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)	209575
Priority or Standard	Standard
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Division/Office	DAAAP/OND
Reviewer Name(s)	Renee Petit-Scott, M.D.
Review Completion Date	18 July 2018
Established/Proper Name	4% Cocaine HCl Topical Solution 10% Cocaine HCl Topical Solution
(Proposed) Trade Name	Numbrino
Applicant	Cody Laboratories, Incorporated
Dosage Form(s)	Topical solution
Applicant Proposed Dosing Regimen(s)	One or two cotton or rayon applicator pledgets that are ½" x 3" containing anesthetic solution should be applied topically per nostril, with a maximum of 2 pledgets used per nostril; maximum 4 pledgets per procedure
Applicant Proposed Indication(s)/Population(s)	For the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities
Recommendation on Regulatory Action	Complete Response Action for Numbrino™ 4% and 10% topical solutions
Recommended Indication(s)/Population(s) (if applicable)	For the introduction of local (topical) anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
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 Council for Harmonization
IND	Investigational New Drug Application
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 or package insert
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

The cocaine hydrochloride topical solutions, hereinafter referred to as cocaine HCl or cocaine, manufactured by Lannett Holdings, Incorporated (Inc.) and subsequently Lannett Company, Inc., have been marketed unapproved drug products in the United States since 2008. The Agency approved a cocaine hydrochloride topical solution 4% manufactured by Genus Life Sciences, Inc. in December 2017. The available formulations from Lannett Company, Inc. include 4% (40 mg/mL) and 10% ((b) (4) topical solutions. Cody Laboratories, Inc., a wholly owned subsidiary of Lannett Company, Inc., is pursuing a 505(b)(2) pathway for approval of their manufactured 4% and 10% cocaine topical solutions relying on published literature to support the efficacy and safety of the drug product and data collected from their own clinical trials.

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. Cody Laboratories, Inc., has developed a (b) (4) .
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.

Cody Laboratories, Inc. intends to manufacture and market cocaine 4% and 10% topical solutions under the trade name of Numbrino. The proposed indication is as follows:

> *for the introduction of local (topical) anesthesia for diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities*

The proposed dosing is two cotton or rayon pledgets, each containing 40 mg for the 4% topical solution or (b) (4), applied to each nasal cavity for 20 minutes prior to surgery. The total proposed maximum dose is 160 mg intranasal for the 4% topical solution and (b) (4).

Of note, Lannett Holdings, Inc. and subsequently Lannett Company, Inc. were the companies

that originally met with Division throughout the Investigational New Drug (IND) and pre-NDA phases of the drug development program.

1.2. Conclusions on the Substantial Evidence of Effectiveness

According to my review of the submitted clinical data in the application and review of the articles in the published literature, I recommend a complete response (CR) action for both Numbrino™ 4% and 10% topical solutions.

The Applicant did demonstrate that both Numbrino™ 4% and 10% topical solutions provided adequate analgesia/anesthesia for successful completion of the diagnostic procedures and surgeries evaluated during the two Phase 3 studies. (b) (4)

My recommendation for a CR action for Numbrino™ 4% is based entirely on lack of information regarding the impact of cocaine topical solutions the QT interval of the ECG. In lieu of a thorough QT (TQT) study, the Applicant conducted a subpopulation analysis of the data obtained from their Phase 3 studies to satisfy the TQT requirement. This subpopulation analysis, discussed in Section 8.4.9 of this review, was not adequate to evaluate the potential impact of Numbrino 4% on the QT interval. Future approval of Numbrino 4% topical solution appears likely if the results from the planned TQT study are supportive of its safety.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Cocaine hydrochloride topical solutions have been used for decades as anesthetic and vasoconstrictive agents for surgeries involving the nasal mucosa, septum, and superficial sinuses. Until December, 2017, cocaine HCl 4% (40 mg/mL) topical solution was a marketed unapproved product in the United States. Cocaine HCl 10% ((b) (4)) topical solution is currently available as a marketed unapproved product. While the 4% and 10% topical solutions have been the most widely used concentrations in clinical practice, additional concentrations of 6% and 8% have also been used. It has been suggested that in general, the more concentrated cocaine solutions result in improved efficacy (i.e., improved topical anesthesia and decreased surgical bleeding), but also result in more notable cardiovascular responses such as hypertension and tachycardia. The Applicant conducted two Phase 3 studies, COCA4vs10-001 and COCA4vs10-002, which evaluated topical anesthesia after administration of 4% and 10% cocaine HCl topical solutions versus placebo during nasal procedures and surgeries. Study COCA4vs10-001 was terminated early due to lack of efficacy (immediate and sustained analgesia) of the 4% cocaine HCl topical solution. The results of Study COCA4vs10-002 did demonstrate immediate and sustained topical anesthesia, primary efficacy endpoint, for performance of the evaluated procedures for both the 4% and 10% cocaine HCl concentrations, when compared to a placebo solution. (b) (4)

In office-based procedures involving conscious, unsedated patients, cocaine topical solutions 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 studies. Invasive procedures such as sinus ostial dilation, however, are likely to cause more discomfort resulting in the need for additional anesthesia beyond topical cocaine. For example, in Study COCA4vs10-002, one of the two patients undergoing sinus ostial dilation required additional anesthesia beyond the administered 10% topical solution for successful completion of the procedure. In my clinical experience, the true therapeutic benefit of topical cocaine administration during diagnostic procedures or surgeries on or through the mucous membranes of the nasal cavities is to decrease nasal congestion, minimize surgical bleeding, and improve visualization. Fiberoptic nasal endoscopes are used to visualize the internal structures of the nasal cavities and sinuses during diagnostic or surgical procedures, and this becomes more challenging in the presence of active bleeding or mucosal swelling, potentially resulting in prolonged surgical/procedural time. During the performance of invasive, painful 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 Applicant evaluated nasal mucosal capillary blood flow and vasoconstriction using laser Doppler in Study LNT-P6-733 and the results support the claim of decreased

surgical bleeding with administration of topical cocaine. However, the Phase 3 studies did not formally evaluate a measurable decrease in surgical bleeding. Investigators provided a subjective assessment (i.e., yes/no response) regarding the adequacy of procedural hemostasis. (b) (4)

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 and diastolic blood pressure. In the Applicant's Phase 3 studies, a large percentage of subjects in both cocaine treatment groups had increases in heart rate greater than 30% above baseline values, which are considered clinically significant and could result in a pharmacological intervention depending on the clinical setting and the patient's co-morbid medical conditions. A higher percentage of subjects in the 10% treatment group experienced these increases compared to subjects in the 4% treatment group. Additionally, increases in blood pressure measurements greater than 30% above baseline values were observed in the Phase 3 studies, with diastolic blood pressure more affected than systolic. In Study COCA4vs10-002, some subjects treated with 10% cocaine HCl topical solution experienced increases in diastolic blood pressure that appeared to be higher than those observed in subjects treated with 4% cocaine HCl topical solution. Similar to the heart rate data, a larger number of subjects treated with 10% cocaine HCl solution experienced increases in diastolic blood pressure compared to subjects treated with 4% cocaine HCl solution. (b) (4) .

