dr. Rajdeep Gill, included primarily utilization data from in-patient hospital pharmacies from 2002 through 2012, as they comprised the largest purchasers of this drug product. In summary, the consult review concluded that the overall use of cocaine topical solution in the clinical setting peaked in 2004 and then steadily declined to the lowest utilization rates in 2012, as depicted in Figure 2.

Figure 2: Hospital and Emergency Department Billings for Cocaine Hydrochloride



3.2. Summary of Presubmission/Submission Regulatory Activity

(b) (4) opened IND 11827 on May 3, 2013 to begin discussions with the Agency concerning a marketing NDA for cocaine topical solution. The following table is a summary of the interactions between (b) (4) GLS (b) (4) and the Agency.

Table 3: Regulatory History Activity

Meeting/Communication/Date	Event/Key Clinical Issues
PIND 118527 WRO/Aug 20, 2013	The safety database should contain ≥500 subjects, evenly distributed between the dose strengths of 4% and 8%. Unequal allocation to the placebo group would be acceptable. Discussion regarding selection of the 8% topical solution as a novel formulation. The protocol needs to clearly state whether study subjects would be eligible to receive

Meeting/Communication/Date	Event/Key Clinical Issues
	additional sedative medications or parenteral analgesics. Primary endpoint definitions need to be clarified relative to success in the placebo group versus in the cocaine treatment arms. Additionally, it needs to be clarified whether treatment success is defined as no additional medication or no additional cocaine administered. There needs to be a more exact calculation of the final dose administered (i.e., how much cocaine solution is absorbed by the pledgets) and clarification of remaining solution documentation. Additional studies will need to confirm efficacy for procedures involving the oral mucosa and larynx. There needs to be adequate monitoring and documentation for abuse, misuse, diversion, and overdose for all subjects in the Phase 3 study. (b) (4) needs to follow the regulations and procedures surrounding the manufacture, distribution, dispensing, storage, recordkeeping, and disposal of study drug set forth in the Controlled Substance Act. (b) (4) must include commonly performed surgical procedures and stratify randomization by procedure type. They should provide results for which procedures may be more successful with the 4% or the 8% topical solution to assist with labeling recommendations. This was not done in the Phase 3 study. Clarify the selection of the 6.1, 100 gm Von Frey Filament (VFF) for use in testing for the

Meeting/Communication/Date	Event/Key Clinical Issues
	primary endpoint, analgesic success. (b) (4) needs to provide a literature-based Executive Summary based on all published literature on cocaine HCl from 1980 through 2013. This summary should contain individual assessments of the studies with discussion of their strengths and weaknesses and provide information to demonstrate the comparability of the study drug(s) to the proposed cocaine HCl solution. If such drug information is unavailable, (b) (4) must provide justification for why data from cited literature is acceptable as a source of information to support the submission. This summary also needs to include literature on the use of cocaine for other indications or administered by other routes.
Special Protocol Assessment (SPA) received/February 06, 2014	The Applicant plans to study only 4% cocaine topical solution versus placebo as outlined in the Special Protocol Assessment. There is non-agreement regarding the study design, planned analysis of the study, proposed primary endpoint, unclear types of procedures to be studied, sample size, secondary endpoints, volume of unabsorbed cocaine solution, absence of rationale for the safety of the proposed cocaine dose, sedative and analgesic use in the study and monitoring of vital signs.
IND 118527 submission received/ May 06, 2014	Treatment arms will include placebo and 4% cocaine topical solution groups. Anticipate 636 subjects enrolled. Subjects with pain scores > 0 on the Verbal Numeric Rating Scale (VNRS) may or may not proceed with administration of additional medication based upon individual clinician assessment.

Meeting/Communication/Date	Event/Key Clinical Issues
	Due to the unblinding of placebo to cocaine topical solution after vFF testing, there are now different primary endpoints between the placebo and cocaine treatment arm. This will affect the language in the label regarding the efficacy of the proposed product when compared to placebo.
IND protocol revision received/ July 23, 2014	The addition of the 8% cocaine topical solution treatment arm to maintain a blind (after the blind to placebo is broken following VFF testing) is acceptable. However, the selection of 8% solution versus the more commonly administered 10% is unclear. (b) (4) anticipates a 1:3:3 randomization (pbo:4%:8%) scheme. Pre- and post-operative nasal examinations and smell assessments are incorporated into the protocols.
PNDA meeting/ July 14, 2015	The 8% cocaine topical solution will be considered exploratory unless the statistical analysis plan is adjusted to control for the study-wise type I error rate. Clarify the administration of which medications would result in the subject being considered an analgesic failure. The NDA must specifically define the maximum daily dose of cocaine. The timing of the unblinding to placebo and cocaine treatment arms needs to be documented. Subgroup analyses by gender, race and age must be conducted. If the Clinical Study Report (CSR) will be

Meeting/Communication/Date	Event/Key Clinical Issues
	incorporated into the statistical analysis plan, then all necessary clinical information needs to be included; i.e., table of efficacy by subject weight, table of adverse events by subject weight, BMI, vital signs, etc. The Agency agreed that a REMS is most likely not necessary unless new safety information becomes available. The Agency agrees that 4% cocaine topical solution is considered an NCE and an NME and that if (b) (4) is the first company to gain approval for a cocaine NDA, they will qualify for the 5-year NCE exclusivity. However, that determination will not be made until after approval of an NDA. Whether or not priority review will be granted will be determined at the time of NDA submission.
Pediatric Study Plan Submission/October 19, 2016	Initial Pediatric Study Plan (iPSP) received.
NDA 209963 Submission/November 23, 2016	NDA received.
NDA Filing/January 22, 2017	NDA filed.
Teleconference/ April 06, 2017	The Agency was contacted regarding the database transposition in the CSR from the Applicant's Phase 3 study. This teleconference was scheduled to discuss the nature of the database transposition and the necessary actions to proceed with the continued evaluation of this NDA. The Applicant stated that the treatment code for the 4% and 8% cocaine-treated subjects was transposed when the data from the clinical study sites was entered into the database at the CRO. During the teleconference, the Agency was assured this was the only data error in the Phase 3 study and that a CAPA

Meeting/Communication/Date	Event/Key Clinical Issues
	was going to be submitted. The Applicant stated that they would resubmit a revised listing of all data including tables, figures, reports, and summaries. The Applicant verified that none of the results from the other clinical studies conducted in support of this NDA submission had been affected.
CAPA received/ April 19, 2017	The Applicant submitted a Corrective and Preventive Action (CAPA) Report to further explain the database transposition. Briefly, on April 4, 2017 a clinical field inspector from the Agency noted a subject's disposition listing in the CSR as randomized to the 4% cocaine topical solution group, but the randomization code for the same subject indicated administration of 8% topical cocaine solution. The Applicant's on-site representative contacted the CRO and it was determined that a definition error had occurred during the migration of the randomization code into the database and the 4% and 8% group assignments had been transposed in the database. The Applicant immediately notified the Agency and the April 6, 2017, teleconference was scheduled.
Database Transfer Error Resubmission and Filing Communication received/ May 1, 2017	The Applicant submitted the correct database listing and the revised CSR, Clinical Overview, Summary of Clinical Efficacy, and Summary of Clinical Safety, and updated datasets and USPI, and Annotated USPI.
Corporate Name Change/May 10, 2017	(b) (4) Genus Lifesciences, Inc.

3.3. Foreign Regulatory Actions and Marketing History

Cocaine topical solutions are marketed throughout the world for use in differing clinical

situations, but all related to its local anesthetic and vasoconstrictor properties. In Australia, they are used in the treatment of pain related to aphthous and pulmonary ulcers. Throughout the United States, they are most commonly used during nasal surgeries to decrease surgical bleeding and provide topical anesthesia. In 1999, the European Medicines Agency granted marketing authorization (number 12064/0016) for cocaine HCl 10%. The approved indication is as follows:

> *…to numb an area of the ear, nose, or throat ready for surgery. It may also be used to reduce the bleeding in the area during surgery*

Similar to the marketing history in the United States, the therapeutic uses for cocaine topical solutions in Europe have been declining most likely due to its high potential for abuse and diversion. Refer to Section 3.1 U.S. Regulatory Actions and Marketing History.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit for three investigative sites for the Phase 3 study was requested. The clinic sites 602, 702, and 703 were initially selected based on the large number of subjects enrolled at these three locations. Further review of the NDA, however, revealed a larger number of documented protocol deviations for sites 702 and 703, both having the same Principal Investigator, when compared to other sites. Sites 702 and 703 reported protocol deviations with a frequency of 64% and 51%, respectively, in the surgical population evaluated. Most of these deviations involved incorrect or out-of-window data collection and out-of-range vital sign or laboratory measurements for which a waiver was not obtained. Despite the large number of protocol deviations at these locations, there do not appear to be inconsistencies in the resulting efficacy or safety data when compared to the other surgical sites. Refer to Table 4, which outlines the study sites and the reported number of protocol deviations.

The investigator brochures and financial disclosures for all sites were as required.

The report from the clinical site inspections indicated that the Applicant adhered to the statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. The inspector had no concerns regarding the conduct of the Phase 3 study that would impact the reported efficacy and safety findings. A subsequent inspection was requested for [redacted] (b) (4) the CRO for the Phase 3 study management, after the Agency became aware of the data transposition error. The inspector concluded that the data transposition error appeared to be isolated, readily corrected, and limited to the Phase 3 study.

Table 4: Clinical Study Sites

Overall			Placebo		8% cocaine topical solution		4% cocaine topical solution		Protocol Deviations (%)
	Site ID #	# of Subjects	N	Success (%)	N	Success (%)	N	Success (%)	
		648	95	9 (9.5)	275	223 (81)	278	215 (77)	
1	(b) (6)	5	1	0 (0)	3	3 (100)	1	1 (100)	20
2		6	1	1 (100)	2	2 (100)	3	1 (33)	16.7
3		7	1	0 (0)	3	3 (100)	3	3 (100)	14.3
4		9	2	1 (50)	4	4 (100)	3	2 (67)	11.1
5		10	2	1 (0)	4	4 (100)	4	4 (100)	30
6		12	2	2 (100)	4	3 (75)	6	5 (83)	16.7
7		17	3	0 (0)	6	4 (67)	8	6 (75)	None reported
8		23	4	0 (0)	9	7 (78)	10	10 (100)	21.7
9		38	5	0 (0)	17	2 (12)	16	4 (25)	15.7
10		44	6	0 (0)	19	16 (84)	19	15 (79)	18.2
11		48	5	0 (0)	19	13 (68)	24	12 (50)	54.2
12		50	8	4 (50)	21	21 (100)	21	20 (95)	10
13		51	7	0 (0)	22	19 (86)	22	13 (59)	21.6
14		55	8	0 (0)	23	17 (74)	24	14 (58)	41.8
15		72	11	0 (0)	34	26 (76)	27	25 (93)	63.9
16		89	12	0 (0)	39	39 (100)	38	34 (89)	22.5
17		112	17	0 (0)	46	40 (87)	49	46 (94)	50.9

*clinical sites inspected

4.2. Product Quality

CMC final review was not available at the time of completion of this review. There appear to be no concerns regarding approvability from the CMC reviewer.

4.3. Clinical Microbiology

Clinical microbiology data were not submitted to this NDA. Cocaine HCl is not a therapeutic antimicrobial drug.

4.4. Nonclinical Pharmacology/Toxicology

The initial 14-day nonclinical, toxicology study conducted by the Applicant utilized 100% ethanol as the diluent for dissolution of the cocaine drug substance. The animals treated with ethanol alone demonstrated similar pathological findings in the nasal mucosa as those found in animals treated with the ethanol-cocaine solution, thereby making conclusions about the safety of intranasal topical administration of cocaine challenging. Because these results of this study are inconclusive, an additional toxicology study has been requested and the Applicant has agreed, however it is not clear if this study will be completed by the end of the review cycle.

Despite the inconclusive results of the nonclinical toxicology study, the data from the Applicant's Phase 3 study does support the safety profile of cocaine topical solution. Nasal examinations of subjects conducted on study Day 8 did not reveal any clinically significant findings. There was a single subject in the 4% treatment group who had a shift from a normal nasal exam on Day 1 to an abnormal exam on Day 8, described as turbinate hypertrophy and bilateral nasal congestion. These results suggest that administration of topical cocaine does not result in local toxicity in the nasal mucosa.

There are three excipients in the to-be-marketed cocaine formulation that have not been previously characterized and are not present in FDA-approved intranasal drug products. They are sodium benzoate, D&C Yellow No. 10, and FD&C Green No. 3. The acceptability of these excipients will be discussed in the pharmocotoxicologic review by Dr. Belinda Hayes.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Cocaine hydrochloride, 3β-hydroxyl-1αH,5αH-tropane-2β-carboxylic acid methyl ester benzoate hydrochloride, is an ester-type local anesthetic and a central nervous system stimulant. The anesthetic properties of cocaine are observed at high concentrations and are due to inhibition of sodium channels in nerve axons resulting in loss of conductance of the neuronal impulse. The interruption of the neuronal impulse results in loss of transmission of sensory information to the central nervous system (CNS) and clinically, loss of sensation at the site of administration. Cocaine exerts the most anesthetic benefit on areas of broken or open skin or when applied to

mucous membranes, such as the nasal mucosa. The anesthetic property of cocaine is the basis for the requested labeling indication by this Applicant.

Cocaine hydrochloride is also a vasoconstrictor agent at low doses and this clinical effect is due to three main sympathomimetic actions. First, cocaine acts at nerve terminals of the sympathetic nervous system (SNS) to cause inhibition of the reuptake of catecholamine neurotransmitters, including norepinephrine and dopamine, into the presynaptic nerve terminal. This reuptake into the presynaptic nerve terminal is a main mechanism by which the action of the released catecholamines is terminated. When reuptake is inhibited by medications such as cocaine, the duration of action of the catecholamine neurotransmitter is extended, resulting in prolonged stimulation of the post-synaptic adrenergic receptors, both alpha and beta. Stimulation of these receptors results in clinically observed increases in measured hemodynamic parameters including heart rate and blood pressure. The inhibition of dopamine reuptake in the CNS results in prolonged stimulation of post-synaptic dopaminergic receptors resulting in the euphoric effects that are observed with cocaine use.

The second sympathomimetic action of cocaine is to stimulate SNS outflow from the CNS, which the results in increased transmission and release of catecholamines. The observed clinical effect is the same as that observed due to reuptake inhibition; i.e., increased heart rate and blood pressure. Lastly, cocaine acts as a sympathomimetic agent by increasing the sensitivity of the adrenergic nerve terminals to norepinephrine, resulting in the same clinical changes observed with the other two mechanisms of increased SNS activity.

Additional mechanisms of action of cocaine not directly involving the SNS but resulting in vasoconstriction are the release endothelin-1, a very potent vasoconstrictor, and the inhibition of nitric oxide, a vasodilator, from endothelial cells. These actions are synergistic to the sympathomimetic properties of cocaine, potentiating vasoconstriction in the area of administration. The Phase 3 study submitted by the Applicant did not evaluate vasoconstriction of nasal mucosal vasculature or surgical bleeding and are requesting only an anesthetic indication for use during nasal surgery.

Cocaine hydrochloride has additional pharmacological properties that are less well-known and potentially less beneficial clinically, including anti-arrhythmic and pro-platelet actions. The anti-arrhythmic properties of cocaine are due to inhibition of sodium and potassium channels in the cardiac myocytes, classified as IC according to the Vaughn-Williams classification of anti-arrhythmic agents. Cocaine, however, is also considered pro-arrhythmic based on its ability to stimulate the SNS resulting in increased heart rate and arrhythmias. In cocaine abusers who experience sudden cardiac death, the generation of fatal ventricular arrhythmias is one clinical explanation. The pro-platelet properties of cocaine are due to stimulation and release of alpha-granules, plasminogen activator inhibitor, fibrinogen, and von Willebrand Factor. The stimulation and release of these factors results in platelet aggregation and thrombus formation. For a single topical application of cocaine, these properties are not believed to exert a clinically relevant or measurable effect.

4.5.2. Pharmacodynamics

Cocaine topical solution increases both heart rate and blood pressure. As previously discussed, the observed increases in measured hemodynamic parameters can exceed 30% above baseline values. The proposed package insert has been edited to more accurately reflect the observed increases and the recommended post-administration monitoring. Refer to section 10 Labeling Recommendations of this review for full prescribing information.

The potential for cocaine to prolong the QT_c was evaluated in the Applicant's clinical study, 2016017. The results suggest there is no clinically relevant QT_c prolongation observed at the clinical concentrations evaluated. Refer to section 8.4.9 Safety Results, QT of this review for a more detailed discussion of the study results and recommended label edits.

4.5.3. Pharmacokinetics

Cocaine hydrochloride, administered topically to mucous membranes or areas of denuded dermis, is primarily metabolized and inactivated by non-enzymatic ester hydrolysis and hepatic carboxylesterase to form benzoylecgonine (BE). An additional metabolite, ecgonine methyl ester (EME) is formed by the action of plasma cholinesterase and hepatic carboxylesterase. Both BE and EME are considered inactive metabolites. These inactive metabolites are excreted by the kidneys in the urine. Norcocaine is an active, minor metabolite formed by N-demthylation in liver microsomes via cytochrome P4503A4 and is present in very low concentrations in human plasma. It has been previously documented that less than 10% of an administered dose of cocaine hydrochloride is excreted unchanged in the urine.

The Applicant did conduct a Phase 1, single-dose, single-center, open-label pharmacokinetic (PK) study, 2015016, in 30 male (14) and female (16) healthy adult volunteer subjects. On study Day 1, subjects received 4% cocaine topical solution via four cottonoid-soaked pledgets, two per nostril, applied to the nasal mucosa for 20 minutes. The total dose administered was 160 mg, the proposed labeling dose. Plasma PK sampling and urinary collections were obtained at predetermined time points. Refer to Table 5 for the study schedule.

Table 5: Schedule of Study Activities for Phase 1 Study 2015016

Study Procedures	Screening (within 21 days prior to 1st dose)	Day 1 (Check in)	Day 1 (Dosing)	Day 1 (End of Study)
Informed consent	X			
Medical History	X			
Subject Eligibility	X	X		
Weight/Height (BMI)	X			
Drug screen	X	X		
Serum Pregnancy Test	X			
Urine Pregnancy Test		X		
Clinical safety labs (hematology, chemistry and urinalysis)	X			X
Physical examination	X			
Twelve-lead EKG	X			
Vital signs (BP and HR)	X		X[1]	
Oral Temperature and Respiration Rate	X			
Admission to clinic		X		
Discharge from clinic				X
Study Drug Administration			X	
Urine Collection		X[3]	X	
PK sampling			X[2]	
Nasal Exam		X		
Adverse event assessment			X	X
Concomitant meds assessment	X	X		X

Source: Applicant's submission, NDA 209963

[1] Vital signs were performed pre-dose and at 5 minutes post pledget removal and at 1, 4, 8 and 12 hours.
[2] PK samples were taken pre-dose and post dose: 7.5, 15, 20, 30, 45, 60, 75, 90, 105 minutes and 2, 3, 4, 6, 8, 10, and 12 hours.
[3] A blank urine sample was collected on Day 1 (pre-dose). Urine was collected from 0-2, 2-4, 4-8, and 8-12 hours after pledget insertion.

The results from this study are consistent with PK parameters documented in the published literature, supporting the claim of rapid absorption and metabolism of cocaine hydrochloride when administered topically to the nasal mucosa. The mean measured peak plasma concentration was 37.0 ± 17.3 ng/mL and was observed at the end of the pledget application time (20 minutes). There was wide variability in the individual measured PK parameters, which

the Applicant attributed to the low bioavailability of cocaine when administered topically to the nasal mucosa. The peak levels fell below quantitation limits (5 ng/mL) within 1.5 and 4 hours after application. The urinary recovery of cocaine and its metabolites was only 0.869% of the administered dose of 160 mg.