With respect to the risks of adverse events associated with topical cocaine administration, the system organ class (SOC) with the largest number of reported treatment-emergent adverse events (TEAE) was vascular disorders, and hypertension was the most frequently reported TEAE. The reported incidence of hypertension was higher for subjects in the 10% cocaine HCl treatment group, compared to subjects in the 4% cocaine HCl treatment group and subjects in the placebo group. The cardiac disorders SOC had the second largest number of reported TEAEs, and included tachycardia, sinus tachycardia, and palpitations. Subjects treated with 10% cocaine HCl solution consistently experienced a larger number of tachycardia, sinus tachycardia, and palpitation TEAEs compared to subjects treated with either 4% cocaine HCl or placebo solutions.

There were no clinically significant atrial or ventricular arrhythmias reported. There was a single episode of myocardial ischemia in a male subject treated with the 10% topical solution, which will be discussed in further detail in the Section 8.4.2, Serious Adverse Events. While the lack of a large number of reported cardiac conduction abnormalities or myocardial ischemic events is reassuring, it does not entirely support a conclusion that there is an acceptable 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 above baseline values that were observed in the Applicant's Phase 3 studies and it appears

that the systemic exposure with these cocaine topical solutions is much higher than that reported for the approved 4% solution. (b) (4) 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 was a marketed unapproved drug product until December, 2017, most of the safety information has come from a limited number of controlled clinical studies, epidemiological studies, published case reports, and provider surveys and anecdotal clinical experiences, none of which are adequate substitutes for the information expected from the regular annual reporting required after NDA approval. Additional risks related to administration of intranasal cocaine include nasal mucosal irritation and alterations in smell. While not formally evaluated in the Applicant's Phase 3 studies, there did not appear to be any patients with such complaints.

In summary, the Applicant's Phase 3 studies did demonstrate that both 4% and 10% cocaine topical solutions are efficacious topical anesthetics in the setting of minimally invasive diagnostic procedures and surgeries 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 for patient comfort and cocaine's primary therapeutic benefit is in the reduction of surgical bleeding. The cardiovascular risks associated with the administration of 4% cocaine HCl topical solution can likely be mitigated by careful patient selection, requiring a thorough history and physical exam, and with continuous hemodynamic monitoring during the entire treatment and post-operative periods. (b) (4)

Lastly, an argument could be made that because the cocaine topical solutions have a long history of clinical use in the practice of otorhinolaryngology, regulatory approval of submitted marketing applications should be somewhat of a foregone conclusion. However, if a long history of clinical use is the threshold for marketing approval, there would then seem to be no scientific justification for recommending drug manufacturers submit applications. The NDA review process for marketed unapproved products must be as diligent and scientifically sound as the review process for any submitted NDA. A large published literature database, composed primarily of case reports, practitioner surveys, and epidemiological studies cannot be a substitute for the information provided from well-designed, controlled Phase 3 clinical studies demonstrating, or confirming, the reported historical safety and efficacy of a drug product.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diagnostic and surgical procedures on or through the mucous membranes of the nasal cavities 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 solutions may be low in the general population, patients requiring nasal surgery have a high likelihood of receiving cocaine. Furthermore, those patients requiring repeat or additional nasal diagnostic procedures may receive subsequent doses of cocaine topical solutions.**
Current Treatment Options	• 4% cocaine topical solution, available from another manufacturer, is the only approved local anesthetic product available in the United States for use in nasal diagnostic and surgical procedures. While there is currently no approved 10% cocaine solution available, it has been used in the past for nasal procedures and surgeries. • Other local anesthetics in combination with a vasoconstrictor agent are commonly used during nasal surgeries. They can be administered via mucosal injection or aerosolized. Examples include lidocaine (typically 2% or 4%) or tetracaine with either epinephrine or phenylephrine. • Other agents commonly administered include benzocaine and the decongestant oxymetazoline available as nasal sprays, and topical silver nitrate for chemical cauterization of small areas of bleeding. • MAC or general anesthesia are used for invasive or painful procedures that cannot be successfully completed in the	**While there are multiple unapproved local anesthetics with acceptable risk benefit profiles for use during nasal procedures and surgeries, there is currently only one approved product, 4% topical cocaine solution from another manufacturer** (b) (4) [redacted] **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
	office under topical anesthesia.	
Benefit	• The results from the Applicant's Phase 3 studies found that both 4% and 10% cocaine topical solutions administered via cotton or rayon pledgets, maximum two per nostril, did result in adequate anesthesia for successful completion of the majority of evaluated procedures, including nasal endoscopy, transnasal laryngoscopy, and sinus endoscopy. In Study COCA4vs10-002, both the 4% and 10% cocaine topical solutions were statistically significantly more efficacious compared to placebo during vFF testing, resulting in fewer subjects reporting pain scores above zero on the NPRS. In Study COCA4vs10-001, (b) (4) the study was terminated early due to lack of efficacy of the 4% solution. • The ability to minimize surgical bleeding with use of topical cocaine administered to the nasal mucosa, albeit difficult to accurately quantify, is a benefit of this medication. The presence of bleeding can obscure the surgical view and result in increased surgical times and potentially increased medical cost. For this reason, nasally administered local anesthetics typically contain a vasoconstrictor agent such as epinephrine or phenylephrine. Because of cocaine's inherent sympathomimetic properties, no additional vasoconstrictor medication may be needed. The Applicant did assess capillary blood flow and vasoconstriction in Study	**For the diagnostic procedures and surgeries evaluated during the Applicant's Phase 3 studies, 4% and 10% cocaine HCl topical solutions provided adequate topical anesthesia.** (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	LNT-P6-733 using laser Doppler. The results indicate that both 4% and 10% solutions significantly decreased capillary blood flow in the nasal mucosa compared to the blood flow observed after administration of placebo. Furthermore, the adequacy of hemostasis was assessed in the Applicant's Phase 3 studies using investigator observation and responses to a yes/no question. (b) (4) generally-speaking, surgeons are acutely aware of surgical bleeding and can easily identify situations when it has not been well-controlled. • An additional benefit of cocaine is the topical route of administration, versus submucosal injection, which results in less trauma to the nasal mucosa. • Because cocaine solutions have a long history of clinical use, there is a large volume of information in the published literature regarding their safety and efficacy. • The vast majority of adverse events and serious adverse events documented in the published literature and the FDA Adverse Event Reporting System (FAERS) attributed to cocaine have been described in cases of illicit use, where the dose and route of administration differ significantly from those observed 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.	(b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety issue of greatest concern is the potential for clinically relevant changes in measured hemodynamic parameters, a well-known risk associated with the clinical and illicit uses of cocaine. Increases in heart rate, and systolic and diastolic blood pressure are the most commonly observed vital sign changes. While increases in core body temperature have been observed, it is more common after administration of significantly larger doses, such as with illicit use. • 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, in doses ranging from 2 to3 mg/kg. The degree of coronary vasoconstriction was greater in subjects with a history of either coronary artery disease or cigarette smoking. • 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 agent such as epinephrine was administered, likely 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	**Aside from the lack of a TQT evaluation, the Applicant otherwise submitted an adequate safety database to evaluate the risks associated with the topical administration of cocaine for use during nasal diagnostic procedures and surgeries. Specifically, in the Applicant's drug development program, 347 patients were exposed to 4% topical solution and 341 were exposed to 10% topical solution.** **The impact of intranasal cocaine administration on the QT interval notwithstanding, the primary safety concern involves increases in measured hemodynamic parameters and adverse cardiac events, including myocardial ischemia and infarction, and arrhythmias. During the Applicant's Phase 3 studies, increases in measured heart rate and systolic and diastolic blood pressure were well-tolerated in the majority of 4%-treated subjects, and none experienced an adverse cardiac event; however, subjects with a history of myocardial infarction, coronary artery disease, congestive heart failure, irregular heart rhythm, abnormal screening ECG, or uncontrolled hypertension, defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, were excluded from the Applicant's Phase 3 studies. The clinical implications of administration of cocaine topical solutions in those patient populations is not known and not recommended, as will be addressed in the final product labeling.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sensitivity, including plasma cholinesterase deficiency, should not receive cocaine topical solution. Additionally, because plasma cholinesterase activity may be diminished by certain medications, including oral contraceptives and plasma cholinesterase inhibitors, the risk of increased plasma levels, prolonged duration of action, and occurrence of adverse events is possible after cocaine administration. • Patients receiving amphetamines, MAOIs, SSRIs, SNRIs, or other medications that act to either inhibit the reuptake or metabolism of catecholamines should not receive cocaine topical solutions. 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). • An additional concern with administration of these cocaine topical solutions involves the systemic exposure. Compared to the approved 4% cocaine solution, this 4% formulation appears to have a much greater systemic exposure, as demonstrated by increased mean C_{max} values (43 ng/mL compared to 142 ng/mL), which may result in larger increases in measured hemodynamic parameters and the occurrence of adverse events. Increased number of AEs with this formulation. (b) (4) [redacted] This apparent increased systemic exposure will also impact the amount of cocaine present in breast milk. Based on its physiochemical properties, cocaine is expected to be present in higher concentrations in breast milk than in	**The hemodynamic changes observed in subjects treated with the 4% solution can likely be mitigated by labeling recommendations, including careful patient selection, continuous hemodynamic and ECG monitoring, and availability of medications necessary for the treatment of clinically significant changes. Premature removal of the pledgets is also an effective mitigation strategy, recognizing, however, that only additional, not on-going, systemic exposure will be limited.** (b) (4) [redacted]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	maternal blood and because the maternal exposure will be higher after administration of these products, the amount of cocaine present in breast milk is also likely to be higher, placing nursing infants at risk for cocaine exposure. • 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 and pledget disposal, is required.	(b) (4) **The presence of cocaine in breast milk can be described in the product label, mitigating the potential risk for neonatal and infant exposure. Other safety concerns, such as the use of concomitant medications, including those which influence catecholamine or local anesthetic metabolism, can be mitigated by information provided in the product label.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		The risk of diversion or abuse by office staff can be mitigated with comprehensive drug inventory and adherence to controlled substance protocols and procedures. **Based on the data presented, the evaluations performed, and my analysis of all submitted information, I recommend a CR action for Numbrino™ 4% and 10% topical solutions. Because an adequate QT evaluation appears to be the single outstanding issue preventing approval of Numbrino™ 4% topical solution, future approval is likely if the results from the planned TQT study are supportive of its safety.** (b) (4) [redacted]

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

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, trachescopy, bronchoscopy, bronchography

Source: Verlander and Johns, 1981

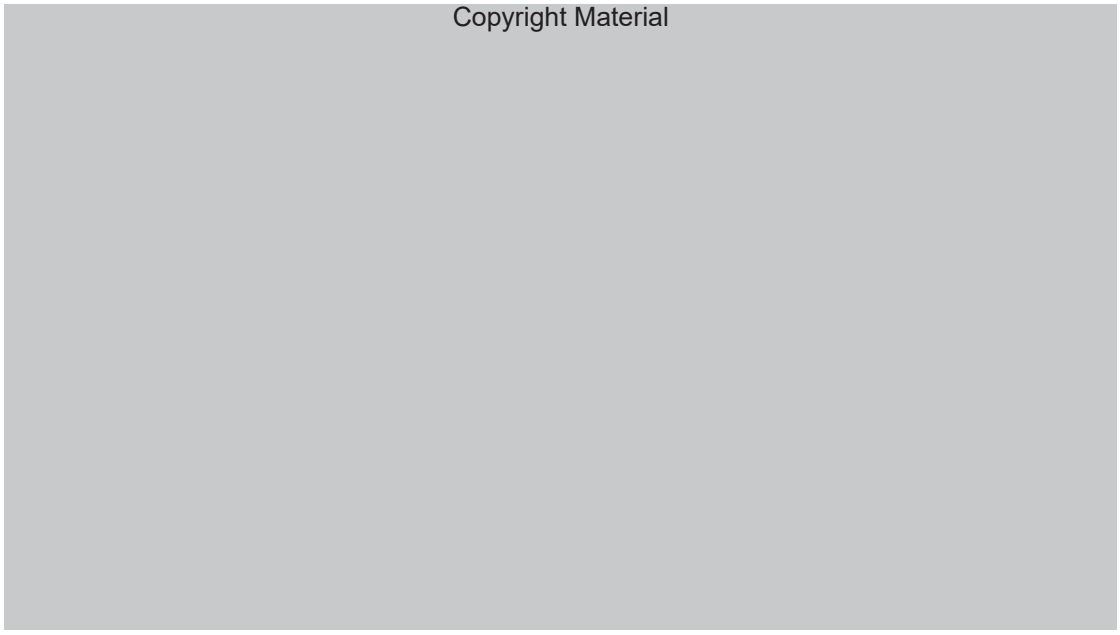
2.2. Analysis of Current Treatment Options