These results suggest that while the rate of absorption of cocaine from the nasal mucosa is rapid, only a very small percentage of the total dose is actually absorbed, measurable, and quantifiable. The recovery of cocaine hydrochloride, BE, and EME as a percentage of the dose administered were 0.1%, 2%, and 1.0% respectively. The apparent clearance of cocaine hydrochloride after intranasal administration was 3,096 ± 1,296 L/h compared to 134 L/h after intravenous cocaine administration as cited in the literature, further supporting the low systemic absorption and bioavailability of cocaine when administered topically to the nasal mucosa. The Applicant states that only four percent of the total 160 mg dose was absorbed during the 20 minute exposure time. The elimination half-life of cocaine reported in this study, 1.04 ± 0.35 h, is similar to what has been previously reported. However, the terminal elimination half-life can range from five to six hours when using a more sensitive quantitative assay, as the observed results from studies 2015013 and 2015014 demonstrated (refer to the clinical pharmacology review for additional information regarding the half-life calculation). Refer to Table 6, Summary of Plasma PK Parameters and Table 7, Summary of Urine PK Parameters.

Table 6: Summary of Plasma PK Parameters

Parameter	unit	n	Mean	SD	CV	Geomean	GeoSD
Cmax	ng/mL	30	37.0	17.3	46.7	32.8	1.69
Tmax	h	30	0.433	0.341	78.6	0.374	1.59
Clast	ng/mL	30	7.18	1.40	19.5	7.05	1.21
Tlast	h	30	2.40	0.709	29.5	2.31	1.31
AUClast	ng h/mL	30	38.4	20.2	52.5	34.2	1.61
AUCinf	ng h/mL	19	54.9	24.1	43.8	50.3	1.54
t1/2	h	25	1.04	0.349	33.7	0.975	1.44
MRT	h	19	1.56	0.45	28.9	1.50	1.34
CL/F	L/h	19	3096	1276	41.2	2843	1.54
CL/F	mL/min	19	51601	21264	41.2	47375	1.54
Vd/F	L	19	3877	1266	32.6	3680	1.40
%EXTRAP	%	19	18.7	5.90	31.6	17.7	1.41

Source: Applicant's submission, NDA 209963

Table 7: Summary of Urine PK Parameters

Total Urinary Recovery, µg[a]

	Cocaine	BE	EME
n	30	30	30
Mean	117	816	275
SD	67.1	440	113
Median	114	769	276
Geomean	96.5	713	252

a - Metabolite recoveries are expressed as cocaine equivalents

Source: Applicant's submission, NDA 209963

Urinary Recovery, % dose[a]

	Cocaine	BE	EME	Total
n	30	30	30	30
Mean	0.0729	0.534	0.262	0.869
SD	0.0419	0.288	0.108	0.362
Median	0.0714	0.504	0.263	0.804
Geomean	0.0603	0.467	0.240	0.801

a - Metabolite recoveries are expressed as cocaine equivalents

Source: Applicant's submission, NDA 209963

It has been previously demonstrated in *in vivo* and *in vitro* studies that cocaine HCl is a direct inhibitor of cytochrome P2D6. The Applicant concludes, however, that based upon the low systemic exposure after a single intranasal administration, the potential to result in clinically significant drug-drug interactions as a result of the cytochrome inhibition is quite low. There is the potential, however, for drug interactions with cholinesterase inhibitors, such as pyridostigmine, and cocaine HCl, potentially resulting in increased plasma concentrations of cocaine HCl. Whether this drug interaction is clinically relevant, is unknown at this time, however, nonclinical studies have demonstrated increased plasma cocaine HCl concentrations and toxicity in mice treated with organophosphates and in those with decreased activity of plasma cholinesterase. In vitro analysis has also demonstrated that cocaine is poorly metabolized by serum from patients with low plasma cholinesterase activity (Hoffman *et al*, 1992), suggesting that increases in systemic exposure may be observed in patients with an inherited cholinesterase deficiency, most commonly presenting as a prolonged response to succinylcholine administration. At the time of this clinical review, suggested edits to the package insert had not been finalized, including the language regarding the concomitant administration of cholinesterase inhibitors and the implications of an inherited cholinesterase deficiency.

4.6. Devices and Companion Diagnostic Issues

Cocaine topical solution is applied to the nasal mucosa via four cottonoid pledgets. The recommended cottonoid pledgets measure 1.3 x 4 cm and are to be purchased separately. The Applicant states that each pledget absorbs *approximately* one milliliter cocaine solution for a

total of up to four milliliters applied to the nasal mucosa. When all four milliliters of the solution are absorbed, the total dose for the 4% solution is 160 mg and for the 8% solution 320 mg. The Applicant clarified that during the Phase 3 study, there were cases of incomplete absorption of the entire four milliliters of solution. Table 8 lists the volumes of residual solution for all treatment groups. The actual dose administered was calculated for each patient based on the residual volume. On average, each patient received a total dose of 148 mg (3.7 mL) of cocaine HCl in the 4% treatment arm and 288 mg (3.6 mL) in the 8% treatment arm.

Table 8: Residual Study Drug Volume (mL)[a]

Statistic	Placebo (N=95)	4% RX0041-002 (N=278)	8% RX0041-002 (N=275)
Mean	0.338	0.332	0.360
Standard deviation	0.4457	0.4712	0.4807
Median	0.150	0.100	0.150
Minimum, maximum	0.00, 1.60	0.00, 2.50	0.00, 2.20

[a]Amount of study drug in the medicine cup after pledget saturation
Source: Applicant's submission, NDA 209963

4.7. Consumer Study Reviews

There is no data from a social science reviewer or the Division of Medication Error Prevention and Analysis.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 9: Phase 3 Study for Safety and Efficacy for Cocaine Topical Solution

Trial Identifier	Trial Design	Regimen/ schedule/route	Study Endpoints/Objectives	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
2013011	Phase 3, randomized, prospective, double-blind, single-dose, placebo/dose controlled, parallel-group, multicenter study	Single, topical intra-nasal administration of 4% or 8% cocaine topical solution or placebo	Primary endpoint: Pain score of 0 on VNRS during Von Frey Filament testing *and* completion of diagnostic or therapeutic procedure without additional analgesic or anesthetic medication	Cocaine or placebo topical solution administered via cotton pledgets placed in each nasal cavity and against the nasal septum for 20 minutes Follow-up nasal exams and smell assessments were conducted on study day 8	4% cocaine solution: 278 subjects 8% cocaine solution: 275 subjects Placebo solution: 95 subjects	Male and female adult subjects undergoing diagnostic or surgical procedures on or through the mucous membranes of the nasal cavities Procedures were completed without general anesthesia or intravenous sedation	17 centers all located within the United States.
Studies to Support Safety							
2015013	Single-dose, open-label, single center study	Single, topical intra-nasal administration of 4% cocaine topical solution	The primary objective was to evaluate the potential effect of renal impairment on the systemic PK of acute intranasal 4% cocaine topical solution	4% cocaine or placebo topical solution administered via cotton pledgets placed in each nasal cavity and against the nasal septum. Plasma[1] and urine[2] samples were collected at predefined time points	16 subjects total: 8 with severe renal impairment[3] and 8 with normal renal function[4]	Study population was comprised of male and female adult subjects without a known allergy to ester-based local anesthetics, matched for renal function	1 center within the United States
2015014	Single-dose, open-label, single center study	Single, topical intra-nasal administration of 4% cocaine topical solution.	The primary objective was to evaluate the potential effect of hepatic impairment on the systemic PK of acute intranasal 4% cocaine topical solution	4% cocaine or placebo topical solution administered via cotton pledgets placed in the nasal cavity and against the nasal septum. Plasma[1] and urine[2] samples were collected at predefined	24 subjects total: 9 with Grade B hepatic impairment[5]; 3 with Grade C hepatic impairment[6]; 12 without hepatic	Study population was comprised of male and female adult subjects without a known allergy to ester-based local anesthetics, matched for renal function.	1 center within the United States

Trial Identifier	Trial Design	Regimen/ schedule/route	Study Endpoints/Objectives	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				time points	impairment.		
2016017	Single-dose, partially blinded, randomized, four-period, four-treatment crossover study	Separate, single topical intranasal doses of 4% and 8% cocaine topical solution, placebo intranasal solution, and a single, oral dose of moxifloxacin Minimum washout period of 4 days	The primary objective was to exclude an effect of cocaine topical solution applied to the nasal membranes on placebo-corrected ΔQTcF exceeding 10 ms at clinically relevant plasma levels using exposure response analysis.	4% or 8% topical cocaine or placebo solution administered via cotton pledgets placed against the nasal septum and oral administration of moxifloxacin 400 mg tablet. This was a four-period, four-treatment crossover study with a four day washout period for each subject per treatment. Total study duration for each subject was 13 days. Safety assessments included physical examination, nasal cavity examination, vital sign measurements, clinical laboratory evaluations, and ECGs.	24 subjects total, each received all four treatments	Study population was comprised of healthy male and female adult (between 18-40 yrs of age) subjects without a known allergy to ester-based local anesthetics.	1 center within the United States

[1]Plasma samples were collected for PK evaluation at time 0 (pre-dose) and 7, 15, 20 (immediately after pledget removal), 30, 45, 60, 75, 90, 105 minutes and 2, 3, 4, 6, 8, 10, 12, 24, and 32 hours, based upon the beginning of dose application
[2]Urine samples were collected for determination of cocaine and its metabolites from 0-2, 2-4, 4-8, 8-12, 12-24, and 24-32 hours after dose application
[3]Estimated glomerular filtration rate of 15 to 29 mL/min/1.73 m^2
[4]Estimated glomerular filtration rate of ≥ 90 mL/min/1.73 m^2
[5]Child-Pugh Grade B classification
[6]Child-Pugh Grade C classification
]

5.2. Review Strategy

This is a 505(b)(2) NDA reliant upon the findings of safety in the published literature and the Applicant's clinical trials, including four Phase 1 studies and a single Phase 3 study.

The following sources were included in the review of this NDA application:

Studies performed by GLS

- Study 2013011: Multi-center, prospective, controlled, randomized, double-blind, single-dose, dose-controlled, parallel-group study to evaluate the safety and efficacy of 4% and 8% cocaine topical solutions vs. placebo solution in adult subjects undergoing diagnostic or surgical procedures on or through the mucous membranes of the nasal cavities.
- Study 2015016: Single-center, single-dose, open-label study to evaluate the plasma and urinary pharmacokinetics of 4% cocaine topical solution and its major metabolites in healthy male and female adult subjects.
- Study 2015013: Single-center, single-dose, open-label study to evaluate the potential effect of renal impairment on the systemic pharmacokinetics of acute intranasal cocaine topical solution in 16 male and female adult subjects, 8 with severe renal impairment and 8 with normal renal function.
- Study 2015014: Single-center, single-dose, open-label study to evaluate the potential effect of hepatic impairment on the systemic pharmacokinetics of acute intranasal cocaine topical solution in 24 male and female adult subjects; 9 with Child-Pugh Grade B hepatic impairment, 3 with Child-Pugh Grade C hepatic impairment, and 12 with normal hepatic function.
- Study 2016017: Single-center, single-dose, partially blinded, randomized, four-period, four-treatment, crossover study to exclude an effect of cocaine topical solution applied to the nasal membranes on placebo corrected ΔQTcF exceeding 10 ms at clinically relevant plasma levels in 24 healthy male and female adult subjects.

Literature provided by GLS

- The Applicant submitted 24 clinical studies from the published literature to support the safety of intranasal administration of cocaine topical solution and provided a summary review of these studies.
- The Applicant also submitted 12 published case reports associated with the intranasal use of cocaine topical solution during nasal procedures.

Review of the FAERS database

- The reports for cocaine HCl in the FDA's Adverse Event Reporting System included only cases of illicit use of this drug product. The Applicant summarized these cases in the NDA submission.

Clinical safety concerns with illicit use of cocaine HCl

- The Applicant provided FAERS database search results where cocaine HCl was reported as the primary suspect or where it was reported. Adverse events reported include the following:
  - Death
  - Cardiac, respiratory, and cardio-respiratory arrest
  - Tachycardia, arrhythmias
  - Myocardial infarction
  - Hypertension, hypotension
  - Agitation, aggression, restlessness, tremor, confusion, hallucinations, panic states
  - Hyperreflexia, seizures, coma
  - Hyperpyrexia, rhabdomyolysis
  - Nausea, vomiting, diarrhea, abdominal cramps

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Phase III Investigation of Topical Application of RX0041-002 on Safety and Efficacy in Local (Topical) Anesthesia for Diagnostic Procedures and Surgeries on or Through the Accessible Mucous Membranes of the Nasal Cavities

6.1.1. Study Design

Overview and Objective

Study 21013011, a Phase 3 study, was conducted by GLS to evaluate the safety and efficacy of cocaine topical solution as a local anesthetic in subjects undergoing diagnostic procedures and surgeries through accessible mucous membranes of the nasal cavities in adult patients. There were two objectives of this study: (verbatim)

- To evaluate the efficacy of cocaine topical solution as an anesthetic for diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities (e.g., nasal/sinus endoscopy, sinusotomy, fracture nasal turbinate(s), lysis intranasal synechia, insertion of nasal septal prosthesis, biopsy intranasal, excision of nasal polyps, excision turbinate(s), removal of foreign body intranasal, septoplasty, sinus debridement).
- To establish a safety database on at least 500 actively-treated (RX0041-002) subjects for a New Drug Application (NDA) submission.

Trial Design

The single Phase 3 study conducted by the Applicant was a randomized, prospective, double-blind, multicenter, single-dose, placebo-controlled and dose-controlled, parallel-group study to evaluate the safety and efficacy of both a 4% and 8% cocaine topical solution for local anesthesia during diagnostic procedures and surgeries through the mucous membranes of the nasal cavities. Diagnostic procedures and surgeries performed for evaluation of the safety and efficacy of the two cocaine topical solutions included nasal/sinus endoscopy, sinusotomy, fracture nasal turbinate(s), lysis intranasal synechia, insertion of nasal septal prosthesis, intranasal biopsy, excision of nasal polyps, excision turbinate(s), removal of an intranasal foreign body, septoplasty, and sinus debridement. Enrolled subjects did not receive general anesthesia or intravenous sedation for the procedure performed. The study consisted of a screening period within 14 days of a diagnostic procedure or surgery; a treatment period on the day of the diagnostic procedure or surgery (Day 1); and a follow-up visit (Day 8). Refer to Table 3, Schedule of Events, for detailed information regarding the assessments and procedures performed at each of the three visits. There were nine investigators participating in the study at 17 separate surgical centers located within the United States; there were no foreign study sites. Of note, the Applicant considered different centers under the same ownership with the same Principle Investigator(s) to be a single site and as such reported only nine investigative sites.

Subjects who met eligibility criteria were enrolled and randomized on Day 1 to receive placebo topical solution, 4% cocaine HCl topical solution, or 8% cocaine topical solution via soaked cottonoid pledgets (approximately 1.3 cm x 4 cm in size) in a 1:3:3 ratio using a randomization schedule provided by Citation Clinical Labeling Systems. Each site was assigned a block of study drug and pulled bottles in sequential order to administer to subjects. Each subject was treated with four cottonoid pledgets each soaked with 1 mL of either placebo topical solution (inactive components of the cocaine topical solutions); 4% cocaine topical solution (40 mg per mL, total 160 mg); or 8% cocaine topical solution(80 mg per mL, total 320 mg). The pledgets were allowed to saturate for 10 minutes prior to placement into each nasal cavity. Two saturated pledgets were inserted into each nasal cavity and against the nasal septum for a total treatment time of 20 minutes.

Once the pledgets were removed, sensation was assessed using a von Frey filament, 6.10 (100 g), the same one used in the screening evaluation. During the von Frey filament assessment, subjects were asked to rate the discomfort using the Visual Numeric Rating Scale (VNRS), 0 to 10. Once the pain score was recorded, the blind to placebo versus cocaine topical solution was broken to the Investigator and subject. The blind for the different concentrations of cocaine topical solution was maintained. Placebo subjects with VNRS scores > 0 were allowed to proceed with the diagnostic procedure or surgery with or without an active topical anesthetic (selected at the discretion of the investigator), but not to include cocaine. Placebo subjects were monitored in the Post-Anesthesia Care Unit (PACU) for at least 60 minutes after pledget removal. Those subjects in the cocaine topical solution treatment arms with scores > 0 on the

VNRS were initially planned to be observed for a period of time not less than 24 hours and then they would be permitted to complete the diagnostic procedure or surgery with additional topical anesthetic administration, not to include additional cocaine. Review of the submitted data from this study, however, reveals that those subjects in the cocaine treatment arms with a greater than 0 score on the VNRS were permitted to complete the diagnostic procedure or surgery on the same day, not the initially planned 24 hours later.

Subjects in the cocaine topical solution treatment arms who reported a 0 on the VNRS but experienced discomfort during the diagnostic procedure or surgery were administered additional topical anesthetics at the discretion of the investigator, but did not receive additional cocaine solution.

Choice of control group

Throughout the drug development process, the Applicant and the Agency engaged in several discussions regarding an acceptable control group for this study and the appropriateness and timing of breaking the blind to placebo versus cocaine topical solution. There was agreement that allowing subjects to undergo a surgical procedure with only a placebo anesthetic solution was unethical, however, there was also concern that unblinding to placebo versus a single dose of cocaine topical solution would not result in a clinically meaningful or relevant endpoint; e.g., cocaine's ability to anesthetize the nasal mucosa for testing with a von Frey filament is not a clinically meaningful endpoint and not a good assessment of the adequacy of surgical anesthesia.

In response to the Agency's concerns surrounding unblinding after the von Frey filament testing, the Applicant selected the additional 8% cocaine topical solution for use in this study for exploratory purposes and to maintain a blind after completion of the von Frey filament testing; subjects and investigators would remain blinded to which cocaine topical solution was administered. The efficacy analysis evaluated the anesthetic effect of the different cocaine topical solutions versus placebo solution on the von Frey filament testing only. There was no placebo (or other comparator) group for the completion of the diagnostic procedure or surgery. Efficacy results between the 4% and 8% cocaine topical solutions were not evaluated.

Diagnostic criteria

Adult subjects (≥ 18 years of age) needing a diagnostic procedure or surgery on or through the mucous membranes of the nasal cavities were eligible to participate in this study. Eligible subjects were required to feel pain in the anterior nasal septum induced by von Frey 6.10 filament testing and be able to communicate this pain sensation.

- **Inclusion criteria** (verbatim)

1. Was able to understand and comply with protocol requirements, provide written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization. Residents of California also reviewed and signed the California Subject Bill of Rights.
2. Was male or female ≥18 years of age, inclusive, at the time of dosing.
3. Had a predetermined need from a physician for a diagnostic procedure or surgery on or through the nasal mucous membranes of either one or both nostrils.
4. Had the ability to feel pain sensation normally in the anterior nasal septum, as verified by Von Frey 6.10 filament testing.
5. Had the ability to clearly communicate pain and sensation of the anterior nasal septum.
6. Females (if of child-bearing potential and sexually active) and males (if sexually active with a partner of child-bearing potential) who agreed to use a medically acceptable and effective birth control method from the first dose and for 8 days following last dose of study drug. Medically acceptable methods of contraception that could be used by the participant and/or his/her partner included abstinence, birth control pills or patches, diaphragm, intrauterine device (IUD), condom, surgical sterilization, and progestin implant or injection. Prohibited methods included: the rhythm method or withdrawal.