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. Prior to the approval of Goprelto, 4% cocaine HCl topical solution, in December, 2017, a long-standing dilemma in the delivery of controlled and measurable anesthesia for the performance of nasal and sinus surgical procedures was that there were no FDA-approved products labeled for this use. Consequently, physicians had been 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 and the recommended delivery route for the approved Goprelto cocaine solution. 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 the use during nasal surgery. It can be administered via soaked cotton pledgets, aerosolized, or via submucosal injections. It can be nebulized for use during endotracheal intubation, however, systemic exposure 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 use 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 Name	Relevant Indication	Year of Approval	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA approved Treatments					
Goprelto®	For the induction of local anesthesia of the mucous membranes when performing diagnostic or surgical procedures on or through the nasal cavities in adults	2017	Intranasal	Predictable topical anesthesia and decongestion	• increases heart rate and blood pressure • vital sign and ECG monitoring recommended • may lower seizure threshold • not to be applied to denuded or damaged skin • not recommended for patients with uncontrolled hypertension, unstable angina, myocardial infarction, coronary artery disease, or congestive heart failure
Other Treatments					
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 artery 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 – longer duration of action • oxymetazoline – not recommended for use in patients with poorly controlled

Product Name	Relevant Indication	Year of Approval	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
					hypertension, acute active thyroid disease, or frequent (≥5 per day) nose bleeds • max dose 1.5 mg/kg (2.5 mg/kg with epinephrine)
Hurricaine® spray (20% benzocaine spray)	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 – a 2 sec spray can cause a statistically significant but 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

The four and ten percent cocaine topical solutions have been manufactured and marketed by Cody Laboratories, Inc., and previously by Lannett Company, Inc., in the United States since December 2008. The recently approved Goprelto® is a four percent solution manufactured and marketed by Genus Lifesciences, Inc. There is data to suggest that the clinical use of cocaine for nasal and sinus surgical procedures is declining. This decline may primarily be due to two reasons. First, the required documentation regarding the administration, waste, and inventory for cocaine topical solutions, because of cocaine's Schedule II classification under the Controlled Substances Act, appears to be increasing and becoming more time-consuming. In an office setting of rapid patient turnover, that presents challenges to efficiency that are not well-tolerated. Second, cocaine has a high abuse potential, making diversion a concern, and while this is not a new concern, it may be influencing prescriber practices to a greater degree. Additional explanations for declining clinical use may include safety concerns, lack of availability in all clinical settings, poor surgical field, and other reasons, as described by De, *et al* (2003).

In 2009, 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 106499. A Phase 3 protocol synopsis was submitted in 2010 and a Special Protocol Assessment (SPA) for Study COCA4vs10-001 was submitted in 2011. A second SPA was submitted in 2015 for Study COCA4vs10-002 (refer to Table 3 for a summary of the regulatory history). During this 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 solutions 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 solutions in the clinical setting peaked in 2004 and then steadily declined to the lowest utilization rates in 2012, as depicted in Figure 2. Subsequent to the completion of this consult, Dr. Gill clarified in email correspondence that the billings described below are for almost exclusively 4% topical solution. There was a very small amount of sales data for unknown strengths and for "100% strength," which is most likely an error in recording and may indicate 10% topical solution.

Figure 2. Hospital and Emergency Department Billings for Cocaine Hydrochloride

3.2. Summary of Presubmission/Submission Regulatory Activity

Lannett Holidings, Inc. requested a pre-IND meeting in September, 2009, to begin discussions with the Agency concerning a marketing application for cocaine topical solutions, both four and ten percent. The following table summarizes the interactions between Lannett Holdings, Inc., Lannett Company, Inc., and Cody Laboratories, Inc. and the Agency.

Table 3. Regulatory History Activity

Meeting/Communication/Date	Event/Key Clinical Issues
Pre-IND 106499/Type B meeting/Dec. 15, 2009	Discussion regarding the following topics: • acceptability of a priority review for this NDA and a clinical SPA agreement • 300 treated subjects may be an acceptable number, with supporting information from the published literature • non-inferiority design not appropriate given no approved products for use as an active comparator • rationale supporting the clinical use of both 4% and 10% solution • possible need for a Risk Evaluation and Mitigation Strategy (REMS)
Phase 3 protocol synopsis received/May 21, 2010	Clinical comments to the Sponsor included the following: • adequate safety and efficacy data to support the proposed indications for the clinical use of both 4% and 10% solutions • placebo, lower dose of cocaine, or other local anesthetic with a vasoconstrictor could be used as a control • vital sign monitoring should include blood pressure, heart rate, cardiac rhythm, and room air oxygen saturation and should be performed at baseline and every 5 minutes until discharge from phase I recovery • 12-lead ECG should be recorded prior to and following administration of study drug • the safety database should include a minimum of 300 subjects and can be supported with information from the published literature • both natural and synthetic Active Pharmaceutical Ingredients (API) do not need to be used in the Phase 3 studies
SPA received/Feb. 2, 2011	Clinical comments to the Applicant and answers to posed questions include the following: • vital sign and ECG data as well as treatment time need to be captured on the Case Report Forms (CRF) • strategies to adjust for multiplicity and missing data need to be included in the statistical analysis plan • sample size should be calculated using a two-sided α=0.05 level of significance