- **Exclusion criteria** (verbatim)

1. Had a known allergy to any ester-based anesthetics, including cocaine HCl, procaine, tetracaine, chloroprocaine, dibucaine, or benzocaine, and/or any other compounds of the drugs and/or devices that were part of this protocol. (Amide-based anesthetic allergies were NOT exclusionary. Amide-based anesthetics were: lidocaine, mepivicaine, bupivicaine, levobupivicaine, ropivicaine, etidocaine, prilocaine, and articaine).
2. Was < 18 years of age.
3. Had previously received study drug during this study.
4. Had a history of abuse of controlled substances, nasal or otherwise, or had damage to the nasal space, that in the opinion of the investigator, might interfere with the ability of the subject or investigator to judge analgesia from the study drug.
5. Had participated in an investigational study or received an investigational drug within 30 days preceding the randomization.
6. Was a pregnant or nursing mother.
7. Women of childbearing potential and men had to be using an acceptable method of contraception to avoid pregnancy throughout the study, and for women 30 days and men 90 days after the last dose of investigational product in such a manner that the risk of pregnancy and risk to pregnancy was minimized.
8. Suffered from a condition, other than the need for a diagnostic procedure or surgery on or through the nasal mucous membranes, which in the opinion of the Investigator, would compromise the safety of the subject, the quality of the data, or the normal wound healing process.
9. Had severely traumatized mucosa or sepsis in the nasal cavity.
10. Had experienced a seizure while taking isoniazid (INH), phenothiazines, chlorpromazine, thioridazine, theophylline, or tricyclic antidepressants such as amitriptyline.
11. Used any analgesic up to 2 days prior to Day 1 (procedure). This included nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, indomethacin, sulindac, tolmetin, ketoprofen, flurbiprofen, and naproxen, opioids such as codeine, hydrocodone,

hydromorphone, morphine, oxycodone and aspirin, or acetaminophen.

12. Used any serotonin–norepinephrine reuptake inhibitors (SNRIs)/selective serotonin re-uptake inhibitors (SSRIs) up to7 days prior to screening or had a need to use these drugs during the screening period and throughout the time period of the trial.
13. Used monoamine oxidase (MAO) inhibitor drugs up to14 days prior to screening or had a need to use these drugs during the Screening period and throughout the time period of the trial.
14. Had experienced a seizure while taking INH, phenothiazines, chlorpromazine, thioridazine, theophylline, or tricyclic antidepressants such as amitriptyline. Had a history of seizure, with the exception of febrile seizures.
15. Had a history of myocardial infarction, coronary artery disease, congestive heart failure, irregular heart rhythm, or uncontrolled hypertensions (defined as an average systolic blood pressure [SBP] ≥140 mmHg or an average diastolic blood pressure [DBP] ≥90 mmHg at the dosing visit) or was taking monoamine oxidase inhibitors. Uncontrolled hypertension was defined as SBP greater than or equal to 140 mm Hg or DBP greater than or equal to 90 mm Hg.
16. Had a known personal or family history of hereditary pseudocholinesterase deficiency. Study participants were screened by asking about personal or family history of anesthetic reaction, anesthetic death, and previous diagnosis of pseudocholinesterase deficiency in a relative or personally. Subjects identified with pseudocholinesterase deficiency were at risk for delayed recovery with certain anesthetics (eg, succinylcholine and ester-based anesthetics).
17. Had a known personal or family history of pheochromocytoma. Study participants were specifically asked if they had been treated for a pheochromocytoma previously or if they had a family member who had been diagnosed with pheochromocytoma (since 10% of these are familial).
18. Had a known personal or family history of adrenal tumor.
19. Had used amphetamines, stimulant prescription and nonprescription products such as catecholamines (direct and indirect acting sympathomimetics), bronchial inhalers containing sympathomimetics (epinephrine or other beta-receptor agonist) or herbal products in the 2 days prior to screening or had a need to use these drugs during the course of the study.
20. Had Screening 12-lead ECG findings of any abnormalities. Generally, these were current or prior myocardial ischemia or infarction, dysrhythmia, or risk of serious dysrhythmia (such as prolonged QT interval). An exception to this was if sinus bradycardia or sinus tachycardia was present, and the Investigator determined whether this finding was clinically relevant and exclusionary.
21. Had a positive urine pregnancy test at Screening or Day 1.
22. Had a positive urine test result for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates and oxycodone) at Screening or Day 1.
23. Hemoglobin not within normal limits for the reference laboratory.
24. White blood cells (WBC) not within normal limits for the reference laboratory.
25. Platelets not within normal limits for the reference laboratory.
26. Serum Potassium not within normal limits for the reference laboratory.
27. Serum Alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin exceeding 2X ULN for the lab's reference values.
28. Is not suitable for entry into the study in the opinion of the Investigator.

Dose selection

The 4% cocaine topical solution was selected for evaluation in this Phase 3 study based upon prior clinical experience and articles in the published literature supporting a therapeutic, anesthetic, benefit during nasal diagnostic procedures or surgeries. The 8% cocaine topical solution was considered exploratory. Information in the published literature suggests that 4%, 6%, and 10% solutions have been used clinically with varying rates of success.

Study treatments

The study treatments include a single administration of either a placebo solution, 4% cocaine topical solution, or 8% cocaine topical solution. The treatments were administered via study personnel at the investigative centers and recorded in the CRF.

Assignment to treatment

Subjects who met all eligibility criteria were randomized to receive either 4% or 8% cocaine topical solution or placebo topical solution in a 3:3:1 ratio. Each study site was assigned a block of study drug and bottles were pulled in sequential order for subject administration. A copy of the randomization code was provided in the NDA submission.

Blinding

Blinding related to the dose of cocaine topical or placebo solution was maintained by use of identically packaged bottles. After the von Frey filament assessment and collection of the subject-reported pain score on the VNRS, the blind to placebo versus cocaine topical solution was broken. Blinding of the dose of cocaine topical solution, 4% versus 8%, remained unbroken. All subjects, including those in the cocaine topical solution groups, with greater than 0 self-reported pain scores on the VNRS were given the opportunity to receive an active anesthetic before undergoing the diagnostic procedure or surgery or to proceed without one. They first, however, underwent recovery for at least 60 minutes post-pledget removal, which consisted of continuous ECG and pulse oximetry monitoring and blood pressure measurements every 5 minutes. All subjects, analgesic successes and failures, underwent the same post-procedural follow-up visits and assessments.

In the event of a medical emergency which required breaking the blind prior to scoring discomfort in response to the von Frey filament test, the sealed disclosure on the label containing the emergency identification of the package contents was to be opened by the investigator and reported to the Medical Monitor within 24 hours. The blind for 4% versus 8% cocaine topical solution remained unbroken until completion of the study.

Refer to section 6.1.2 Study Results, Protocol Violations/Deviations for further discussion regarding the instances when the blind was broken prematurely, the unblinding time was not

recorded, or the unblinding time and collection of subject-reported pain score was the same.

Dose modification, dose discontinuation

The study medications were administered in the clinic by study personnel. There were no dose modifications or discontinuations.

Procedures and schedule

Table 10 represents the schedule of events for the Phase 3 trial.

Table 10: Schedule of Events

STUDY PROCEDURES	Screening (Day -14 to -1)	Treatment (Day 1)	Follow-up Visit (Day 8)
Informed consent	X		
Eligibility (inclusion/exclusion)	X	X[a]	
Prior medication assessment	X	X[a]	
Medical/Family Medical history	X		
Vital signs	X	X[b]	
Physical examination	X[c]		
Clinical laboratory tests	X		
Pregnancy test (females)[d]	X	X	
Urine drug screen[e]	X	X	
Safety 12-lead electrocardiogram (Holter monitor)		X[f]	
ECG	X		
Von Frey Monofilament Test	X	X	
Study drug application[g]		X	
Pulse Oximetry		X[f]	
Von Frey Filament Test[h]		X	
Visual Numeric Rating Scale (VNRS)[i]		X	
Drug Application Site Assessment (Nasal Exam)		X	X
Assessment of Smell		X	X
Adverse event assessment		X	X
Concomitant medication assessment	X	X	X

[a] Eligibility and prior medications were reviewed and updated as needed.

[b] Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) were measured prior to each application of the study drug, continuously during the nasal application of study drug and throughout the diagnostic or surgical procedure in RX0041-002-treated subjects and one hour from the time the pledgets were removed. Blood pressure and heart rate every 5 minutes. Respiratory rate and temperature every 15 minutes.
[c] The physical examination included measurement of height and weight.
[d] A serum pregnancy test was done for all females of childbearing potential at Screening and a urine pregnancy test was done for all females of childbearing potential on prior to dosing with study drug on Day 1.
[e] The urine drug screen tested for drugs of abuse (cannabinoids, cocaine metabolites, amphetamines, barbiturates, oxycodone and opiates).
[f] ECG and pulse oximetry monitoring were conducted continuously during the nasal application of study drug, and throughout the diagnostic or surgical procedure in the RX0041-002treated subjects.
[g] Study drug was applied using a cotton pledget for 20 minutes prior to the surgery or diagnostic procedure.
[h] The nasal site was tested with a Von Frey Filament (6.10, 100 gm) following the application of study drug.
[i] Pain was assessed following application of study drug based on the Von Frey Filament Test.

Source: Applicant's submission, NDA 209963

Dietary restrictions/instructions

There were no dietary restrictions or instructions with the exception of what was outlined in the diagnostic exclusion criteria.

Concurrent medications

Patients were excluded from participation in this study if:

1. They had received the study drug during this study or had participated in an investigational study within 30 days preceding randomization.
2. They had a history of controlled substance abuse, either ongoing or historically.
3. They had used any analgesic medication up to 2 days prior to Day 1 (procedure day). This included nonsteroidal anti-inflammatory drugs (NSAIDS), aspirin, and acetaminophen.
4. They had used any serotonin-norepinephrine reuptake inhibitors (SNRIs)/ selective serotonin reuptake inhibitors (SSRIs) up to 7 days prior to screening or had a need to use these medications during the screening period and throughout the time period of the trial.
5. They had used monoamine oxidase inhibitors (MAOIs) up to 14 days prior to screening or had a need to use these medications during the screening period and throughout the time period of the trial.
6. They had used amphetamines, stimulant prescription and nonprescription products such as catecholamines (direct and indirect acting sympathomimetics), bronchial inhalers containing sympathomimetics (epinephrine or other beta-receptor agonist) or herbal products in the 2 days prior to screening or had the need to use these medications during the screening period and throughout the time period of the trial.

The above list of prohibited medications was reasonable and appropriate given the mechanism of action of cocaine. Prohibited concomitant use of sympathomimetic, stimulant, and amphetamine medications was necessary based upon concern for significant increases in measured hemodynamic parameters. Similarly, the concomitant use of MAOIs can also result

in unstable hemodynamic parameters potentially leading to serious cardiovascular complications. The use of analgesic medications, including over the counter formulations, may have impacted the efficacy results of this study, thus their prohibition was also appropriate.

Treatment compliance

The treatment compliance was 100% due to the study design. This study involved administration of a single dose of cocaine to the nasal mucosa by study personnel in an ambulatory surgical center or clinic. The study did not involve patient-administered medication.

Rescue medication

Subjects in both treatment groups and the placebo group who reported greater than a 0 on the VNRS during the pre-procedure von Frey filament test were permitted to complete their diagnostic or surgical procedure with additional topical anesthetic, selected at the discretion of the investigator. The individual investigators determined the need for additional analgesic medication during the diagnostic or surgical procedures in the cocaine treatment groups based upon his/her clinical impression of patient discomfort. This clinical impression was not based on standardized patient feedback or reported pain scores. Additional medications were administered at the discretion of the investigator and not standardized. No subject received additional cocaine for successful completion of the procedure.

Rescue medications included lidocaine, lidocaine with phenylephrine, xylocaine with epinephrine, benzocaine, or sliver nitrate, all standard but unapproved medications for this indication.

Subject completion, discontinuation, or withdrawal

All subjects enrolled and randomized received a study drug or placebo and completed the surgical procedure. Of the 648 patients in the three groups, only a single patient in the 4% cocaine topical solution group was lost to follow-up.

Study Endpoints

The primary efficacy endpoint for this trial was analgesic success immediately after application of study drug and sustained throughout the diagnostic or surgical procedure for each nostril that received study drug application. Analgesic success, however, was defined differently for the placebo and cocaine subjects. Analgesic success for the subjects in the placebo group was defined as a score of 0 on the VNRS after von Frey Filament testing. Analgesic success for the subjects in the cocaine treatment groups was defined as a score of 0 on the VNRS after von Frey Filament testing *and* sustained analgesia throughout the diagnostic or surgical procedure as demonstrated by not requiring additional anesthetic or analgesic medication.

Statistical Analysis Plan

The primary efficacy endpoint was evaluated as follows:

- Placebo vs. 4% cocaine topical solution
- Placebo vs. 8% cocaine topical solution (*exploratory*)
- There was no analysis performed between the two active treatments

A subject was considered a treatment success if both of the following criteria were met:

- Prior to the surgery, the subject scored 0 on the VNRS during the von Frey filament testing, *and*
- During the diagnostic or surgical procedure, no further analgesic or anesthetic medication was required. The need for additional medication was determined by the individual investigator's assessment of the subject's discomfort. No further subject-reported pain scores were collected during this portion of the protocol.

If either of the above criteria were not met, the subject was considered a treatment failure. The proportion of successes between the placebo and each active treatment group was compared using a two-tailed Fisher's Exact Test, tested at the alpha=0.05 level of significance. The primary comparison tested was 4% cocaine topical solution versus placebo. The 8% cocaine topical solution versus placebo was considered exploratory as previously discussed.

Subgroup analyses were conducted on the following subject populations:

- sex
- race (black, white, and other races pooled)
- age
- weight
- type of procedure

There were no adjustments for missing data and there were no interim analyses conducted.

Protocol Amendments

The final IND protocol was dated July 20, 2014. There were two protocol amendments and two administrative changes.

- Amendment #1, dated August 18, 2014
  - The purpose of this amendment was to remove a sentence from exclusion #3 that was stated later in the protocol, remove "MAO inhibitors" from exclusion #11, update the urine drug screen to be more relevant to the subject population, remove exclusions 28-30, remove serology, clarify bullet point 3 in section 10.2, and clarify that subjects who failed screening could be rescreened at the judgement of the investigator. (Source NDA 209963, Study Report Body 2013011, verbatim)
- Amendment #2, dated November 25, 2014

  - The purpose of this amendment was to clarify multiple paragraphs, update exclusion #11 to exclude the use of analgesics up to 2 days prior to Day 1 instead of screening, clarify that uncontrolled hypertension in exclusion #15 was based on blood pressure at the dosing visit, remove specific laboratory values mentioned in exclusions 23-26, and correct the assumed underlying success rate for the combined first and second phases of the study for the RX0041-002 (4 or 8%) groups. (Source NDA 209963, Study Report Body 2013011, verbatim)
- Administrative change #1, dated December 13, 2014
  - This administrative change was to clarify Exclusion 19 and Section 9.10.2 Prohibited Therapies. Protocol Amendment #2, dated November 25, 2014, read: "Has used amphetamines, stimulant prescription and nonprescription products such as catecholamines (direct and indirect acting sympathomimetics), bronchial inhalers containing sympathomimetics (epinephrine or other beta-receptor agonists) or herbal products in the 2 days prior to screening or has a need to use these drugs during the course of the study."
  - The above statement in Protocol Amendment #2 was changed to read as follows: "Has used amphetamines, stimulant prescription and nonprescription products such as catecholamines (direct and indirect acting sympathomimetics), or herbal products in the 2 days prior to screening or has a need to use these drugs during the course of the study. Bronchial inhalers containing sympathomimetics (epinephrine or other beta-receptor agonist) may not be used in the 2 days prior to study drug application or during the course of the study."
- Administrative change #2, dated March 20, 2015
  - This administrative change was to clarify Section 10.2 Double-Blind Treatment (Day 1). The Protocol Amendment #2, dated November 25, 2014, read: "Perform application site assessment" at the end of the Day 1 treatment period.
  - The Day 1 assessment was an error and was removed under this Administrative change. The original intent was to capture safety data through a nasal examination beginning with the baseline (pre-treatment) assessment and then a follow-up assessment on Day 8 of the protocol. An additional assessment on Day 1, the treatment day, would be impacted by tissue damage caused by the diagnostic or surgical procedure.

Data Quality and Integrity: Sponsor's Assurance

As previously mentioned under Executive Summary, Section 1.2 Conclusions on Substantial Evidence of Effectiveness, the Applicant's original NDA submission received on November 23, 2016 contained incorrect data listings for the cocaine treatment arms. On April 4, 2017, the Applicant notified the Agency of a database transposition error that occurred during the migration of the randomization code into the database at the Contract Research Organization (CRO). This error was detected during a clinical field inspection for this NDA when the inspector queried as to why a subject's disposition was listed in the 2013011 Clinical Study Report (CSR) as having received 4% cocaine topical solution but the assigned randomization code indicated

receipt of 8% cocaine topical solution. The Applicant's representative then queried the CRO and the Chief Information Officer of the CRO stated that a definition error had occurred during the migration of the randomization into the database and the 4% and 8% treatment group assignments had been transposed in the database (Source: NDA 209963 communication cover letter dated April 17, 2017). This data transposition resulted in incorrect initial results, conclusions and summaries from the 2013011 study and required re-analysis of the correct group data and resubmission of those key elements to the NDA application.

Subsequent to detection of this error, the Applicant notified FDA and requested a teleconference, held on April 6, 2017, to further discuss the necessary steps to resolve the error and permit continued review of the NDA. The Applicant submitted a Corrective and Preventive Action (CAPA) Report on April 19, 2017, further explaining the database transposition. During the teleconference and outlined in the CAPA, the Applicant assured the Agency that the transposition of the randomization code was the only error that occurred in collection and reporting of their data and that this error affected only the Phase 3, 2013011, study. The data collection and reporting from the four Phase 1 studies was not impacted by this error.

On May 1, 2017, FDA received revised data listings, clinical summaries and conclusions, and responses to outstanding 74-day letter issues as well as clinical information requests.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant noted on the title page of the protocol for Study 2013011 that "this trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline".

Financial Disclosure

William Reightler, Vice President of Regulatory Affairs, signed FDA form 3454 on November 8, 2016, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

Table 11 outlines the disposition of all subjects in the Phase 3 trial.

Table 11: Subject Disposition, Study 2103011

Study Population	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8% RX0041-002 (N=275) n (%)	Overall (N=648) n (%)
Number of Subjects Enrolled				925
Number of Subjects Completed Study	95 (100.0%)	277 (99.6%)	275 (100.0%)	647 (99.8%)
Number of Subjects Discontinued from Study	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
LOST TO FOLLOW-UP	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)

Source: Applicant's submission, NDA 209963

There was a single subject (subject # (b) (6)) in the 4% cocaine treatment arm lost to follow-up after treatment on Day 1. The subject was a 21 year old Caucasian male with a past medical history of asthma who underwent nasal endoscopy on (b) (6), under topical anesthesia with 4% cocaine topical solution. He had no reported adverse events on the day of treatment and did not require additional topical anesthesia. Collected vital sign data were stable throughout the procedure and recovery phase. There is no indication this subject withdrew from the study due to safety reasons.

Protocol Violations/Deviations

There were numerous protocol deviations during the conduct of this study. The three investigative sites with the highest number of protocol deviations occurred under the same Principle Investigator, Dr. Robert Puchalski, M.D. of South Caroline ENT Allergy and Sleep Medicine. The study sites and the protocol deviation percentages are as follows:

- Study site 701 had 54.2% protocol deviations in 47.9% of treated subjects
- Study site 702 had 63.9% protocol deviations in 50% of treated subjects
- Study site 703 had 50.9% protocol deviations in 41.1% of treated subjects

Refer to Table 4, Clinical Study Sites, for additional listings.