Meeting/Communication/Date	Event/Key Clinical Issues
	• the total number of cocaine applications should be considered in the analysis • a Data Safety Monitoring Board composed of a single individual is not appropriate, however, one may not be needed given the widespread clinical use of cocaine in the proposed setting • foreign trial sites are permitted provided the findings can be extrapolated to the U.S. population • subjects' body temperature will need to be assessed • a pharmacovigilance plan will not be required • the proposed indication for use on the mucous membranes of the oral and laryngeal cavities is not being evaluated in the Phase 3 studies • primary efficacy endpoint(s) need to be clarified • the protocol does not appear to be powered to detect a difference in hemostasis between the two cocaine concentrations (b) (4) • randomization should include all study treatments and only those subjects treated with cocaine topical solutions should be advanced to the next phase of the study • investigators should remain blinded to the active treatment(s) • study stopping criteria are needed • the Informed Consent Document (ICD) needs to clarify which subjects will receive $200 compensation
Teleconference/March 14, 2011	Discussion was focused on selection of endpoints, randomization, consideration of a different design strategy, and the statistical analysis plan. The Division informed the Sponsor that additional advice would be provided in response to the submitted SPA.
SPA No Agreement letter issued/March 18, 2011	Phase 3 protocol deficiencies conveyed to the Sponsor, as outlined above.
SPA resubmission/received June 27, 2011	The Division agreed that many of the previous outstanding issues had been adequately addressed, and those remaining were conveyed in a letter to the Sponsor dated Aug. 11, 2011.
Written communication, SPA No Agreement/Aug. 11, 2011	Rather than specifically address the questions provided and responses to previous advice, a protocol description

Meeting/Communication/Date	Event/Key Clinical Issues
	was provided to the Sponsor to adequately address the Division's needs. The following are key components of the protocol: • the patient population needs to include the most commonly performed procedures as well as procedures that would be expected to require only the 4% formulation and only the 10% formulation • comparing success rates of the two cocaine formulations for each procedure will inform labeling recommendations as to which formulation is more appropriate for each procedure • treatment success should be defined as lack of discomfort during vFF testing and during the surgical procedure • safety database needs to include at least 500 subjects • use of an Independent Physician Monitor is acceptable but not required • foreign sites are acceptable • (b) (4) • acceptable study stopping criteria • for subjects receiving a second application of cocaine, it is not acceptable to test the null hypothesis that the expected numbers of successes are the same for the cocaine and placebo groups
SPA resubmission/received Nov. 9, 2011	The following changes were made to the proposed protocol: • surgical procedures involving the pharyngeal and laryngeal cavities will not be included in the study protocol and those indications will be removed from future labeling • the Phase 3 protocol will be randomized, prospective, multisite, double-blind, placebo-controlled, parallel-group study • secondary objectives were modified • treatment failures will be followed for safety • vital sign data will be captured on the CRF • total number of cocaine-exposed subjects will be 556 • (b) (4)

Meeting/Communication/Date	Event/Key Clinical Issues
	• cocaine and placebo treatment groups may receive a second application of study drug if the Numeric Pain Score (NPS) is >0 during vFF testing using two different filaments
SPA Agreement/Dec. 16, 2011	Additional comments included advice regarding adverse event causality, clarification for presumed typographical errors, documentation of solution volume administered, and protocol for following subjects in the safety only group.
IND 106499 submitted/Feb. 6, 2013	The IND was placed on Full Clinical Hold for the following reasons: • 16 mL of cocaine solution is double the previously agreed upon maximum dose • the dose and type of local anesthetic used as a rescue medication was not specified and cocaine solution should not be part of the anesthetic management for placebo subjects or as a rescue medication for cocaine treatment failures • no immediate access to ACLS equipment • the agreed upon exclusion criterion of hypertension was changed to uncontrolled hypertension • Phase I recovery needs to greater than 10 minutes post-procedure • clarification of the use of sedation Additional non-hold comments included the following: • clarification regarding the intent to collect efficacy data on the 476 subjects enrolled in the safety only portion • proposed vFF is not an appropriate stimulus for baseline sensation assessments • allergic reaction to either all ester local anesthetics or all local anesthetics should be included as an exclusion criterion • “reportable adverse events” should be changed to “Adverse Events of Special Interest” • pseudocholinesterase deficiency is not associated with malignant hyperthermia The following additional information was provided to address questions posed in this submission: • data collected from patients undergoing general anesthesia with concomitant cocaine application

Meeting/Communication/Date	Event/Key Clinical Issues
	would not contribute to the primary endpoint of analgesic success
Teleconference/March 7, 2013	Sponsor informed of the IND status (Full Clinical Hold) due to safety issues, including dosing and safety monitoring.
Full Clinical Hold letter issued/April 5, 2013	The Full Clinical Hold letter included the clinical issues discussed above.
Complete Response to Full Clinical Hold/Aug. 13, 2013	The Sponsor's responses to the Full Clinical Hold issues are as follows: • subjects in all treatment groups will receive a single topical dose of study drug – maximum dosing includes 160 mg for the 4% solution and 400 mg for the 10% solution (one 4 mL vial per subject per procedure) • cocaine will not be administered as a rescue anesthetic for treatment failures or placebo subjects • ACLS-certified physician and emergency crash cart immediately available at all study sites • post-procedure monitoring will be for a minimum of 75 minutes following pledget removal • all subjects with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg will be excluded • ECG findings of sinus bradycardia and sinus tachycardia will be evaluated by the investigator to determine the need for study exclusion • sedation will not be administered; however, drugs to "lessen anxiety" may • efficacy data will be capture for the 476 subjects in the safety only portion of the study • subjects with a known allergy to ester local anesthetics will be excluded • Adverse Events of Special Interest included in the protocol • clarification that subjects with pseudocholinsterase deficiency may be at risk for delayed recovery from certain anesthetics • enrolled subjects and staff personnel will be monitored for abuse, misuse, diversion, and overdose
Teleconference/Sept. 5, 2013	Teleconference held to seek clarification for outstanding issues. The discussion included the following topics:

Meeting/Communication/Date	Event/Key Clinical Issues
	• size and type of pledget proposed for use • 4 mL solution would be sufficient to soak two pledgets • pledgets applied for 20 minutes • post-procedure monitoring will be for a minimum of 90 minutes following pledget removal • placebo subjects and cocaine treatment failures will have the procedure postponed until the following day • sedatives administered only for anxiolysis • study drug will be tracked and monitored with appropriate documentation
Removal of Full Clinical Hold/Sept. 12, 2013	The Phase 3 clinical trial can proceed.
SPA Modification Agreement/Sept. 24, 2013	SPA modified according to previously agreed upon protocol changes and edits.
Medical Necessity Determination/Feb. 17, 2014	Lannett Company, Inc. was being inspected regarding issues related to another manufactured product. There was not a concern regarding the manufacture of cocaine topical solutions, however, the inspector requested a determination of medical necessity, which was granted.
Type A meeting/Jan. 6, 2015	Lannett Company, Inc. requested this meeting to discuss the unanticipated outcome of lack of efficacy for the 4% cocaine solution. The following information was provided: • the current study cannot be continued with a revised sample size estimation but should continue to capture remaining safety data • a new clinical study should be conducted to evaluate efficacy of the 4% cocaine solution compared to placebo • because the efficacy portion of the study is complete, the SPA cannot be amended Lannett Company, Inc. proposed the following changes for the planned additional Phase 3 study protocol: • all four pledgets will be soaked with 1 mL of study drug and the number of pledgets used will be at the discretion of the investigator based on the procedure performed • a vFF of 5.88 (60 gram force) will be used instead of the 5.18 (15 gram force) with specific instructions for anesthesia testing

Meeting/Communication/Date	Event/Key Clinical Issues
	• standardize language regarding pressure versus pain for enrolled subjects • Sponsor suggested that the required 24 hour waiting period for placebo subjects and treatment failures may bias subjects against waiting and increase the number of false positives in the placebo group
New Phase 3 protocol submission/Feb. 25, 2015	This protocol is the result of the Type A meeting held on Jan. 6, 2015. Outstanding issues included the following: • use of validated pain scale as opposed to the subjective statement, "are you comfortably numb?" • unblinding after vFF testing is not acceptable given no other treatment arms • placebo subjects and treatment failures will wait a minimum of 90 minutes, as opposed to the previously planned 24 hours – During the meeting, however, the Agency indicated 110 minutes would be an acceptable waiting time • adverse reaction intensity of "very minor" not descriptive
SPA submitted/received May 11, 2015	Withdrawn. No protocol was submitted.
SPA submitted/ received May 28, 2015	Protocol reviewed. No significant clinical issues identified. The Agency recommended a new protocol number be assigned to differentiate the studies.
SPA Modification Agreement letter issued/July 9, 2015	No additional advice provided.
Initial Pediatric Study Plan (iPSP) submitted/Oct. 21, 2015	Written feedback in the form of a tracked-changes document sent to Sponsor.
Agreed iPSP/Oct. 14, 2016	No additional advice provided.
Type B Meeting/Teleconference/April 18, 2017	The following advice was provided: • the conditionally acceptable proprietary name and proposed generic names are acceptable for use in the NDA • cocaine is a Schedule II substance according to the Controlled Substances Act • a review of the published literature should include a comprehensive review and analysis of the worldwide published literature and also narratives involving the misuse and abuse of cocaine

Meeting/Communication/Date	Event/Key Clinical Issues
	• determinations regarding the safety and effectiveness of cocaine topical solutions will be made during the review cycle • the Integrated Summary of Efficacy should be more than a pooled analysis of the clinical studies • simple or naïve pooling is not appropriate for the studies conducted as the randomization ratios differ, however, a weighted meta analysis is acceptable • an integrated safety data pool containing all studies conducted is acceptable and should include summaries of specific adverse events known to occur with cocaine toxicity • cocaine application via pledgets should be described in the label • a REMS is likely not indicated • the 4-month, 120-day safety update should include any new information, foreign or domestic
Proprietary Name Request Conditionally Acceptable/Aug. 28, 2017	No additional advice provided.
NDA 209575 Submission/Sept. 21, 2017	NDA received.
NDA Filing/Nov. 20, 2017	NDA filed.
Teleconference, March 12, 2018	Discussion with the Applicant regarding the completed review by the QT-IRT team and the conclusion that the subpopulation analysis is not adequate to fulfill the thorough QT evaluation requirement.
Study COCA-QT-01 Protocol Submission/April 30, 2018	The Applicant submitted a TQT study in response to our teleconference on March 12, 2018. The QT-IRT reviewed the protocol and has provided the following feedback (paraphrased from Dr. Lars Johannesen's primary review, dated May 31, 2018, and follow-up memorandum, dated June 1, 2018): • Because of the anticipated changes in heart rate, the proposed supratherapeutic dose should be replaced with 4% topical solution • Because a dose-dependent increase in heart rate was observed in subjects in the Phase 3 studies, an alternate method for assessing QT changes will be needed • The analysis and reporting of results should be consistent with the recommendations described in

Meeting/Communication/Date	Event/Key Clinical Issues
	the articles by Garnett, et al (2017) and Garnett, et al (2018) • Additional guidance provided for documents required with submission of the QT study report

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 associated with aphthous and other types of ulcers. Throughout the United States, they are most commonly used during nasal surgeries to provide topical anesthesia and decrease surgical bleeding. In 1999, the European Medicines Agency granted marketing authorization (number 12064/0016) for cocaine HCl 10% solution. The approved indication is as follows:

> *…to provide local anaesthesia and vasoconstriction of accessible mucous membranes prior to surgery especially in the oral, laryngeal, and nasal cavities. Vasoconstriction prevents excessive blood loss and reduces obstruction/restriction of the operative field*

Similar to the marketing history in the United States, the therapeutic uses for cocaine topical solutions in Europe have been declining, which may also be due to its high potential for abuse and diversion, as well as other reasons discussed in 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 two investigative sites, 1130 and 1190, for the Phase 3 studies was requested. These sites were initially selected based on the large numbers of enrolled subjects in both Phase 3 study protocols, COCA4vs10-001 and COCA4vs10-002. Further review of the NDA, however, revealed a large number of protocol-defined SAEs, characterized by a severe, ≥ Grade 3, change in measured vital signs for site 1190. This site reported 21 SAEs in 29 treated subjects. The majority of which were hypertension and hyperventilation. These SAEs did not require treatment and were felt to be due to procedural anxiety or monitoring errors. One subject did experience myocardial ischemia and a slight increase in serum creatine kinase-MB, meeting the regulatory definition of an SAE. This subject and his clinical outcome will be discussed in full detail in the safety portion of this review. Refer to Table 4 for additional information regarding the study sites.