The majority of protocol deviations across all investigative sites appear to involve missing vital sign or laboratory data, out-of-range vital sign collection, and missing signed waivers. Across all treatment groups, there were a total of 16 instances of reported unblinding that occurred prior to the von Frey filament testing and 19 instances where there was no recorded time of the unblinding. Additionally, over half of the subjects in all three treatment groups were unblinded at the same time as the von Frey filament test, which is possible if the two events did occur in the same 60 seconds.

Major protocol deviations that involved the use of a prohibited medication are listed in Table

12 below. The treatment assignments in black font have not been corrected by the Applicant for the data transposition error. The treatment assignments corrected by this reviewer are in blue font.

Table 12: Major Protocol Deviations Involving a Prohibited Medication

Subject number	Group	Prohibited Medication
(b) (6)	8% (4%) RX0041-002	Lidocaine IM injection single dose prior to abscess lancing
	8% 4% RX0041-002	Lortab (hydrocodone bitartrate/acetaminophen) PRN for neck pain
	8% (4%) RX0041-002	Fioricet (butalbital/acetaminophen/caffeine) PRN for abdominal pain
	8% (4%) RX0041-002	Chlorpheniramine/hydrocodone PRN for postnasal drainage
	4% (8%)RX0041-002	Acetaminophen single dose for post-op pain
	4% (8%) RX0041-002	Ultram (tramadol) PRN for arthritis
	4% (8%) RX0041-002	Ultram (tramadol) PRN for fibromyalgia
	4% (8%) RX0041-002	Ultracet (tramadol/acetaminophen) PRN for generalized pain

PRN=as needed.

Source: Applicant's submission, NDA 209963

Missing vital sign data

There appears to be approximately 22% of vital sign data that was not captured in subjects in the 4% cocaine topical solution treatment group. For example, recorded heart rate data should include measurements every five minutes. Data collected at this frequency would result in each subject having a minimum of three measurements for every 15 minute time period, suggesting that for 278 subjects, there should be 834 recorded heart rate measurements. The Applicant included at most, 649 recorded measurements for any 15 minute time period of HR recording. The table below summarizes the frequency of missing heart rate data at each 15 minute time period for subjects in the 4% treatment group. The table includes only data points up to 60 minutes post-pledget removal, the requisite time per study protocol, for recovery monitoring. The numbers of missing vital sign data was similar for the 8% cocaine treatment group and the placebo group.

Table 13: Summary Table of Missing HR Data, Study 2013011

Time Period	Number of Data Point Recorded (% of Missing Values)
Pre-dose	782 (6.2%)
0 to ≤15 min	646 (22.5%)
15 to ≤30 min	642 (23%)
30 to ≤45 min	647 (22.4%)
45 to ≤60 min	649 (22.2%)

The concern regarding the missing data was outlined in the 74-day letter to the Applicant. The response to this concern was addressed in the NDA resubmission that was received on May 1, 2017. The Applicant's additional analysis involved evaluation of the number of data points captured for every 5 minute time period. The Applicant stated that the overall number of missing data was low and that the interpretation of the data captured adequately characterizes the hemodynamic profile during and after topical cocaine administration.

Table 14: Demographic and Baseline Characteristics

Characteristic	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8% RX0041-002 (N=275) n (%)	Overall (N=648) n (%)
Age (Yrs)				
Mean	44.9	42.7	45.3	44.1
SD	16.9	16.6	15.3	16.1
Median	46	42	45	44
Minimum, Maximum	18, 80	18, 86	17, 83	17, 86
Sex				
Female	55 (57.9%)	170 (61.2%)	167 (60.7%)	392 (60.5%)
Male	40 (42.1%)	108 (38.8%)	108 (39.3%)	256 (39.5%)
Ethnicity				
Hispanic or Latino	10 (10.5%)	23 (8.3%)	12 (4.4%)	45 (6.9%)
Not Hispanic or Latino	85 (89.5%)	254 (91.4%)	263 (95.6%)	602 (92.9%)
Race				
American Indian or Alaska	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Asian	1 (1.1%)	1 (0.4%)	3 (1.1%)	5 (0.8%)
Black or African American	16 (16.8%)	49 (17.6%)	51 (18.5%)	116 (17.9%)
Other	3 (3.2%)	7 (2.5%)	4 (1.5%)	14 (2.2%)
White	75 (78.9%)	220 (79.1%)	216 (78.5%)	511 (78.9%)
Height (cm)				
Mean	168.73	167.89	168.47	168.26
SD	9.77	10.93	10.56	10.6
Median	170	167.6	168	168
Minimum, Maximum	144.7, 195.5	139.0, 213.3	132.1, 198.1	132.1, 213.3
Weight (kg)				
Mean	83.69	81.57	83.94	82.88
SD	22.91	21.45	22.99	22.32
Median	81	79.8	80	80
Minimum, Maximum	46.0, 175.0	40.4, 189.0	45.0, 183.3	40.4, 189.0
BMI (kg/m^2)				
Mean	29.24	28.92	29.58	29.25
SD	6.91	7.11	7.79	7.37
Median	28.40	27.15	28.10	27.80
Minimum, Maximum	15.5, 57.0	17.2, 64.5	16.6, 70.1	15.5, 70.1

Note: Subjects who had missing data were included in the denominator for percentage calculation.
Source: Applicant's submission, NDA 209963

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The percentage of patients with a previous medical condition was similar across all treatment

groups and is as follows:

- 94.7% in the placebo group
- 92.4% in the 4% cocaine topical solution group
- 94.2% in the 8% cocaine topical solution group

The most common prior medical conditions were allergic rhinitis, sinusitis, and nasal septum deviation. Other, common, non-ENT related medical conditions across all three treatment groups included GERD, hyperlipidemia, type 2 diabetes mellitus, asthma, and headache.

Prior medications were taken with the following frequency:

- 14.7% of subjects in the placebo group
- 24% of subjects in the 4% cocaine topical solution group
- 24.5% of subjects in the 8% cocaine topical solution group

The most common prior medication taken in the placebo and 4% cocaine topical solution groups was ibuprofen/Motrin. The most common prior medication taken in the 8% cocaine topical solution was acetaminophen with oxycodone.

Corticosteroids were the most common concomitant medications taken across all three treatment groups.

None of the prior or concomitant medications were thought to influence the efficacy or safety outcomes of the study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

[The subjects were administered the treatment topical solutions by study personnel in a clinic setting; therefore, compliance with the treatment medication was 100%.

For concomitant medications, subjects were permitted to receive previously prescribed medications with the exception to those specifically listed in the exclusion criteria.

Rescue medications were administered to the treatment failures, defined as those subjects reporting a greater than 0 pain score on the VNRS or those subjects who required additional anesthetic medication during the procedure. The treatment failures requiring additional medication(s) were as follows:

- 55 of the 95 placebo subjects (57.9%) received additional anesthetic medications. Some placebo subjects received more than one additional anesthetic medication
- 4 of the 278 subjects (1.4%) in the 4% cocaine topical solution group received additional anesthetic medications
- 1 of the 275 subjects (0.36%) in the 8% cocaine topical solution group received an additional anesthetic medication

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was analgesic success, defined by the following criteria:

- Subject had a score of 0 on the VNRS based on the von Frey filament test prior to the diagnostic procedure or surgery, *and*
- Subject had no need for further medication (with the exception of antibiotics or cardiac medications) during the diagnostic procedure or surgery

Of note, in the Applicant's original NDA submission there was an additional statement clarifying this second analgesic criterion and how the determination for additional anesthetic administration was made. It read, *"investigator/physician based upon his/her clinical impression of the presence of pain or excessive bleeding"*. In the resubmission received on May 1, 2017, this statement was deleted. There were no additional pain scores collected for subjects during the diagnostic procedure or surgery.

Table 15 describes the analgesic success and failure rates for all treatment groups and includes:

- those subjects who failed because they reported >0 pain score on the VNRS during the von Frey filament testing *and*
- those subjects who reported a pain score = 0 on the VNRS during the von Frey filament testing but required additional medication during the diagnostic procedure or surgery

Table 15: Analgesic Success Rates

	Placebo (N=95)	4% RX0041-002 (N=278)	8% RX0041-002 (N=275)
Event	**n (%)**	**n (%)**	**n (%)**
Success	9 (9.5%)	215 (77.3%)	223 (81.1%)
Failure	86 (90.5%)	63 (22.7%)	52 (18.9%)
P-value*		<0.0001	<0.0001

*Fisher's Exact Test. Pairwise comparison on active drug to placebo.
Source: Applicant's submission, NDA 209963

The majority of the treatment failures occurred during the von Frey filament testing, as outlined in Table 16.

Table 16: Analgesic Failures by VNRS Pain Scores and Need for Additional Medication

Treatment Group	Pain score >0 on VNRS during vFFT* (n)	Pain score >0 on VNRS during vFFT *and* required additional medication during procedure/surgery (n)	Pain score=0 on VNRS during vFFT but required additional medication during procedure/surgery (n)
Placebo	86	55	–
4% cocaine	62	3	1
8% cocaine	51	0	1

*von Frey Filament Test

Of the 63 treatment failures in the 4% cocaine topical solution group, four required additional anesthetic medication to successfully complete the procedure. As indicated in Table 16, only a single subject in this group who required additional medication reported a 0 on the VNRS during von Frey filament testing. Stated another way, 59 of the 63 treatment failures defined by their >0 pain scores on VNRS were able to complete the diagnostic procedure or surgery *without* additional anesthetic medication administration.

Similar results were reported for the 8% treatment group. Of the 52 treatment failures in the 8% treatment group, 51 reported a >0 pain score on the VNRS during von Frey filament testing but none of those required additional anesthetic medication for successful completion of the procedure. The subject who required additional medication for successful completion, reported a 0 on the VNRS during von Frey filament testing but experienced discomfort during the procedure.

There was a slight dose response (77.3% to 81.1%) observed for analgesic success between the 4% and 8% cocaine topical solutions, however, the study was not powered to evaluate for statistically significant differences in efficacy between the two cocaine treatment groups.

Data Quality and Integrity – Reviewers' Assessment

As previously mentioned, the Applicant had a major data transposition error that resulted in the cocaine treatment groups having incorrect, transposed data submitted in the original NDA received on November 23, 2016. This data transposition involved the randomization code for the two treatment groups being incorrectly recorded such that those subjects originally coded as receiving 4% topical solution actually received 8% and vice versa. This error was detected during a routine investigative site inspection and was traced back to the CRO. The Applicant has assured FDA that the transposition of randomization codes was the only error in the data submission.

During my initial review of the NDA submission in preparation for filing, I did notice several inconsistencies in the data that did not support a dose response for the two different

concentrations, which was not explained in the clinical summaries. Additionally, it appeared that the observed changes in vital sign data were greater in the 4% cocaine topical solution group than in the 8% cocaine topical solution group. It is concerning that the Applicant did not appreciate these inconsistencies and further inquire into potential causes prior to detection of the data transposition error. The 8% cocaine topical solution is ***double*** the concentration of the 4% cocaine topical solution and yet there was no explanation as to how the results of the Phase 3 study were not aligned with previous studies in the published literature demonstrating improved efficacy and greater observed hemodynamic changes in topical solutions with higher cocaine concentrations.

An additional concern unrelated to the data transposition error is the frequency of missing data, previously discussed. Refer to section 6.1.2 Study Results, Missing Vital Sign Data for a more detailed discussion.

Efficacy Results – Secondary and other relevant endpoints

There were no secondary or other relevant efficacy endpoints in this study.

Dose/Dose Response

A slight dose response (from 77.3% to 81.1%) was observed for analgesic success between the 4% and 8% cocaine topical solutions, however, the study was not powered to evaluate for statistically significant differences in efficacy between the two cocaine treatment groups.

Persistence of Effect

The 4% cocaine topical solution provided adequate anesthesia for the duration of the diagnostic procedure or surgery in all but four subjects. The procedures performed were of relatively short duration. Most nasal endoscopies were performed in under five minutes. The longest procedure duration was 18 minutes in this study. These results are supported by pharmacokinetic information in the published literature suggesting the elimination half-life in plasma is approximately 1 hour.

Additional Analyses Conducted on the Individual Trial

The Applicant performed additional sensitivity analyses of the primary efficacy endpoint to address concerns conveyed in the Agency's 74-day letter regarding the following:

a) The timing of the unblinding to placebo vs. topical cocaine treatment – this additional analysis, which biased the results against analgesic success for the cocaine treatment groups by not including the need for additional medication in the placebo group, did demonstrate that cocaine was significantly more effective than placebo on the primary efficacy endpoint. The mild dose response observed in the primary efficacy analysis also is noted here. Refer to Table 17.

Table 17: Sensitivity Analysis of Analgesic Success Rates (VNRS=0 for placebo only) in Phase 3, 2013011, Study

	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8% RX0041-002 (N=275) n (%)
Success	14 (14.7)	215 (77.3)	223 (81.1)
Failure	81 (85.3)	63 (22.7)	52 (18.9)
P-value*		<0.0001	<0.0001

Source: t-14-2-success.
*Fisher's Exact Test. Pairwise comparison on active drug to placebo. VNRS=visual numeric rating scale.
Source: Applicant's submission, NDA 209963

b) The apparent minimally invasive nature of the surgical procedures performed – this additional analysis was performed to address concerns surrounding the apparent minimally invasive nature of surgical procedures performed and indicates that rates of analgesic success are similar between nasal endoscopy and other procedures and the observed slight dose response between the two cocaine solutions is maintained.

Table 18: Sensitivity Analysis of Analgesic Success Rates in Nasal Endoscopy Alone and in Other Procedures

Type of Procedure	Placebo, n (%)	4% topical cocaine solution, n (%)	8% topical cocaine solution, n (%)
Nasal endoscopy alone	5 (9.6)	124 (73.4)[a]	129 (78.7)[a]
Other procedures	4 (9.3)	91 (83.5)[a]	94 (84.7)[a]

[a]p<0.0001
Adapted from Applicant's submission, NDA 209963

7 Integrated Review of Effectiveness

7.1. Additional Efficacy Considerations

7.1.1. Considerations on Benefit in the Postmarket Setting

Cocaine topical solutions are marketed unapproved products in the United States that have not previously been monitored for safety and efficacy, beyond a limited number of published clinical trials and case reports. The most widely published information regarding cocaine is in

the setting of illicit use, which is not completely relevant to its use in the surgical setting, particularly regarding the safety profile. Approval of this product would allow FDA to monitor the post-marketing data of this product.

7.1.2. Other Relevant Benefits

It may not be of primary concern in approvability of this application, however, it is worth noting that there currently are no FDA-approved products for use as topical anesthetics during surgery on or through the nasal cavities. Many local anesthetics are currently used in this capacity, but FDA has not evaluated the safety or efficacy of these products. Approval of topical cocaine would offer clinicians an FDA-approved product for use in these types of surgical procedures.

7.2. Integrated Assessment of Effectiveness

The results from the single Phase 3 study conducted by the Applicant did demonstrate efficacy on the tested primary endpoint of analgesic success. However, there are three issues that impact the interpretation of the efficacy results and, therefore, impact the labeling indication. First, the placebo comparison of clinical responsiveness to von Frey filament testing is not an entirely adequate surrogate for surgical discomfort, as most nasal procedures would result in a measurable increase in reported pain when compared to testing with a von Frey filament. Second, while the second primary endpoint of no additional anesthetic medication administration was also met, the diagnostic procedures and surgeries performed were relatively non-invasive and potentially less painful than other commonly performed nasal procedures. Table 19 summarizes the number and percentages of the procedures performed by treatment group in the overall study population. The table indicates that the vast majority of evaluated procedures were nasal endoscopy, which comprised 60.8% of all procedures performed in subjects in the 4% treatment group. The total number of endoscopic procedures performed in the 4% treatment group without an additional surgical procedure, comprised 86% of evaluated procedures. Only 14% of performed procedures are considered invasive and likely more painful.

And third, 40 of the 95 placebo subjects (42.1%) underwent the diagnostic procedure or surgery without additional anesthetic medication beyond the placebo solution; i.e., no anesthetic was used for the performance of the procedure in these subjects. Additionally, the overwhelming majority of analgesic failures in the cocaine treatment groups (either VNRS >0 during von Frey filament testing or discomfort during the procedure), underwent the procedure without additional medication administered. Fifty nine of the 63 subjects (93.6%) in the 4% treatment group and 51 of the 52 subjects (98.1%) in the 8% treatment group completed the surgical procedure without additional anesthetic or analgesic medication.

The interpretation of the results with consideration of the above caveats, further supports the conclusion that the efficacy of cocaine topical solution as an anesthetic was demonstrated in non-invasive, less painful procedures, and the label should reflect the tested surgical

population.

Table 19: Summary of Benign Diagnostic Procedures and Surgeries Performed

Procedure	Placebo (N=95) n (%)	4% Cocaine HCl (N=278) n (%)	8% Cocaine HCl (N=275) n (%)
Nasal Endoscope Alone			
Nasal Endoscopy	52 (54.7)	169 (60.8)	164 (59.6)
Other Procedures			
Nasal Laryngoscopy	14 (14.7)	43 (15.5)	33 (12.0)
Nasopharyngeal Laryngoscopy	12 (12.6)	18 (6.5)	23 (8.4)
Nasal Debridement	3 (3.2)	15 (5.4)	19 (6.9)
Nasal Endoscopy with Debridement	0 (0.0)	9 (3.2)	11 (4.0)
Intraturbinate DepoMedrol Injection	5 (5.3)	7 (2.5)	7 (2.5)
Laryngoscopy	3 (3.2)	6 (2.2)	5 (1.8)
Transnasal Esophagoscopy	2 (2.1)	2 (0.7)	1 (0.4)
Turbinate Reduction	1 (1.1)	2 (0.7)	3 (1.1)
Nasal Endoscopy with Polypectomy	0 (0.0)	2 (0.7)	2 (0.7)
Sinuplasty	0 (0.0)	0 (0.0)	2 (0.7)
Nasal Endoscopy and Stroboscopy	0 (0.0)	0 (0.0)	1 (0.4)
Nasal Cauterization	0 (0.0)	0 (0.0)	1 (0.4)
Nasal Endoscopy and Nasal Laryngoscopy	0 (0.0)	1 (0.4)	0 (0.0)
Nasal Stroboscopy	1 (1.1)	0 (0.0)	0 (0.0)

Source: Applicant's submission, NDA 209963

A final consideration when evaluating the efficacy of cocaine topical solution is the true clinical setting of use. As previously mentioned, and discussed in the article by Long *et al* (2004), the therapeutic use of cocaine has been declining over the past several years for a variety of reasons, including the increased burden of documentation and inventory and the clinical setting for use. According to the article by Long *et al*, of the respondents to their 2004 survey, 78% reported administering cocaine topical solutions only in the operating room or hospital-based ambulatory surgical centers. When used in this clinical situation, patients are most likely to receive intravenous sedation or general anesthesia in addition to cocaine topical solution, suggesting that its vasoconstrictive properties outweigh its clinical usefulness as a topical anesthetic.

In summary, the results from the Applicant's Phase 3 clinical study suggest cocaine topical solution is most efficacious as a sole anesthetic for office-based, minimally invasive nasal procedures such as nasal endoscopy or nasal laryngoscopy. Its more frequent use in the operating room, in combination with intravenous sedation, MAC, or general anesthesia, suggests desired clinical endpoints (e.g., vasoconstriction) that were not assessed in the Phase 3 study conducted by this Applicant.

7.2.1. Subpopulations

Subgroup analyses were performed for age, race, sex, weight, and type of procedure. Refer to Table 20 for a summary of the subgroup analgesic success rates. Briefly, the significant p value for analgesic success seen with 4% cocaine topical solution vs. placebo in the overall subject population was maintained for sex, white and black race, age, and type of procedure performed. Statistical significance was not demonstrated for other races pooled or low body weight (<50 kg) due to the small number of subjects in these subgroups. Similar success rates for subgroups were observed for the 8% cocaine topical solution treatment group and there was a slight dose response observed between the 4% and 8% treatment groups.

Table 20: Analgesic Success Rates in Subgroups

	Placebo n/N (%)	4% RX0041-002 n/N (%)	8% RX0041-002 n/N (%)
Sex			
Males	3/40 (7.5)	88/108 (81.5)[a]	89/108 (82.4%)[a]
Females	6/55 (10.9)	127/170 (74.7)[a]	134/167(80.2)[a]
Race			
White	7/75 (9.3)	166/220 (75.5)[a]	175/216 (81.0)[a]
Black	2/16 (12.5)	40/49 (81.6)[a]	43/51 (84.3)[a]
Other races pooled	0/4 (0)	9/9 (100.0)[c]	5/8 (62.5)[b]
Age			
≥44 years	7/53 (13.2%)	99/134 (73.9)[a]	121/149 (81.2)[a]
<44 years	2/42 (4.8)	116/144 (80.6)[a]	102/126 (81.0)[a]
Weight			
≥80 kg	1/49 (2.0)	109/138 (79.0)[a]	112/138 (81.2)[a]
<80 kg	8/46 (17.4)	106/140 (75.7)[a]	110/136 (80.9)[a]
<50 kg	1/3 (33.3)	6/8 (75.0)[d]	7/9 (77.8)[e]
<60 kg	3/14 (21.4)	32/40 (80.0)[f]	26/33 (78.8)[g]
Type of procedure			
Nasal endoscope alone	5 (9.6)	124 (73.4)[a]	129 (78.7)[a]
Other procedures	4 (9.3)	91 (83.5)[a]	94 (84.7)[a]

[a]p<0.0001. [b]p=0.0808. [c]p=0.0014. [d]p=0.4909. [e]p=0.2364. [f]p=0.0002. [g]p=0.0006.
Source: Applicant's submission, NDA 209963

7.2.2. Dose and Dose-Response

The cocaine topical solutions used in this study, 4% and 8%, were administered as single doses to the nasal mucosa by study personnel. Statistical analyses compared the two concentrations to placebo individually but did not evaluate efficacy between the two groups. The study was not adequately powered to detect statistically significant differences in response between the two doses. The Applicant previously stated the use of 8% topical solution was for exploratory purposes and to maintain a blind after von Frey filament testing.

8 Review of Safety

8.1. Safety Review Approach

This application is a 505(b)(2) thus the Applicant is relying on information in the published literature to support the safety of cocaine topical solution for use as an anesthetic in diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. In addition to reliance on findings of safety in the published literature, the Applicant conducted five clinical studies, four Phase 1 and one Phase 3, with safety data that will be presented in this review. The clinical studies conducted by the Applicant are briefly summarized in Table 9.

The safety issue of greatest concern is the potential for clinically relevant changes in measured hemodynamic parameters. Hemodynamic instability during administration of cocaine is well-characterized in the published literature, in controlled clinical trials and case reports, and occurs in both the setting of clinical use as a topical anesthetic and in cases of illicit use and abuse. The hemodynamic changes most commonly observed include increases in heart rate and systolic, diastolic , and mean arterial blood pressure. Increases in these measured parameters can result in serious adverse cardiac events including myocardial ischemia and infarction, and ventricular arrhythmias. The more serious adverse outcomes are generally associated with higher concentrations of cocaine administration such as those observed in cases of abuse, however, clinically relevant hemodynamic changes have also been observed in cases of clinical use as a topical anesthetic.

The safety review will consist of a review of the studies conducted by the Applicant and inclusion of information from the published literature as relevant.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Applicant is seeking approval of 4% cocaine topical solution for use as a topical anesthetic during diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities. In the drug development program, 372 subjects, or 55% of total cocaine exposures, received the 4% solution. Refer to Table 21 for subject exposures across the clinical development program for this NDA. The 8% cocaine topical solution was exploratory, as described by the Applicant.

Cocaine has been used for decades as a topical anesthetic and local vasoconstrictor during otolaryngological procedures, but the extent of overall exposure to 4% topical solution and the incidence of adverse events is difficult to quantify for three reasons. First, cocaine is a marketed unapproved drug product making any precise monitoring of clinical use difficult. Second, a variety of cocaine concentrations have been used in this clinical setting, including 4%, 6%, and 10%. And third, because there currently is no post-marketing safety surveillance program, the monitoring of adverse events relies heavily on the published literature and

spontaneous case reports, which have not been entirely useful. The majority of adverse events in the published literature and in the FAERS database involve cases of illicit use, which generally suggest a much higher exposure than that observed in the clinical setting.

Table 21: Safety Population Exposed to 4% Cocaine Topical Solution

Clinical Trial	4% Cocaine Topical Solution (n=372)	8% Cocaine Topical Solution (n=299)	Intranasal Placebo (n=119)
2015016 PK Study healthy subjects	30	–	–
2015013 PK study 8 subjects with normal renal function, 8 subjects with renal impairment[a]	16	–	–
2015014 PK study 12 subjects with normal hepatic function, 12 subjects with hepatic impairment[b]	24	–	–
2016017 QT prolongation study 4-period, 4-treatment, 4-way crossover healthy subjects	24	24	24 Intranasal placebo and 24 oral moxifloxacin placebo
2013011 MC, R, DB, PC study,	278	275	95

[a] Renal impairment defined as glomerular filtration rate of 15-29 mL/min/1.73m²
[b] Hepatic impairment defined as Child-Pugh Classification B (9 subjects) or C (3 subjects)
Source: Adapted from Clinical Review Template

8.2.2. Relevant characteristics of the safety population:

The safety population in the five submitted studies and the literature reviewed was a reasonably diverse adult population, including ASA physical status classification I – III and small study populations of subjects with renal and hepatic impairment.

8.2.3. Adequacy of the safety database:

The totality of the safety database is adequate. This submission is a 505(b)(2) application relying on the published literature for findings of safety in addition to the Applicant's clinical drug development program. As previously mentioned, because cocaine topical solutions are

marketed unapproved products, there is no post-marketing surveillance program and the reports in the FAERS database involve cases of illicit use of cocaine.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

As previously discussed, this application had a data transposition error that resulted in the first submission having the incorrect treatment assignments. The corrected database was resubmitted and received on May 1, 2017. The majority of the data tables were corrected and new analyses performed. Revised clinical summaries and conclusions were also submitted. The resubmission was organized and information was reasonably easy to locate.

8.3.2. Categorization of Adverse Events and Routine Clinical Tests

The clinical study reports did provide definitions for adverse events (AE), serious adverse events (SAE), and treatment emergent adverse events (TEAE). The adverse events were categorized by severity and causality relationships were documented. Adverse events of special interest included changes in nasal mucosa, presence of inflammation or erythema, and changes in smell. Vital sign changes greater than 30% were not considered adverse events, but anticipated hemodynamic responses to the administration of intranasal topical cocaine. The following safety information was provided in the clinical study reports:

Study 2015016 (refer to section 4.5.3 Pharmacokinetics for further discussion of this study)
The safety assessments conducted during this study included monitoring adverse events, vital sign measurements, 12-lead ECG evaluation, nasal mucosa examinations, and laboratory tests. Vital sign monitoring included measurement of heart rate, respiratory rate, blood pressure and body temperature. The laboratory assessments included timed measurement of plasma and urinary pharmacokinetic parameters for cocaine and the metabolites, BE and EME after bilateral intranasal administration of 4% cocaine topical solution. Additional laboratory assessments included evaluation of the following parameters at the screening visit and on study Day 1 (end of the study):

- Hematology – red blood cell count, hemoglobin, hematocrit, white blood cell count and differential, and platelet count
- Serum chemistry – sodium, potassium, chloride, carbon dioxide, calcium, blood urea nitrogen, creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, triglycerides, and cholesterol.
- Urinalysis – pH, specific gravity, protein, glucose, ketones, bilirubin, blood nitrites, leukocytes, microscopic urine analysis if dipstick positive
- Pregnancy test – for women of childbearing age, serum pregnancy testing at screening visit and urine pregnancy testing on Day 1
- Urine drug screen – cannabinoids, cocaine, amphetamine, barbiturates, opiates, and benzodiazepines

Study 2015013
The safety assessments conducted during this study were similar to those conducted in study 2015016. Vital sign monitoring was more frequent and extended to the 32-hour time point (end of study). Additional laboratory assessments included the evaluation of the cocaine metabolite norcocaine in the serum. Serum and urine collection for evaluation of pharmacokinetic parameters after bilateral intranasal administration of 4% cocaine topical solution extended to the 32-hour time point. Serology for the presence of HIV and hepatitis C virus antibodies and hepatitis B surface antigen was also conducted. Other laboratory assessments including hematology, biochemistry, and urinalysis were similar to those conducted in study 2015016.

Study 2015014
The safety assessments conducted during this study were similar to those conducted in study 2015013. Additional laboratory assessments included the evaluation coagulation status (PT/INR). Other laboratory assessments including hematology, serum biochemistry, and urinalysis were similar to those conducted in study 2015016 and study 2015013.

Study 2016017 (refer to section 8.4.9 QT for further discussion of this study)
The safety assessments conducted during this study occurred during and after each administration of treatment drug. The safety assessments and the respective time points are summarized as follows:

- Adverse events
- Vital sign monitoring was performed at screening, predose, 5 minutes, and 2, 4, 8, and 12 hours after pledget insertion and oral moxifloxacin dose, and at the end of the study.
- 12-lead ECGs for review and interpretation at the site by the Investigator were recorded at screening, predose (for three recordings: -45 minutes, -30 minutes, -15 minutes), 1 and 12 hours after pledget insertion and post-moxifloxacin dosing, and at the end of the study
  - On the day of dosing in each treatment period, a minimum 25-hour continuous 12-lead ECG was recorded, beginning at least 1 hour before dosing. ECGs were *extracted* at various time points including –
    - Predose time points -45 minutes, -30 minutes, and -15 minutes
    - 20 minutes, 40 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after pledget insertion and moxifloxacin dosing
- Nasal cavity examinations occurred prior to intranasal drug dosing

Laboratory assessments were similar to those conducted in the other three Phase I studies and included hematology, serum biochemistry, urinalysis, serology, urine drug tests, and serum and urine pregnancy tests in women of childbearing potential. Additional laboratory assessments included the following:

- Urine alcohol and cotinine tests
- Follicle-stimulating hormone tests were conducted for women of post-menopausal age

Additional safety measures included the close monitoring of subjects during each period in the research facility. Subjects were required to remain seated for the first 4 hours after receiving a study drug dose. Subjects were escorted by research personnel when they needed to move for personal or other reasons. A physician remained on-site for a minimum of 4 hours after each dose administration.

Study 2013011

Similar to the safety assessments conducted during the four Phase 1 studies, this study also assessed adverse events, vital sign measurements, Holter monitoring, nasal mucosa examinations, smell assessments, and laboratory tests. Vital sign measurements occurred throughout the study drug application and the diagnostic or surgical procedure, and during the recovery period. Continuous ECG and pulse oximeter were monitored throughout study drug application and the diagnostic or surgical procedure, and during the recovery period. Nasal mucosal examinations were performed on study Day 1, prior to study drug application, and on study Day 8, the follow-up visit. The additional smell assessment was conducted using the Sensonics 3-Odor, Forced-Choice Screening Test and is designed to detect potential gross olfactory dysfunction. This smell assessment was performed on study Day 1 (treatment) and Day 8 (follow-up). Laboratory testing included hematology, serum biochemistry, urinalysis, urine drug tests, and serum and urine pregnancy testing in women of childbearing potential.

8.4. Safety Results

8.4.1. Deaths

There were no subject deaths reported during the Applicant's Phase 3 study or throughout the drug development program. Review of the published literature and the FDA's Adverse Event Reporting System (FAERS) has not identified any deaths related to topical cocaine administration for the purposes of anesthesia during nasal surgery. The deaths that have been reported in the FAERS database, where cocaine was listed as the primary suspect or was reported, are associated with the illicit use of cocaine.

8.4.2. Serious Adverse Events

No serious adverse events were reported in any of the clinical studies conducted by the Applicant.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No subject discontinued either study drug treatment or withdrew from the study because of an adverse event in any of the clinical studies (verbatim from the Applicant's NDA 209963 submission, Clinical Safety Summary).

8.4.4. Significant Adverse Events

Mild AEs were the most commonly reported adverse events and include headache, epistaxis, and nausea. Headache was the most frequent AE and was reported in 3.5% of subjects in the 4% cocaine topical solution group and in 2.0% of subjects in the 8% cocaine topical solution group. There was no appreciable dose response for AEs observed with 4% and 8% cocaine topical solutions. Refer to Table 22 for a summary of frequency of AEs by severity.

Table 22: Overview of Adverse Events (Overall Safety Population)

AE	Placebo N=119, n (%)	4% cocaine N=372, n (%)	8% cocaine N=299, n (%)	Overall cocaine N=647, n (%)	Overall N=742, n (%)
At least 1 AE	3 (2.5%)	21 (5.6%)	17 (5.7%)	38 (5.9%)	41 (5.5%)
AEs by max severity					
Mild	2 (1.7%)	12 (3.2%)	12 (4.0%)	24 (3.7%)	26 (3.5%)
Moderate	1 (0.8%)	6 (1.6%)	5 (1.7%)	11 (1.7%)	12 (1.6%)
Severe	0 (0.0%)	3 (0.8%)	0 (0.0%)	3 (0.5%)	3 (0.4%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study drug relationship					
Not related	0 (0.0%)	4 (1.1%)	6 (2.0%)	10 (1.5%)	10 (1.3%)
Unlikely related	0 (0.0%)	8 (2.2%)	3 (1.0%)	11 (1.7%)	11 (1.5%)
Possibly related	1 (0.8%)	8 (2.2%)	6 (2.0%)	14 (2.2%)	15 (2.0%)
Probably related	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Related	2 (1.7%)	0 (0.0%)	2 (0.7%)	2 (0.3%)	4 (0.5%)
At least 1 SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinuation of study drug due to AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinuation of study due to AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Adapted from Applicant's submission, NDA 209963

The Applicant states that there were no cardiovascular AEs reported and changes in measured hemodynamic parameters above 30% were not considered adverse and not reported as such. There was one subject, [redacted] (b) (6) in the Phase 3 study who experienced an unspecified arrhythmia and uncontrolled hypertension on post-procedure day 3. This subject was randomized to the 4% cocaine topical solution arm and underwent nasal endoscopy on December 29, 2014. The screening visit occurred on December 14, 2014 and the arrhythmia and uncontrolled hypertension occurred on January 1, 2015.

The subject was a 57 year old white female with a past medical history of hypertension,

insomnia, and post-menopausal. Hypertension was being treated with amlodipine, the dose of which had been increased from 5 mg po QD to 5 mg po BID 3 days prior to the procedure (December 26, 2014). Screening vital sign measurements, ECG analysis, and laboratory tests were within normal limits.

Blood pressure measurements on study Day 1, pre-dose, were normal to mildly elevated (140/86 mmHg). Heart rate measurements were within normal limits. During study drug application and the surgical procedure, recorded systolic blood pressure measurements were between 124 to 167 mmHg, recorded diastolic blood pressure measurements were between 78 to 94 mmHg, and recorded heart rate measurements were between 73 to 89 beats per minute. The procedure duration was 2 minutes. The subject did not receive antihypertensive or additional anesthetic medication during the procedure. Blood pressure measurement at the time of discharge was 152/88 mmHg and heart rate was 80 beats per minute. The subject was considered stable for discharge one hour after completion of her procedure.

On post-procedure Day 3, the subject visited an unspecified medical clinic with complaints of palpitations. She was diagnosed at the clinic with uncontrolled hypertension (recorded measurements not known) and arrhythmia. She was treated with atenolol 25 mg po QD. Vital sign measurements on subsequent follow-up visits with a study Investigator have reportedly been within normal limits. No additional information was provided.

An additional subject, 101-0009, randomized to receive the 8% cocaine topical solution, swallowed a single pledget during treatment. The subject was a 33 year old African American male who underwent nasal endoscopy with debridement. The subject did not experience shortness of breath or other respiratory distress and a plain film x-ray of the upper GI tract did not locate the pledget. It was never recovered from the GI tract. The subject remained stable and had no complaints at the follow-up visit.

There were three reported severe AEs in the 4% cocaine topical solution treatment group. All three severe AEs were headache, two subjects participated in the Phase 3 study, 2013011 and one subject in the Phase 1 study, 2015016. Table 21 summarizes the clinically relevant information regarding the severe AEs.

Table 23: Summary of Subjects with Severe AE of Headache

Rx group/Study Subject	AE PT Verbatim term	Onset time relative to study drug administration	Duration	SAE	Relationship to study drug	Action taken and outcome	Additional details
4% cocaine Study 2015016 Subject (b) (6) 29 yo female	Headache	4 hours	2 hours	No	Unlikely related	None Resolved	No PMH of headache
4% cocaine Study 2013011 Subject (b) (6) 21 yo male	Headache	2 hours	9.3 hours	No	Not related*	None Resolved	Other AEs include nausea, blurred vision, and "cold sweat"
4% cocaine Study 2013011 Subject (b) (6) , 71 yo female	Headache	0 hours	24 hours	No	Unlikely related	Treated with acetaminophen Resolved	PMH of migraine

Adapted from Applicant's submission, NDA 209963
Rx: treatment group; yo: year old; PMH: past medical history
*headache not related but other documented AEs related to treatment

Subject (b) (6) in Study 2015016 experienced a migraine headache beginning approximately 4 hours post pledget removal and extending until approximately 6 hours post pledget removal. The subject's vital sign measurements were stable throughout the course of the study. The largest measured increase in systolic and diastolic blood pressure measurements were observed at 1 hour post pledget removal. Systolic blood pressure increased by 34 mmHg and diastolic decreased by 2 mmHg. Heart rate remained unchanged at this time point. At four hours post pledget removal, the approximate onset time of the headache, blood pressure measurement was 134/66 mmHg and heart rate was unchanged from baseline. In conclusion, it is unlikely the subject's headache was related to the study drug.

Subject (b) (6) in Study 2013011 developed a headache on Study Day 1 approximately 1 hour and 40 minutes after pledget removal and approximately 1 hour and 30 minutes after procedure completion. The subject had been discharged from the investigative site at the time of AE onset, hence there is no reviewable vital sign data. It is worth noting that the other AEs experienced by this subject, nausea, blurred vision, and cold sweat, all occurred at the same time and during the procedure and appear to be related to the procedure. This subject's vital sign data prior to pledget application and procedure initiation and during complaints of the three AEs was as follows:

Table 24: Vital Sign Data for Subject (b) (6)

Time	HR (bpm)	SBP/DBP (mmHg)	**Pledget insertion time:** 1346-1406
Baseline, 1344	76	123/80	
1402	59	121/75	**Procedure and time:** Turbinate reduction 1409-1417
1408*	**61**	**91/53**	
1414*	**68**	**101/68**	
1420	84	113/75	
1426	78	108/67	**AE time:** 1410-1416

bpm: beats per minute; mmHg: millimeters of Mercury

This subject experienced a decrease in measured heart rate and blood pressure following pledget removal and during the procedure, vital sign measurements highlighted above in red font. These data potentially support the conclusion that this subject experienced a clinically relevant vaso-vagal reaction. Vital sign data at additional time points would have clarified the hemodynamic profile for this subject during the time of the adverse events.