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

The preliminary 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 studies that would impact the reported efficacy and safety findings.

Table 4. Clinical Study Sites

Site ID #	COCA4vs10-001 Number of randomized subjects	COCA4vs10-002 Number of randomized subjects	Additional Site Information Protocol Deviations
1000	8	1	• Large number of major protocol deviations in four subjects for Study COCA4vs10-001
1010	11		• Previous site inspection in 2009 with OAI (Official Action Indicated) outcome for not following investigational plan. Repeat inspection in 2011 resulted in NAI (No Action Indicated) • 3 subjects with major protocol deviations
1080		6	
1090	1		
1100	2		
1120	1	10	
1130*	44	167	• 2 subjects with major protocol deviations
1190*	29	131	• Large number of protocol-defined SAEs
1200	47	43	
1220	11	54	
1230	2	23	
1240		26	
1270		5	
1280		1	
1300		25	
1320		9	
1330		3	
1340		36	
1360		59	Recent PDUFA inspection, Oct. 2017, with preliminary classification of NAI. Previous inspection in 2015, also NAI classification

*Clinical sites inspected for both Phase 3 study protocols

4.2. Product Quality

The CMC final review was not available at the time of completion of this review. There appear to be no concerns regarding the 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 inactive ingredients in the topical solutions include purified water USP (diluent), sodium benzoate USP/NF (b) (4) citric acid USP (b) (4), and approved GRAS (generally regarded as safe) coloring, including D&C Yellow No. 10; FD&C Green No. 3.

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 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 Applicant did evaluate nasal mucosal capillary blood flow using laser Doppler in Study LNT-P6-733 and hemostasis via a questionnaire in Studies COCA4vs10-001 and COCA4vs10-002. While the Applicant is only requesting an anesthetic indication for the cocaine topical solutions during nasal surgery, (b) (4)

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 draft product label has been edited to more accurately reflect the observed increases and the recommended post-administration monitoring. Once the proposed Study COCA-QT-01 is complete, any pertinent information regarding the impact of Numbrino™ on the QT interval will be included in the final product label.

4.5.3. Pharmacokinetics

Cocaine hydrochloride 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 in the urine by the kidneys. Norcocaine is an active, minor metabolite formed by N-demethylation via cytochrome P4503A4 in liver microsomes 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, randomized, single-dose, double blind, laboratory blinded, two-period, six-sequence, cross-over pharmacokinetic (PK) study, LNT-P6-733, in 36 healthy adult volunteer subjects. On study Day 1, subjects were randomized to receive either Test-1 (cocaine HCl topical solution 4%), Test-2 (cocaine HCl topical solution 10%), or placebo solution. For each administration, four cotton pledgets measuring 0.5 inch by 3 inches, were treated with 4 mL of the assigned solution and applied to the nasal mucosa, two pledgets per nostril, for 20 minutes. The total dose of cocaine HCl administered was 160 mg in Test-1 and 400 mg in Test-2, the proposed labeling doses. There was a washout period of seven days separating drug administrations. Refer to Table 5 for schedule of planned treatments.

Table 5. Study Treatments Sequence Planned

	Period 1	Period 2
Sequence 1 (n= 6)	Test-1	Test-2
Sequence 2 (n= 6)	Test-2	Test-1
Sequence 3 (n= 6)	Test-1	Placebo followed by Test-2*
Sequence 4 (n= 6)	Test-2	Placebo followed by Test-1*
Sequence 5 (n= 6)	Placebo followed by Test-1*	Test-2
Sequence 6 (n= 6)	Placebo followed by Test-2*	Test-1

* For those subjects assigned to receive treatment with placebo followed with treatment with one of the two Test products, all clinical activities (blood sampling, ECG, vital signs, etc.) were timed relative to treatment with the Test product (2nd pledget wear of the study period).

Source: Study LNT-P6-733 Report Body, p. 31 (PDF), Applicant's submission, NDA 209575

In each study period for each subject, both serum and urinary samples were collected and analyzed for the following compounds:

- cocaine
- benzoylecgonine (BE)
- ecgonine methyl ester (EME)
- ecgonine
- norcocaine

The first samples were collected prior to pledget placement and the remaining samples were collected over 24 hours following pledget placement. Refer to Table 6 for study design and timing of assessments.

Table 6. Study Design and Schedule of Assessments

	Pre-Trial	Period 1			Wash- Out	Period 2			End of Study
Days [a]	-35 to 0	0	1	2	1-7	7	8	9	9
Informed Consent Form Signed [b]	X								
Admission to Unit		X				X			
Medical History	X								
Physical Examination	X								X
Laboratory Tests	X								X
HIV Ag/Ab Combo, HBsAg (B) (Hepatitis B) and HCV (C) Tests	X								
Alcohol and Drugs of Abuse Screening	X	X				X			
12-lead ECG [c]	X	X	X			X	X		X
Nasal Cavity Examination	X		X				X		X
Pregnancy Test	X	X				X			X
Vital Signs [c] **(including oxygen saturation of blood)**	X		X				X		X
Vasoconstriction Measures [d]			X				X		
Drug Administration			X				X		
Blood Sampling [c]			X	X			X	X	
Urine Sampling [c]			X	X			X	X	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X

a. The days assigned to each period may have changed according to the exact wash-out determined between the drug administrations
b. The last version was to be signed prior to subject's inclusion (first drug administration)
c. For those subjects assigned to receive treatment with placebo followed with treatment with one of the two Test products, all clinical activities (blood sampling, ECG, vital signs, etc.) were to be timed relative to treatment with the Test product (2nd pledget wear of the study period).
d. To be measured for each treatment administration (including placebo treatment).

Source: Study LNT-P6-733 Report Body, p. 25 (PDF), Applicant's submission, NDA 209575

The percent of total cocaine absorbed systemically was calculated based on the amount of residual cocaine extracted from administered pledgets and resulting concentration data. A mean (n=34) of 23% of the total administered dose for Test-1 and a mean (n=32) of 33% of the total administered dose for Test-2 was absorbed. These results suggest only a very small percentage of the total dose is absorbed, measurable, and quantifiable. The serum PK parameters for cocaine are presented in Table 7 below.