Subject (b) (6) experienced a severe AE of headache beginning at an unspecified time on study Day 1 on continuing into the following day. This subject had a past medical history of migraines but it was not specified if the headache experienced and classified as a severe AE was a migraine. The headache was treated with acetaminophen and resolved. Upon review of the vital sign data for this subject, there were several systolic and diastolic blood pressure measurements that were more than 25% higher than the baseline measurements, which may suggest the onset of headache was related to the increased in measure hemodynamic parameters.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following table, 25, is a summary of treatment-emergent adverse events (TEAE) by severity from study 2013011. The cocaine treatment groups had a higher incidence of all AEs when compared to placebo, but most were mild and included headache and epistaxis.

Table 25: Treatment-Emergent Adverse Events

	Placebo (N=95)	4% RX0041-002 (N=278)	8% RX0041-002 (N=275)
Subjects with AEs, n (%)	1 (1.1)	13 (4.7)	14 (5.1)
Severity			
Mild AEs, n (%)	1 (1.1)	8 (2.9)	10 (3.6)
Moderate AEs, n (%)	0	3 (1.1)	4 (1.5)
Severe AEs, n (%)	0	2 (0.7)	0
Deaths due to AEs, n (%)	0	0	0
Serious AEs, n (%)	0	0	0
Subjects discontinued due to an AE, n (%)	0	0	0

Source: Adapted from Clinical Study Report submitted on June 05, 2017, page 52.

The following is a summary of TEAEs by System Organ Class and Preferred Term from study 2013011.

Table 26: TEAEs by System Organ Class and Preferred Term

System Organ Class Preferred Term	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8 % RX0041-002 (N=275) n (%)
ANY PRIMARY SYSTEM ORGAN CLASS	1 (1.1%)	13 (4.7%)	14 (5.1%)
Eye disorders	0	1 (0.4%)	1 (0.4%)
Foreign body sensation in eyes	0	0	1 (0.4%)
Vision blurred	0	1 (0.4%)	0
Gastrointestinal disorders	0	1 (0.4%)	1 (0.4%)
Lip swelling	0	0	1 (0.4%)
Nausea	0	1 (0.4%)	0
General disorders and administration site conditions	0	2 (0.7%)	1 (0.4%)
Cold sweat	0	1 (0.4%)	0
Facial pain	0	0	1 (0.4%)
Fatigue	0	1 (0.4%)	0
Injury, poisoning and procedural complications	0	0	1 (0.4%)
Medication error	0	0	1 (0.4%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.4%)
Neck pain	0	0	1 (0.4%)
Nervous system disorders	1 (1.1%)	7 (2.5%)	5 (1.8%)
Dizziness	0	1 (0.4%)	1 (0.4%)
Headache	1 (1.1%)	7 (2.5%)	4 (1.5%)
Psychiatric disorders	0	0	2 (0.7%)
Anxiety	0	0	2 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.1%)	6 (2.2%)	3 (1.1%)
Dysphonia	0	1 (0.4%)	0
Epistaxis	0	3 (1.1%)	2 (0.7%)
Nasal congestion	1 (1.1%)	0	1 (0.4%)
Rhinorrhea	0	1 (0.4%)	0

System Organ Class Preferred Term	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8 % RX0041-002 (N=275) n (%)
Sneezing	0	1 (0.4%)	0
Upper-airway cough syndrome	1 (1.1%)	0	0
Skin and subcutaneous tissue disorders	0	0	2 (0.7%)
Cold sweat	0	0	1 (0.4%)
Dermatitis allergic	0	0	1 (0.4%)
Vascular disorders	0	1 (0.4%)	0
Hypertension	0	1 (0.4%)	0

Source: Adapted from Clinical Study Report submitted on June 05, 2017, page 53.

8.4.6. Laboratory Findings

The Phase 3 study, 2013011 did not evaluate laboratory data post-treatment. Baseline laboratory data was collected as outlined in section 8.3.2 Categorization of Adverse Events and Routine Clinical Tests.

8.4.7. Vital Signs

As previously discussed in section 6.1.2 Study Results, Protocol Violations/Deviations, there were large numbers of missing vital sign data, particularly HR data, across all treatment groups. The Applicant was informed of this concern in the 74-day letter and responded with a table indicating the number of subjects with missing values at 5 minute intervals. This tabular representation of the data did not specify which vital sign parameter was missing and presents the missing data in smaller numbers than when considering the values missing over a longer time interval such as 15 minutes.

Heart rate

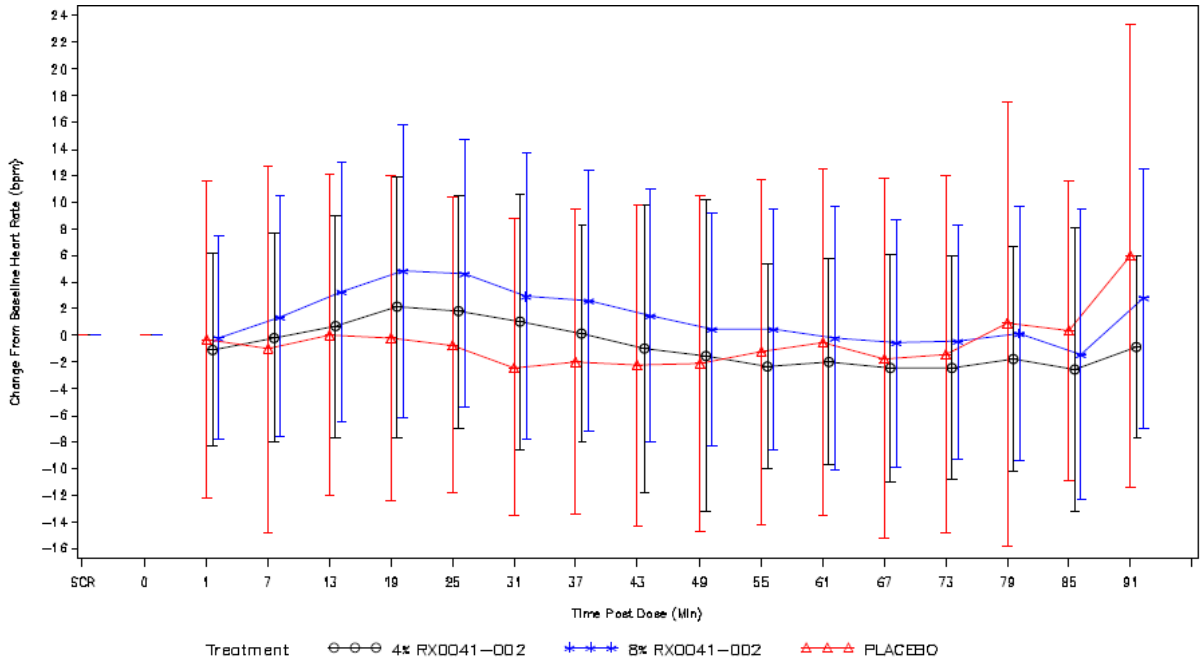
There were several subjects across all treatment arms who experienced increases in HR above 30% of the baseline value. The number subjects in each treatment group who experienced such increases is as follows:

- Placebo group – 9 (9.5%) subjects experienced increases in HR above 30% of baseline values during the treatment period. Two subjects experienced these increases throughout the duration of the procedure and into the recovery phase.
- 4% cocaine topical solution group – 17 (6.1%) subjects experienced increased in HR above 30% of baseline values during the treatment period. One subject experienced these increases throughout the duration of the procedure and into the recovery phase.
- 8% cocaine topical solution group – 36 (13.1%) subjects experienced increased HR above 30% of baseline values during the treatment period. Two subjects experienced these increases throughout the duration of the procedure and into the recovery phase.

The Applicant presented the data as mean change from baseline heart rate and reported larger changes (increases) from baseline in the 4% and 8% treatment groups when compared to

placebo, refer to Figure 6. These changes were observed beginning at 7 to 12 minutes post-dose and extending through the 72 minute post-dose time period. The increases in HR were higher in the 8% treatment group compared to the 4% treatment group. The Applicant proposed that the moderate increases in HR in the cocaine treatment groups was expected due to the sympathomimetic actions of cocaine.

Figure 3: Mean Change from Baseline Heart Rate



Source: Applicant's submission, NDA 209963

Systolic and Diastolic Blood Pressure

Mean changes from baseline measurements in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were larger in the 4% and 8% cocaine treatment groups when compared to the placebo group beginning at 7 to 12 minutes post-dose through 72 minutes post-dose. Additionally the observed increases in the 8% cocaine treatment group were larger than those observed in the 4% cocaine treatment group. It does appear, however, that the number of subjects who experienced ≥40% increases in SBP measurements from baseline was higher in the placebo and 8% cocaine treatment groups compared to the 4% cocaine treatment group. Refer to Table 27 for the Applicant's tabular representation of blood pressure data.

Table 27: Number of Subjects with Percent Change from Baseline in SBP or DBP ≥40%

Flag	Placebo (N=95) n (%)	4% RX0041-002 (N=278) n (%)	8% RX0041-002 (N=275) n (%)
Systolic BP	3 (3.2%)	2 (0.7%)	6 (2.2%)
Diastolic BP	8 (8.4%)	17 (6.1%)	22 (8.0%)

Source: Applicant's submission, NDA 209963

Clinically relevant changes in measured hemodynamic parameters, which may necessitate the administration of medication, are often defined as those greater than 30% of baseline. I evaluated subject data in all three treatment groups in the Applicant's Phase 3 study for increases in SBP or DBP >30%. Table 28 displays these results.

Table 28: Number of Subjects with Percent Change from Baseline in SBP or DBP >30%

Blood pressure parameter	Placebo (N=95) n (%)	4% cocaine topical solution (N=278), n (%)	8% cocaine topical solution (N=275), n (%)
SBP >30%	6 (6.3%)	6 (2.2%)	20 (7.2%)
DBP >30%	15 (15.8%)	50 (18%)	63 (22.9%)

A larger number of subjects across all treatment groups, including the placebo group, experienced increases in DBP when compared to those who experienced increases in SBP, suggesting cocaine exerts a great effect on the vasculature during diastole versus systole. Some of the reported increases in systolic and diastolic blood pressure measurements were observed for 60-70 minutes post-pledget removal, supporting the need for prolonged post-procedure monitoring in subjects receiving cocaine topical solution. The blood pressure response to placebo administration may be explained by procedural anxiety and discomfort, particularly given that 42% of subjects receiving placebo did not receive additional anesthetic or analgesic medication to complete the procedure. As previously discussed in Section 8.4.4 Significant Adverse Events, one subject in the 4% cocaine group experienced an AE of uncontrolled hypertension on post-operative day three. No other subject in any treatment group received treatment for elevated systolic or diastolic blood pressure.

Pulse Oximetry

Oxygen saturation was assessed only in the Phase 3 study. There were no clinically meaningful differences in oxygen saturation in the cocaine treatment groups when compared to the placebo group, however 30% of subjects across all groups had saturations ≤88%. The Applicant defined three distinct monitoring periods as Period 1 (setup), Period 2 (procedure including pledget insertion), and Period 3 (post-procedure monitoring) and stated that the majority (78.6%) of oxygen desaturations ≤88% occurred in Period 1 and/or 3. Only 21.4% of desaturations occurred in Period 2 or in a combination of Periods 1, 2, and 3. Thirty five cases of desaturation ≤88% occurred in Period 2; 14 of which occurred during the time of pledget insertion. The Applicant felt these cases of desaturation that corresponded to pledget insertion were most likely due to movement artifact, caused when a subject suddenly moved the hand. No explanation was provided for the other 21 desaturations of ≤88% that occurred during Period 2. Refer to Table 29 for desaturation data by treatment group.

Table 29: Oxygen Saturation in Phase 3 Study (2103011)

Pulse Oximetry Variable	Placebo N=95	4% RX0041-002 N=275	8% RX0041-002 N=275
Mean (SD) O_2 values			
Entire measurement interval			
Mean highest	98.9 (0.5)	98.9 (0.4)	99.0 (0.3)
Mean lowest	89.2 (8.55)	88.5 (9.77)	89.4 (7.99)
Number (%) subjects with O_2 value			
<90%	38 (40.0%)	97 (34.9%)	97 (35.3%)
<88%	29 (30.5%)	82 (29.5%)	76 (27.6%)
<80%	9 (9.5%)	39 (14.0%)	28 (10.2%)
<70%	3 (3.2%)	13 (4.7%)	8 (2.9%)
<60%	3 (3.2%)	7 (2.5%)	2 (0.7%)
Duration (sec) with O_2 value			
<90%	73.8 (59.1)	33.4 (20.1)	44.1 (27.0)
<88%	59.1 (409.78)	20.1 (70.93)	27.0 (150.91)
<80%	23.8 (212.20)	5.3 (28.82)	4.3 (24.65)
<70%	11.1 (106.07)	1.5 (12.40)	0.7 (6.72)
<60%	0.2 (1.35)	0.7 (5.69)	0.2 (2.71)

SD=standard deviation
Source: Applicant's submission, NDA 209963

Eight subjects with an oxygen desaturation level ≤88% had a total of 12 AEs. Six of these AEs were unrelated to hypoxia; one case of medication error, two cases of epistaxis, 1 case of foreign body sensation in the eye, 1 case of nasal congestion, and 1 case of dysphonia. The remaining six AEs that occurred in subjects with desaturation levels ≤88% were possibly related to hypoxia as described by the Applicant. Four of the AEs occurred prior to the desaturation and were therefore further described as unrelated to hypoxia. Two AEs, headache, were noted after the oxygen desaturations ≤88% were recorded. Of these two headaches, the first occurred 89 minutes after an oxygen desaturation to 87% and was felt to be unrelated to the desaturation. The second AE of headache occurred in a subject with a recorded oxygen saturation of 88% near the end of monitoring Period 3 that lasted for seven seconds. The time of headache onset was not recorded so a causal relationship is difficult to determine. Table 30 lists the AEs related to oxygen saturations ≤88% and >88%.

Table 30: AEs Potentially Related to Hypoxia in Subjects with an O2 Saturation Level ≤88%

	Overall (N=648)	O_2 ≤88% (N= 187)	O_2 >88% (N= 461)
All AEs	28 (4.3%)	8 (4.3%)	20 (4.3%)
Headache	12 (1.85%)	3 (1.6%)	9 (1.95%)
Dizziness	2 (0.003%)	1 (0.005%)	1 (0.002%)
Anxiety	2 (0.003%)	1 (0.005%)	1 (0.002%)
Fatigue	1 (0.002%)	1 (0.005%)	0 (0.0%)

Source: Applicant's submission, NDA 209963

Body Temperature

The mean and median change from baseline in oral temperature was similar in all treatment groups in the Phase 3 study.

8.4.8. Electrocardiograms (ECGs)

In the Phase 3 study, 2013011, baseline ECGs were analyzed and continuous ECG was monitored, via Holter, throughout study drug application and surgical procedure, and in the recovery phase for up to one hour. There were no reports of clinically significant changes in PR, QRS, or QTc duration or the ST segment. The number of supraventricular and ventricular ectopic beats was similar in the placebo and cocaine treatment groups. There were no clinically significant arrhythmias observed in any treated subject. There was a single subject who was described as having experienced an arrhythmia on post-procedure day 3 in combination with uncontrolled hypertension. That subject has been previously discussed in section 8.4.4. Significant Adverse Events.

8.4.9. QT

The Applicant conducted a Phase 1, dedicated study, 2016017, to examine the potential effects of cocaine topical solution on the QT interval. This study was a randomized, single-dose, partially blinded, four-period, four-treatment, four-way crossover design evaluating both the 4% and 8% cocaine topical solutions, placebo solution, and oral moxifloxacin, known to prolong the corrected QT interval. The Division of Anesthesia, Analgesia, and Addiction Products consulted the Interdisciplinary Review Team for QT Studies (IRT-QT) for a thorough review of the submitted QT study. The following discussion is based primarily on information and findings from that consult.

Study Design

Study 2106017 was a randomized, partially blinded, four-period crossover study evaluating the effects of cocaine topical solution on QTc interval in 24 healthy adult subjects. Subjects received treatment with each of the following drug treatments:

- 4% cocaine topical solution, 160 mg

- 8% cocaine topical solution, 320 mg
- Placebo solution
- Oral moxifloxacin, 400 mg

Overall Summary of Findings:
The study employed Fridericia method for analyzing the QTc interval, which generally suggests that increases in QTc less than 5 msec are probably of no concern and increases greater than 20 msec are of definite concern. The corrected QT interval based upon heart rate using the Fridericia method does work well for drugs that do not have an effect on heart rate and there is less confidence in this method when evaluating drugs with significant heart rate effects, defined as heart rate changes of > 10 beats per minute (bpm). Cocaine is one such drug that can significantly increase heart rate, which then impacts the ability to interpret the ΔΔQTcF, particularly for the 8% cocaine topical solution. The following table (31) was taken from the IRT-QT consultation review and indicates the change in heart rate for the two different cocaine topical solutions:

Table 31: The ΔΔHR Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for RX0041-002 (160 mg and 320 mg) (FDA Analysis)

Treatment Group	Time (hour)	ΔΔHR (bpm)	90% CI (bpm)
4% cocaine topical solution (160 mg)	0.67	7.0	(4.0; 10.0)
8% cocaine topical solution (320 mg)	0.33	15.3	(11.6; 19.0)

Adapted from IRT-QT consult review, FDA.

For the 4% cocaine topical solution, no significant QTc prolongation effect was detected in this QT study. Increases in the QTc were less than 10 msec. Because the 8% cocaine topical solution significantly increased heart rate, the interpretability of the QTc is more challenging, however, based on the preclinical data and the observed mean ΔΔQTcF of less than 10 msec, it seems unlikely that this dose would cause increases of clinical concern; e.g., >20 msec, particularly in the setting of a single topical administration. The table (32) below indicates the mean ΔΔQTcF findings at both dose of the cocaine topical solution. The table also demonstrates that the largest lower bound of the 90% confidence interval for the ΔΔQTcF for moxifloxacin was greater than 5 msec, supporting adequate assay sensitivity.

Table 32: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for RX0041-002 (160 mg and 320 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
4% cocaine topical solution (160 mg)	0.33	4.6	(2.2; 6.9)
8% cocaine topical solution (320 mg)	0.33	7.1	(4.7; 9.5)
Moxifloxacin 400 mg	4	15.0	(12.4; 17.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 11.5 ms.

There was a concentration-QT relationship between the 4% and 8% cocaine topical solutions, however, the upper bound of 90% CI for predicted ΔΔQTcF at Cmax is less than 10 msec.

Proposed Labeling Language

The IRT-QT proposed the following labeling language:

Cardiac Electrophysiology

The effect of Cocaine Hydrochloride Topical Solution on the QTc interval was evaluated in a randomized, placebo- and positive-controlled four-period crossover thorough QTc study in 24 healthy subjects. No clinically relevant QTc prolongation was observed at highest clinically relevant concentrations with single therapeutic dose.

8.5. Analysis of Submission-Specific Safety Issues

The Phase 3 study conducted by the Applicant in support of this NDA evaluated changes in nasal mucosa and smell in addition to the safety assessments previously discussed.

Nasal Examinations

A nasal examination was conducted on all subjects pre-dose on study Day 1 and on the follow-up visit on study Day 8. The examination consisted of visual inspection of the nasal mucosa for the presence of irritation that may have been due to the topical application of study drug. Two subjects had a shift from a normal exam on Day 1 to an abnormal exam on Day 8.

Subject (b) (6) received 4% cocaine topical solution for nasal endoscopy. Turbinate hypertrophy and bilateral nasal congestion were noted at the follow-up visit on Day 8. Subject (b) (6) received 8% cocaine topical solution for nasal endoscopy and polypectomy. A small amount of yellow mucous was noted at the follow-up visit on Day 8. None of the clinical findings in these two subjects was reported as an AE.

Smell Assessments

To evaluate the potential olfactory dysfunction caused by the application of cocaine topical solution to the nasal mucosa, smell assessments were performed on all subjects pre-dose and on the follow-up visit on study Day 8 using the Sensonics 3-Odor, Forced-Choice Screening Test. Briefly, subjects were presented with three different "scratch and sniff" odors and were asked to match the odor to the appropriate smell from a provided list of choices. A score of 0 indicated the subject could not correctly identify any of the odors presented; a score of 1 indicated one odor was correctly identified; a score of 2 indicated two odors were correctly identified and a score of 3 indicated that all odors were correctly identified.

Most subjects across all treatment groups were able to correctly identify two or three odors immediately following surgery on Day 1 and at the follow-up visit on Day 8. The number of subjects unable to identify any of the odors or only one was low and similar in all three treatment groups. In all treatment groups, the number of subjects able to correctly identify three odors increased from Day 1 to Day 8. Refer to Table 33 below for specific results.

Table 33: Assessment of Smell

Visit	Category (# of correctly identified odors)	Placebo (N=95) n (%)	4% cocaine (N=278) n (%)	8% cocaine (N=275) n (%)	Overall (N=648) n (%)
Visit 2, Day 1	0	2 (2.1%)	6 (2.2%)	12 (4.4%)	20 (3.1%)
	1	1 (1.1%)	9 (3.2%)	7 (2.5%)	17 (2.6%)
	2	12 (12.6%)	25 (9.0%)	31 (11.3%)	68 (10.5%)
	3	80 (84.2%)	238 (85.6%)	225 (81.8%)	543 (83.8%)
Visit 3, Day 8	0	2 (2.1%)	3 (1.1%)	10 (3.6%)	15 (2.3%)
	1	1 (1.1%)	7 (2.5%)	3 (1.1%)	11 (1.7%)
	2	8 (8.4%)	22 (7.9%)	21 (7.6%)	51 (7.9%)
	3	84 (88.4%)	245 (88.4%)	241 (87.6%)	570 (88.1%)

Source: Adapted from Applicant's submission, NDA 209963

8.6. Safety Analyses by Demographic Subgroups

Demographic subgroups that were analyzed for safety in this NDA included gender, race (white, black, and all other races pooled), age (≥44 years and <44 years), weight (≥80 kg and <80 kg; <50 kg and <60 kg), and type of procedure (nasal endoscopy alone and other procedures). The adverse event subgroup safety analysis also included presence of a past medical history.

The frequency of AEs in females was greater than that observed in male subjects across all treatment groups. Headache was reported with a higher frequency in females vs. males in the 4% cocaine treatment group (4.3% vs, 2.5% respectively) but with a similar frequency in both genders in the 8% cocaine treatment group (2.2% for females and 1.7% for males). Epistaxis

was only reported in female subjects in both cocaine treatment groups, but not in the placebo group.

The majority of subjects in the overall safety population, 97%, were either white or black/African American. Because other race categories made up only 3% of the overall safety population, there were too few subjects for comparisons of AE frequency. A higher percentage of whites, compared to blacks, in the cocaine treatment groups experienced at least one AE. There did not appear to be an association between the type of AE and race.

The frequency of AEs was similar in the predefined age groups of <45 years of age and ≥45 years of age. In the 4% treatment group, the frequency of AEs was 5.1% for subjects <45 years of age and 6.2% for subjects ≥45 years of age. In the 8% treatment group, the frequency of AEs was 7.1% for subjects <45 years of age and 4.1% for subjects ≥45 years of age. In the placebo group, the frequency of AEs was 4.5% for subjects <45 years of age and 0% for subjects ≥45 years of age. Comparisons of AEs in subjects <65 and ≥65 years of age suggested that the frequency of subjects experiencing at least one AE was similar across all treatment groups. For subjects ≥65 years of age, the frequency of AEs was 4.4% in the 4% treatment group 6.7% in the 8% treatment group, and 0% in the placebo group. These frequencies were similar to those observed in subjects <65 years of age. Separate evaluation of observed changes in measured hemodynamic parameters did not reveal large differences in those subjects <65 years of age and those ≥65 years of age.

The incidence of AEs in enrolled subjects of low body weight (either <50 kg or <60 kg) was low, however the number of subjects in these body weight subgroups was quite low (i.e., 24 subjects weighing <50 kg and 97 subjects weighing <60 kg across all treatment groups). There were two reported severe AEs (headache) in the 4% cocaine treatment group; one subject in the <50 kg subgroup and one in the <60 kg subgroup. The incidence of AEs was slightly higher in those subjects who received a topical dose of cocaine that exceeded the recommended 1-3 mg/kg (the recommended dosing for topical cocaine is based upon a publication by Fleming et al, 1990, which quoted a publication by Barash et al., 1977, suggesting 1-3 mg/kg is the maximum safe dose). The incidence of AEs in those subjects who received a dose of cocaine >3 mg/kg was 6.2% and for those subjects who received a dose ≤3 mg/kg, the AE incidence was 5.3%.

The AE profile in subjects with a past medical history was similar to that observed in the overall subject population; however, both severe AEs of headache occurred in subjects with a past medical history. In subjects with a cardiovascular past medical history, no AEs were reported in either the 4% or 8% cocaine treatment group; however one subject in the placebo group experienced AEs of headache, nasal congestion, and upper airway cough syndrome. The frequency of AEs in subjects with a past medical history of hypertension was 7.0% in the 4% cocaine treatment group, 3.8% in the 8% cocaine treatment group, and 0% in the placebo group. As previously discussed, the single AE defined as hypertension by the Applicant occurred in subject (b) (6) who had a past medical history of hypertension.

In subjects with a CNS past medical history, there was a higher incidence of AEs in the 4% and 8% treatment groups. The percentage of subjects with a CNS past medical history and at least one AE was 9.2% in the 4% cocaine treatment group, 9.3% in the 8% cocaine treatment group, and 0% in the placebo treatment group. The most frequent AEs were headache and epistaxis in the cocaine treatment groups.

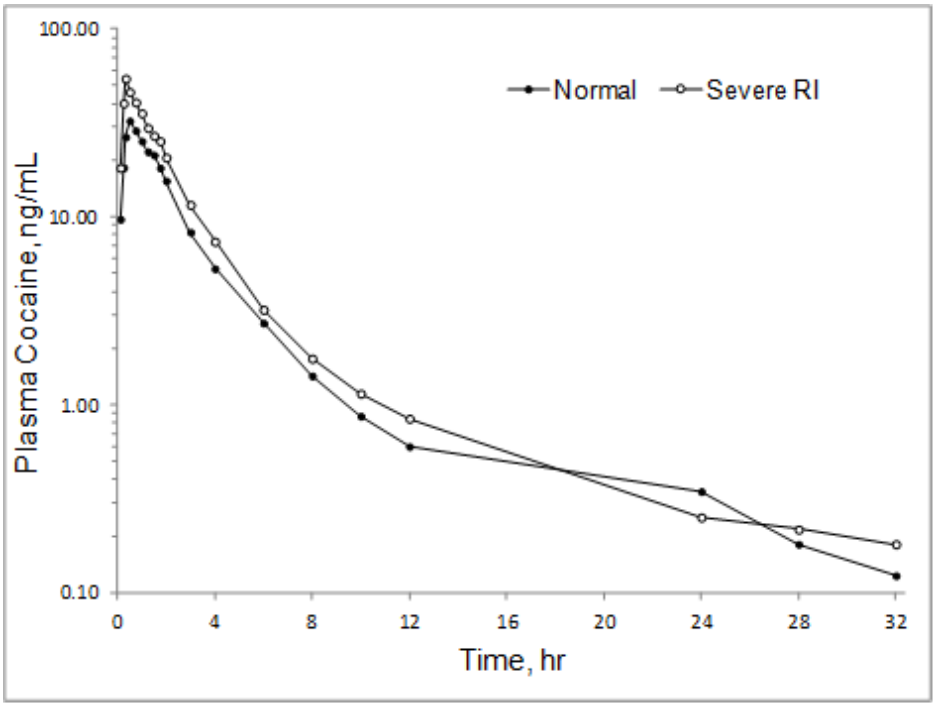
8.7. Specific Safety Studies/Clinical Trials

The Applicant conducted two Phase I studies to evaluate the effect of renal (study 2015013) and liver (study 2015014) impairment on the PK profile of topically administered cocaine.

Study 2015013 – A Phase 1 Study Comparing the Pharmacokinetics of Intranasal Cocaine in Subjects with Severe Renal Impairment and Subjects with Normal Renal Function

The results of this study indicate that severe renal impairment, defined as 15-29 mL/min/1.73 m^2, did increase plasma concentrations by 33-34% more than those observed in subjects with normal renal function. In subjects with normal renal function, mean cocaine C_{max} was 35.9 ng/mL and the median T_{max} was 30 minutes. In subjects with renal impairment, the mean cocaine C_{max} was 47.9 ng/mL and the median T_{max} was 25 minutes. Apparent clearance was approximately 26% lower and renal clearance was approximately 43% lower in subjects with renal impairment compared to subjects with normal renal function. However, there was no statistically significant difference between groups of subjects in cocaine C_{max}, $AUC_{0\text{-}inf}$, apparent clearance, and renal clearance. These findings suggest that renal impairment exerts a small, but measurable effect on the pharmacokinetic profile of intranasal cocaine. Refer to Figure 7 for graphical representation of cocaine plasma concentrations over time in subjects with normal and impaired renal function.

Figure 4: Cocaine Plasma Concentration vs. Time Profiles in Subjects with Normal Renal Function and Those with Severe Renal Impairment



Source: Applicant's submission, NDA 209963

The plasma concentration of the inactive cocaine metabolites BE and EME were found to be at least 2-fold higher and declined more slowly in subjects with renal impairment compared to those with normal renal function. The concentration of the active metabolite norcocaine was below the limit of assay quantitation (0.1 ng/mL) in most plasma samples, with the exception of one subject in the renal impairment group who had four measured levels slightly above the assay limit, 0.101 ng/mL to 0.115 ng/mL. The total amount of parent drug and the metabolites excreted in the urine over the course of the study remained relatively stable, suggesting the bioavailability of cocaine was not impacted by renal impairment.

Laboratory data for hematology, blood chemistry, and urinalysis were collected at Screening and on Day 2 of this study. There were no significant changes in mean lab values over the course of the study in either group. Individual subject data indicated that there were no significant trends in the occurrence of abnormalities in either group.

The vital sign data indicates that subjects with renal impairment had higher screening and pre-dose systolic and diastolic blood pressure measurements when compared to subjects with normal renal function, but the mean change from baseline was similar in both groups across all measured time points (i.e., 15, 30, 60 and 120 minutes and 4 and 24 hours post-dose). Heart rate measurements were similar in both groups at screening and pre-dose and did the mean changes from baseline were similar in both groups across all time points.
Nasal examinations were similar in both groups of subjects and there were no reports of

abnormal findings.

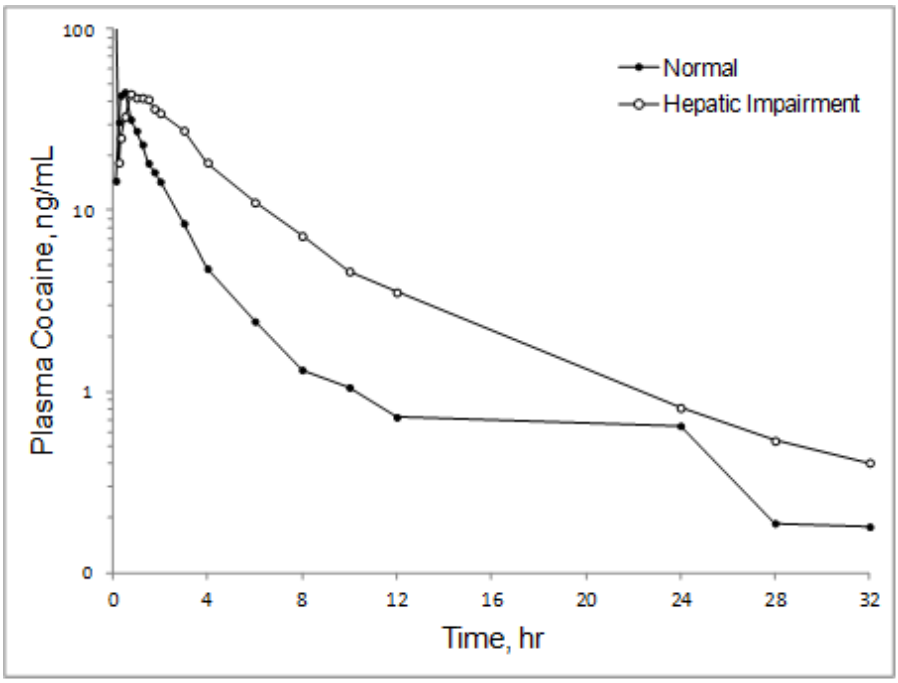
There were no deaths, SAEs, or other AEs reported during this study.

Based upon the above laboratory/pharmacokinetic results and clinical findings, the Applicant states that intranasal cocaine is safe and well-tolerated in subjects with severe renal impairment, and has therefore not proposed a reduced dose for this population.

Study 2015014 – A Phase 1 Study Comparing the Pharmacokinetics of Intranasal Cocaine in Hepatic-Impaired Individuals and Subjects with Normal Hepatic Function

The results of this study indicate that hepatic impairment, defined as Child-Pugh Classification B or C, delays T_{max} and slows the decrease in plasma concentration during the initial 12 hour post-dose time period. The plasma concentrations were approximately 2.5 times higher in subjects with hepatic impairment compared to those with normal liver function. There was a single subject with Grade B hepatic impairment with one measured plasma cocaine concentration 40 times higher than that observed for other subjects at the 7-minute post-dose time point. This value was felt to be an outlier but pharmacokinetic analyses were performed with the high value, with the exception of the primary interpretations of C_{max}. In subjects with normal hepatic function, mean cocaine C_{max} was 44.2 ng/mL and the median T_{max} was 30 minutes. In subjects with hepatic impairment, the mean cocaine C_{max} was 41.2 ng/mL (56 ng/mL including the outlier) and the median T_{max} was 45 minutes. Geometric mean AUC0-inf values were 82.4 ng·hr/mL in subjects with normal hepatic function and 204 ng·hr/mL in subjects with hepatic impairment. Apparent and renal clearance were approximately 60% lower in subjects with hepatic impairment compared to subjects with normal hepatic function. There was no statistically significant difference between groups of subjects in cocaine C_{max}; however, there was substantial overlap in individual parameters between the two groups. Plasma cocaine AUC_{0-t} was 2.8-times higher in subjects with Grade B hepatic impairment and 1.8-times higher in subjects with Grade C hepatic impairment compared to those with normal hepatic function. Apparent clearance was reduced by 64% in subjects with Grade B hepatic impairment and 45% in subjects with Grade C impairment. Refer to Figure 8 for graphical representation of cocaine concentration vs. time in subjects with normal hepatic function and those with hepatic impairment.

Figure 5: Cocaine Plasma Concentration vs. Time Profiles in Subjects with Normal Hepatic Function and Those with Grade B or Grade C Hepatic Impairment



Source: Applicant's submission, NDA 209963

The plasma concentrations of the inactive metabolites BE and EME were higher in subjects with hepatic impairment compared to those with normal hepatic function. BE and EME concentrations rose more slowly and had a delayed T_{max} in subjects with impaired hepatic function. The C_{max} for BE and EME was 1.5 to 2 times higher than those observed in subjects with normal hepatic function. The active metabolite norcocaine was detected at low levels in four of the 12 subjects with hepatic impairment but in none of the subjects with normal hepatic function. Three Grade B impaired subjects had multiple detectable levels (≤0.31 ng/mL) of norcocaine and one Grade B impaired subject had a single detectable level (0.354 ng/mL). Cocaine, BE, and EME were all excreted in the urine in both groups of subjects.

Laboratory data for hematology, blood chemistry, and urinalysis were collected at Screening and on Day 2 of this study. There were no significant changes in mean lab values over the course of the study in either group. Individual subject data indicated that there were no significant trends in the occurrence of abnormalities in either group.

The vital sign data indicates that subjects with normal hepatic function and those with hepatic impairment had similar screening and pre-dose systolic and diastolic blood pressure measurements. Additionally, the mean change from baseline was similar in both groups across all measured time points (i.e., 15, 30, 60 and 120 minutes and 4 and 24 hours post-dose). Heart rate measurements were similar in both groups at screening and pre-dose and the mean changes from baseline were similar in both groups across all time points.

Nasal examinations were similar in both groups of subjects and there were no reports of abnormal findings.

There were no deaths, SAEs, or other serious AEs reported during this study. Only three adverse events in two subjects were reported in this study. A subject with normal hepatic function experienced the mild AEs of headache and nausea, which were deemed probably related to study drug, and another subject with Grade B hepatic impairment experienced the moderate AE of worsening anemia, which was deemed possibly related to study drug. This subject had a screening hemoglobin of 7.8 g/dL which decreased to 5.9 g/dL at the end of the study. This subject was felt to have fluid retention, demonstrated by ascites and peripheral edema, with intravascular volume depletion potentially elevating the pre-procedure hematology values. During the course of the study, the subject was rehydrated and underwent several blood draws, both potentially lowering the hemoglobin level. There was no evidence of blood loss or acute hemolytic anemia during the study.

Based upon the above laboratory/pharmacokinetic results and clinical findings, the Applicant states that intranasal cocaine is safe and well-tolerated in subjects with Grade B and C hepatic impairment, and has therefore not proposed a reduced dose for this population.

It is worth noting, however, that the number of subjects with hepatic impairment in this study was quite low.

8.8. Additional Safety Explorations

8.8.1. Human Reproduction, Pregnancy, and Lactation

The Applicant did not evaluate the effect of cocaine topical solution administration on human reproduction or pregnancy. There have been no clinical trials evaluating therapeutic cocaine use in pregnant women. The information provided in the NDA submission is from the published literature and involves primarily the illicit use of cocaine in pregnant women, which represents much higher exposures than those used therapeutically. There has been no association demonstrated between cocaine abuse and congenital anomalies when other confounding variables were controlled (e.g., polysubstance abuse, maternal lifestyle, and socioeconomic factors). Prematurity, stillbirth, low birth weight, reduced head circumference, and placental abruption associated with illicit cocaine use have been documented in the published literature, but when a history of polysubstance abuse and lifestyle factors are controlled, these findings are not reported. There is, however, an association between intrauterine growth retardation and *heavy* cocaine use.

The published literature suggests that infant outcomes after low intrauterine exposure, defined as less than 70 ng BE in 10 mg of maternal hair, are similar to those with no in utero exposure. The reported systemic exposure after a therapeutic dose of cocaine is 10- to 100-fold less than that observed in low intrauterine exposure pregnancies, and therefore poses no risk of fetal

harm.

Animal data suggest that the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL) exposures were roughly ≥50-fold higher than the anticipated C_{max} after clinical exposure. Slight reductions in fetal growth have been observed in monkey studies but postnatal development in rats, rabbits, and monkeys was not significantly affected at toxic maternal doses. Reductions in birth weight, postnatal growth delays, and behavioral differences have been observed in rats at lethal maternal doses.

Neonatal exposure to cocaine can result in convulsions, hypertension, tachycardia, agitation, and irritability. Due to the chemical properties of cocaine and the acidic pH of human breast milk relative to plasma, ingested cocaine reaches higher concentrations in breast mild than in the plasma. Published reports of milk to blood ratios of 20 for cocaine have been suggested. The Applicant has estimated the total possible neonatal exposure to cocaine in the breast mild would be approximately 21 ng/mL (2-fold lower than the maximum maternal C_{max} of 43 ng/mL) after administration of 4% topical solution. This is considered an overestimation given that cocaine bioavailability is not likely 100%. Cocaine is estimated to be almost entirely eliminated from human breast milk in approximately 24 hours, or 5 half-lives.

8.8.2. Pediatrics and Assessment of Effects on Growth

There have been no clinical trials evaluating the safety and efficacy of cocaine topical solution in the pediatric population. The Applicant submitted an initial pediatric study plan (iPSP) on October 19, 2016. The Applicant requested deferral of studies in the entire age range of pediatric patients (age 0 to 18 years) until completion of the juvenile nonclinical studies. The Applicant proposed to conduct three clinical studies, as outlined in Dr. Kwatra's clinical pharmacology review:

(b) (4)

2. A Phase 4 study of the PK and safety of 4% RX0041-002 as a topical nasal anesthetic in pediatric patients from >2 years to <17 years of age for diagnostic procedures and surgeries on or though the mucous membranes of the nasal cavities; (b) (4)

3. A Phase 4 PK, efficacy, and safety study of 4% RX0041-002 as a topical nasal anesthetic in pediatric patients from 0 years to 2 years for diagnostic procedures and surgeries on or though the mucous membranes of the nasal cavities; (b) (4)

The plan was presented at the Pediatric Review Committee (PeRC) meeting on August 9, 2017.

The committee agreed with the Division that the Applicant's request for a deferral should be granted, however, there was concern that the proposed timeline was too long. This concern was conveyed to the Applicant in a teleconference on October 12, 2017, and agreement was subsequently reached on a shortened timeline.

8.8.3. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The single, intranasal administration of cocaine HCl to subjects participating in the clinical studies conducted by the Applicant was done by a study investigator. The subject participants did not have access to the cocaine solution. There were no reports of overdose signs or symptoms in any subject in either the 4% or 8% cocaine treatment groups throughout the development program. There were greater increases in heart rate and systolic and diastolic blood pressure in those subjects receiving the 8% topical solution, but no subjects experienced any other symptoms commonly associated with cocaine overdose (e.g., death, cardiac arrest, myocardial infarction, stroke, convulsions, agitation, etc.). For cases of cocaine overdose, supportive care is recommended as there is no antidote for reversal of symptomatology.

Cocaine is classified as a Schedule II substance under the Controlled Substances Act and as such has a high potential for abuse, psychological and/or physical dependence, and criminal diversion. In the clinical development plan for 4% cocaine topical solution, the proper DEA protocols were utilized for drug transfer, storage, and record keeping of administration and waste. Subject participants had no access to the cocaine solutions and each subject received only a single application. The Applicant, based upon previous input from FDA, closely monitored and recorded residual solution not absorbed by the cottonoid pledgets. Table 8, in Section 4.6 Devices and Companion Diagnostic Issues, indicates the average volumes of residual solution in the Phase 3 study. The residual volumes for all treatment groups were similar.

The protocols for transfer, storage, administration, and waste record keeping will be recommended for use of the marketed product.

The single application of cocaine to the nasal mucosa of study participants did not result in psychological or physical dependence and there were no withdrawal or rebound effects observed.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There are no reports for topical cocaine in FDA's Adverse Event Reporting System.
The reports where cocaine was listed as the primary suspect or was reported were due to illicit cocaine abuse and included death, cardio-respiratory arrest, cardiac arrest, respiratory arrest, tachycardia, myocardial infarction, agitation, and hypotension.

8.9.2. Expectations on Safety in the Postmarket Setting

Cocaine topical solution is a marketed unapproved product with a long history of clinical use in nasal and sinus surgery. While it has not been formally regulated by the Agency, there have been no reports of serious adverse events related to its use in this context. As previously mentioned, the majority of adverse event reporting in the published literature is from cases involving illicit use and abuse of the drug. The postmarketing experience with cocaine once approved, should remain similar to those reports in the published literature.

8.10. Additional Safety Issues From Other Disciplines

The pharmacology/toxicology review team has two concerns related to the nonclinical development program. First, the toxicology information required from the published literature for a thorough evaluation of the safety of the product and for labeling recommendations was not provided in the NDA submission. Second, the original non-clinical toxicology studies did not characterize the potential for local toxicity caused by the cocaine topical solution versus the diluent solution. Repeat studies were requested and on-going at the time of this review. The non-clinical toxicology concerns are of particular importance given the original formulation of the to-be-marketed product. GLS does not manufacture the marketed unapproved cocaine topical solution currently available, therefore the clinical experience with this product is limited to the clinical trials the Applicant conducted. Furthermore, the large amount of safety information in the published literature may not completely reflect the safety of the proposed marketed formulation. Please refer to the pharmacology/toxicology review for the final recommendations regarding the approvability of the NDA.

8.11. Integrated Assessment of Safety

This application is a 505(b)(2) application, thus the Applicant is relying on findings of safety for cocaine topical solution in the published literature. Additionally, the Applicant has conducted four Phase 1 and one Phase 3 study to support the safe use of their proposed marketed product, which is not currently marketed in the U.S. The Applicant's clinical development program included 372 subject exposures to their 4% cocaine topical solution, including subjects with a history of renal and hepatic impairment. The primary safety concerns regarding the administration of this drug product include increases in measured hemodynamic parameters and related adverse events, and the potential clinical effects on the nasal mucosa and ability to smell.

The sympathomimetic actions of cocaine raise safety concerns regarding elevations in measured hemodynamic parameters, including heart rate, and systolic, diastolic, and mean arterial blood pressure. In clinical practice, hemodynamic changes, either increases or decreases, are typically considered clinically relevant when they are equal to or greater than 30% above or below the baseline values. Measured changes to that degree generally result in a clinical intervention; e.g., increasing the depth of general anesthesia or administration of a beta blocking medication for increases in heart rate greater than 30% above baseline values. The

number of subjects who experienced increases in diastolic blood pressure equal to or greater than 30% of baseline values was much higher across all groups, including placebo, than the number who experienced increases in systolic blood pressure, suggesting cocaine may exert a greater effect on the vasculature during diastole. Increases in these measured parameters in the placebo-treated subjects may be due to procedural anxiety or discomfort, particularly considering 42% of placebo-treated subjects completed the procedure with no anesthetic or analgesic medication.

With the exception of a single subject, there were no reported adverse events related to hemodynamic changes in the Applicant's Phase 3 study. While these findings are reassuring, they do not entirely support the conclusion that there is no risk for the development of a cardiovascular-related adverse event for four reasons. First, there have been case reports of patients developing ventricular arrhythmias, myocardial ischemia, myocardial infarction, and cardiogenic shock associated with intranasal cocaine administration (Lormans et al, 1992; Lenders et al, 2013). Second, not all patients who receive intranasal cocaine may tolerate increases in heart rate and blood pressure of 30% above baseline values. Third, cocaine can cause vasoconstriction of the coronary arteries (Lange et al, 1989) and patients with a history of coronary artery disease may be at increased risk of developing myocardial ischemia and infarction. And lastly, because cocaine is a marketed unapproved drug product, most of the safety information has come from a limited number of controlled clinical studies, published case reports, and anecdotal clinical experiences, none of which are adequate substitutes for a large post-marketing safety database.

With respect to signs or symptoms of local toxicity, only two subjects, one in each of the cocaine treatment arms, had a shift from normal to abnormal nasal mucosa observed on Day 8 of the study. The observed changes were not considered adverse events. There appear to be no clinically relevant nasal mucosal changes as a result of topical cocaine solution. Similarly, there were no clinically relevant changes in smell assessments observed in subjects across all treatment arms. The number of subjects able to differentiate three odors during the testing increased from Day 1 to Day 8 of the study, suggesting improved smell.

The adverse event database from the Applicant's clinical studies supports the safe use of 4% cocaine topical solution as a topical anesthetic for nasal surgery. There were no deaths and no SAEs reported and no AE led to subject discontinuation. The severe AEs that were reported were headaches and based on the onset of the headache, it is not clear that there was a causal relationship to the administration of the cocaine solution. The vast majority of reports in the published literature of severe AEs, SAEs, and deaths are related to the illicit use of cocaine, which involves the administration of much higher concentrations and repeated use. A single, intranasal exposure is not expected to result in the AEs that have been reported with illicit use.

The clinical studies conducted by the Applicant in subjects with renal and hepatic impairment support the safe use of 4% cocaine topical solution in these patient populations. The results of the study in patients with hepatic impairment, however, should be interpreted with the

following caveat: certain measured plasma PK parameters for cocaine and its metabolites were higher in subjects with Child-Pugh Class B hepatic impairment compared to those with Class C impairment. Plasma cocaine and BE AUC_{0-t} and geometric mean C_{max} values were higher in the subjects with Class B impairment compared to those with Class C. . Based on these findings, it is recommended that subjects with hepatic impairment not receive a second dose of 4% cocaine topical solution in a 24-hour period.

In summary, the safety profile for this 4% cocaine topical solution appears similar to that of the currently marketed cocaine product as reported in the published literature and there are no outstanding safety concerns preventing approvability of this NDA.

9 Advisory Committee Meeting and Other External Consultations

There were no Advisory Committee Meetings or other external consultations requested during the clinical review of this NDA submission.

10 Labeling Recommendations

10.1. Prescribing Information

The proposed label underwent several revisions. The major edits, by section, are included below.

Section 1 Indications and Usage
As discussed throughout this NDA review, the proposed indication for cocaine topical solution is too broad. Edits were made to more accurately reflect the degree of anesthesia to be expected with the administration of topical cocaine, which then informs providers regarding the applicability of its use during procedures on or through the nasal cavities.

Section 2 Dosage and Administration
Suggested edits to this section further clarify the composition and size of the pledgets recommended for use with the cocaine solution and the maximum total dose recommended.

Section 5 Warnings and Precautions
Suggested edits to this section clarify the following clinical concerns:

- the potential for cocaine hydrochloride to lower the seizure threshold
- the potential for cocaine hydrochloride to increase blood pressure and heart rate
- the potential for a positive cocaine toxicology screening

Section 6 Adverse Reactions
The suggested edits to this section clarify the two most common adverse reactions, headache and epistaxis.

Section 7 Drug Interactions
Disulfiram, epinephrine and phenylephrine, and inhibitors of plasma cholinesterase were included in this section.

Section 8 Use in Specific Populations
The Division of Pediatric and Maternal Health has made extensive revisions to sections 8.1, Pregnancy, and 8.2, Lactation. The clinical pharmacology team has made revisions to section 8.7, Hepatic Impairment, and included section 8.8, Patients with Reduced Plasma Cholinesterase Activity. Refer to those reviews for complete labeling recommendations.

Section 14 Clinical Studies
The suggested edits to this section clarify the evaluated procedures during the Phase 3 study, the number of subjects who completed the study, and that no additional sedation or anesthesia was administered.

Suggested edits from other team disciplines are discussed in those reviews and consultations, including sections 8, 9, 10, 11, 12, and 13.

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not indicated at this time. If FDA becomes aware of future safety concerns, one may become necessary.

12 Postmarketing Requirements and Commitments

The pharmacology/toxicology team may request a PMR. Refer to that review.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 2013011

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

<table>
<tr><td colspan="3">0</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 0

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in

Sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from Applicant)</td></tr>
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<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
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/s/

RENEE L PETIT-SCOTT
12/13/2017

RIGOBERTO A ROCA
12/13/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 209963 **Applicant:** (b) (4) **Stamp Date: 23 Nov 2016**

Technologies, Inc.

Drug Name: Cocaine HCl **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?		X		The Sponsor has submitted a Summary of Clinical Safety for the 5 studies they conducted and tabular data from the FAERS database from 4th Quarter 1997 to 2nd Quarter 2016. Absent from the submission was incorporation of safety data from the published literature. Whether the safety data from the 5 studies is adequate to support approval of this NDA, will be a matter for review.
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		The Sponsor has submitted a Summary of Clinical Efficacy for their Phase 3

	Content Parameter	Yes	No	NA	Comment
					Study. Absent from the submission was incorporation of efficacy data from the published literature. Whether the efficacy data from their single Phase 3 study is adequate to support approval of this NDA, will be a matter for review.
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? <u>Study Number: 2015016</u> Study Title: Systemic Pharmacokinetics of Acute, Topical, Intranasal Administration of RX0041-002 in Healthy Male and Female Subjects Sample Size: 30 subjects Treatment Arms: 4% cocaine topical solution, single dose intranasal Location in submission: 5.3.3.1 <u>Study Number: 2013011</u> Study Title: A Phase III Investigation of Topical Application of RX0041-002 on Safety and Efficacy in Local (Topical) Anesthesia for Diagnostic Procedures and Surgeries on or Through the Accessible Mucous Membranes of the Nasal Cavities Sample size: 684 subjects (1:3:3 randomization; placebo:4%:8%) Treatment Arms: • 4 x 40 mg cocaine pledgets intranasal (4%, 160 mg) • 4 x 80 mg cocaine pledgets intranasal (8%, 320 mg) • Placebo Location in Submission: 5.3.5.1	X			
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			As stated in the Pre-IND Written Responses Only

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: 2013011 Indication: To determine analgesic success immediately after application of the drug product, and sustained analgesia throughout the diagnostic procedure or surgery for each nostril that received the study drug application.				document from Aug 2013, "whether a single clinical trial and your critical review of the available clinical literature will be sufficient evidence for approval of your marketing application will be a matter of review".
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			There were concerns expressed during the drug development plan about the unblinding of the placebo arm after the Von Frey Filament testing, prior to the surgical procedure. Our thorough review of the NDA submission will consider whether continued blinding of the 4 and 8% arms is sufficient.
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		There is no justification as to why the Von Frey Filament 6.1 (100 gm force) was selected for assessment of efficacy. Refer to prior correspondence from us, August 2013.
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		While this product is not currently approved anywhere in the world, it has a long history of clinical use and there is substantial published literature describing its biochemical and

	Content Parameter	Yes	No	NA	Comment
					pharmacological properties. The applicant has submitted (F)AERS data from 4th quarter 1997 to 2nd quarter 2016, which includes reports of cocaine as both the *primary* and *possible* causal agent of an adverse event. The Applicant will also be submitting a summary of the published literature per our request in the 74-day letter.
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			We advised the Applicant that the safety database requires a minimum of 500 subjects exposed to the proposed marketing product. In the development plan for this product, 647 total subjects were exposed, with 369 (57%) exposed to the 4% topical solution, the proposed marketing product. Whether this database captures all of the necessary safety information will be a matter for review, particularly because the Applicant has not provided an ISS incorporating safety information from sources other than their clinical trial database.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			The Applicant has submitted data collected from hemodynamic and respiratory monitoring from all 5 of their studies. It appears, however, that there are large portions (~25%) of these data that are missing and this appears to not have been adequately explained in the protocol deviation summaries.
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			The Applicant provided the narrative summary for a subject who had the adverse event of arrhythmia and uncontrolled HTN in response to an Information Request sent on 06 Jan 2017.
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			This product will be marketed as a single-dose administered by a licensed practitioner in a controlled and monitored setting. In this setting, there is no risk to patients for abuse or misuse. Storage, inventory, dispensing, and preparation, however, are areas of concern for office and surgery center staff misuse and diversion.
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			The datasets are in a reviewable format, however, there appears to be large numbers of missing vital sign data without apparent explanation. Please refer to comments under Question 26 of this checklist.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Safety database concerns:
   - The safety database submitted in this NDA may be adequate to characterize the safety of cocaine 4% topical solution intranasal. Specifically, the safety database contains a total of 647 subjects exposed to a dose of cocaine topical solution intranasal, with 369 of those subjects (57%) exposed to the proposed marketing dose of 4%, including those in the four Phase I studies. This may be an adequate number of exposures. If, however, there are signals that are identified concerning the safety of this product in any of the clinical studies, this database may need to be expanded.
   - In prior communication with the Agency, you indicated that you would be relying on safety information in the published literature in support of your application and would incorporate summaries of your findings into the NDA submission. In response to an Information Request sent on 06 Jan 2017 inquiring about the location of this information, however, you stated, *"...(b) (4) no longer was relying on referenced literature to support this NDA, but on (b) (4) own data, and therefore, although referenced, where applicable throughout our NDA, a comprehensive critical evaluation of the relevant literature data was not provided"*. Whether the data collected from your studies will be adequate to support this NDA submission, will be a matter of review, but referenced summaries from the published literature in support of the safety profile of this product are recommended.
2. Phase 3 study concerns:
   - The Phase 3 trial was conducted using a 6.10 Von Frey Filament for assessment of anesthetic/analgesic efficacy prior to initiation of the diagnostic or surgical procedure. During a prior correspondence, Pre-IND meeting, Written Responses Only, in Aug 2013, we requested justification for filament selection as a means of assessing efficacy. No such justification has been provided. A thorough review of the NDA submission will determine if the 6.10 filament was the appropriate mechanism to assess efficacy in both the placebo and cocaine treatment arms.
   - Unblinding the subjects and investigators to placebo vs. cocaine treatment was expressed previously as a concern during prior correspondence with the Agency. The primary endpoints for placebo and treatment arms are different due to unblinding; i.e. treatment success in the placebo group is defined as 0 on the VNRS during Von Frey Filament testing and success in the cocaine groups is defined as 0 on the VNRS during the Von Frey Filament testing *and* throughout the diagnostic or surgical procedure. Determination of the appropriateness of this unblinding will be a matter for review.

- Preliminary review of the endpoint data suggests a lower success rate in the 8% topical cocaine treatment arm when compared to the 4% cocaine treatment arm. This does not seem consistent with what would be expected as a result of administration of a higher concentration of topical local anesthetic to the nasal cavities. Additionally, preliminary review of the heart rate and blood pressure data suggests a higher percentage of subjects in the 4% cocaine treatment arm experienced higher systolic and diastolic blood pressure and heart rate readings when compared to those subjects in the 8% cocaine treatment arm. This does not seem consistent with what would be expected as a result of administration of a higher concentration of cocaine to the nasal cavities. Determining adequate resolution and explanation of these discrepancies will be a matter for review of the NDA submission.
- It will be a matter for review whether the increases observed in hemodynamic variables (SBP, DBP, and HR) are considered acceptable due to cocaine administration or whether significant increases, those above 30%, need to be considered adverse events and expressed as such in the labeling of the final marketed product.
- During previous correspondence with the Agency regarding the accuracy of the cocaine topical dose, advice was provided regarding measurement of residual cocaine solution not fully absorbed by the cotton pledgets. Preliminary review of the submission did not reveal a mechanism for assessing the accuracy of the dose of cocaine absorbed or for quantifying any residual solution. This poses a potential dosing error in addition to potentially becoming an inventory documentation concern for this Schedule II drug product.

3. Missing data:
    - There appears to be large numbers of subjects with incomplete vital sign data; i.e. there is only 75.5% of heart rate data captured/recorded for the 4% cocaine treatment arm during the 0 to 15 min time interval after application. Preliminary review of the NDA submission did not find adequate explanations for all of these missing data in the protocol deviation summaries. Determining the actual number and significance of this missing data will be a matter for review.
4. Labeling concerns:
    - The proposed labeling states the indication for use of this product is "…*for the induction of local anesthesia when performing diagnostic procedures and surgeries on or through the mucous membranes of the nasal cavities in adults"*. Preliminary analysis of the surgical procedures performed using the proposed marketing dose of 4% cocaine topical solution has revealed that 164 subjects (59.6%) had nasal endoscopy alone, which does not typically cause significant discomfort and generally requires minimal anesthetic for successful completion. The proposed indication, therefore, may be too broad and can only include the surgical procedures in which the drug product was tested and demonstrated to be safe and effective. Additional indications would need to be confirmed with future Phase 3 studies.
    - The literature supports the safety of cocaine dosing of 1-3 mg/kg or a maximum dose of 400 mg during a single application. The proposed marketing dose for this product is 160 mg, which for a small adult patient, <53 kg, would be greater than 3 mg/kg and could result in a higher incidence of adverse events. The labeling of the final product may need to reflect this body weight restriction.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

RENEE L PETIT-SCOTT
01/19/2017

RIGOBERTO A ROCA on behalf of LEAH H CRISAFI
01/19/2017