Table 7. Pharmacokinetic Parameters - Cocaine in Plasma

Parameter (Units)	Test-1 (n=33)		Test-2 (n=30)	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	142.68	(44.9)	433.53	(49.3)
ln (C_{max})	4.8668	(9.0)	5.9804	(7.0)
T_{max} (hours)[a]	0.50	(0.17-1.00)	0.50	(0.33-1.00)
AUC_{0-T} (ng·h/mL)	279.01	(46.6)	950.54	(43.5)
ln (AUC_{0-T})	5.5528	(6.8)	6.7761	(5.9)
$AUC_{0-\infty}$ (ng·h/mL)	286.68	(45.6)	960.09	(43.1)
ln ($AUC_{0-\infty}$)	5.5828	(6.7)	6.7874	(5.9)
$AUC_{0-T/0-\infty}$ (%)	97.05	(1.2)	98.88	(0.7)
λ_Z ($hours^{-1}$)	0.4576	(13.7)	0.3757	(26.1)
T_{half} (hours)	1.54	(13.5)	2.01	(36.8)

[a] Median (range)

Source: Study LNT-P6-733 Report Body, p. 54 (PDF), Applicant's submission, NDA 209575

The serum PK data for cocaine indicates that those subjects treated with cocaine HCl topical solution 10% had a mean peak plasma concentration (C_{max}) that was approximately three times that measured in the plasma from subjects treated with cocaine HCl topical solution 4%, 433.53 ng/mL compared to 142.68 ng/mL respectively. The time to C_{max} for both concentrations was similar, approximately 30 minutes. The measured PK data for the 4% solution represent much higher systemic levels and exposure than those observed in subjects treated with the approved Goprelto®, 4% cocaine HCl topical solution; 142.68 ng/mL compared to 43.2 ng/mL. The difference in the measured PK parameters is due to differences in systemic absorption, which may be partially explained by a difference in the pledget size used for topical administration. The size of the pledgets used in this PK study are much larger, measuring ½ inch x 3 inches, while those used in the Goprelto® clinical studies measured ½ inch x 1.6 inches. Refer to Dr. Deep Kwatra's clinical pharmacology review for additional information regarding the increased systemic exposure observed with administration of this product.

The dose and method of application used in this study was based on information in the published literature suggesting adequate topical anesthesia with limited systemic absorption when cocaine HCl solutions are applied to cotton or rayon pledgets and delivered to the nasal mucosa. Comparable doses of cocaine applied directly to the nasal mucosa produce cocaine plasma concentrations 4-5 times greater than when delivered by a pledget, which would likely result in a significant increase in adverse events and serious adverse events.

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 and is also consistent with previously reported PK data obtained after topical cocaine administration.

The urinary PK results indicate that only a small portion of cocaine is eliminated unchanged in the urine, which has been previously documented in the published literature.

In addition to an analysis and evaluation of the captured PK data, the degree of vasoconstriction and capillary blood flow was measured using the moorVMS-LDF Laser Doppler Flow Monitor at specific time points in each study period after treatment. Flux measurements were considered the primary measure of the degree of vasoconstriction, with DC measurements considered secondary supportive indices. Per the Applicant, the DC measurement is not a vasoconstriction parameter, but rather indicates the backscattered laser light intensity and is used to check the function of the laser Doppler probes. It was provided as an indicator of the completeness of the vasoconstriction measurements. If the probe is not positioned properly, the DC value is high and with perfect probe placement, the value decreases and will remain constant over a range of measurements, approximately 50 to 100 arbitrary units (AU).

The results of the capillary blood flow assessment, via flux measurements, support the previous assertion that cocaine does cause vasoconstriction when applied topically to the nasal mucosa. The mean flux values in the cocaine HCl topical solution 4% and 10% (Test-1 and Test-2, respectively) groups were statistically significantly lower than those measured in the placebo group, suggesting reduced capillary blood flow and vasoconstriction. Refer to Table 8 for flux measurements and analysis.

Table 8. Summary of Flux Measurement

	LSMean	LSMean difference	SE	P value	95%CI	
Test-1 vs Placebo	392.15 vs 502.94	-110.79	15.5036	<0.0001	-143.13	-78.4536
Test-2 vs Placebo	377.35 vs 493.75	-116.39	14.2620	<0.0001	-146.14	-86.6450

Source: Study LNT-P6-733 Report Body, p. 92 (PDF), Applicant's submission, NDA 209575
Test-1: Cocaine HCl topical solution 4%; Test-2: Cocaine HCl topical solution 10%

The results of the DC measurements are presented in Table 9. The DC measurement mean value for the cocaine HCl 4% group was found to be statistically significantly lower than that observed for the placebo group, but there was not statistical significance reached in the comparison between cocaine HCl 10% and placebo groups. The Applicant stated that this DC

measurement is provided for completeness and as an assessment of proper probe placement, and that while the difference between the cocaine HCl 10% and placebo groups did not meet statistical significance, the mean values were within the range (50 to 100 AU) indicating optimal probe placement.

Table 9. Summary DC Measurements

	LSMean	LSMean difference	SE	P value	95% CI	
Test-1 vs Placebo	58.6109 vs 63.9576	-5.3467	1.7975	0.0075	-9.0961	-1.5973
Test-2 vs Placebo	61.5609 vs 63.0232	-1.4622	1.7795	0.4209	-5.1743	2.2498

Source: Study LNT-P6-733 Report Body, p. 92, Applicant's submission, NDA 209575
Test-1: Cocaine HCl topical solution 4%; Test-2: Cocaine HCl topical solution 10%

Additional PK results, analyses, and discussion will be provided in the Clinical Pharmacology review by Dr. Deep Kwatra.

4.6. Devices and Companion Diagnostic Issues

Cocaine topical solution is applied to the nasal mucosa via four cotton or rayon applicator pledgets. The recommended applicator pledgets measure ½" x 3" and are to be purchased separately. The Applicant states that each pledget absorbs approximately one milliliter cocaine solution for a maximum dose of four milliliters of either the 4% or 10% cocaine solution 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 10% solution 400 mg. For all studies combined, the mean doses of study drug administered, in mL and mg, were as follows:

- 3.17 mL, 126.8 mg of 4% cocaine HCl topical solution
- 3.17 mL, 317 mg of 10% cocaine HCl topical solution

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 10. Clinical Trials Supporting NDA 209575

Trial Identity	NCT no.	Trial Design	Regimen, Schedule, and Route	Study Objectives	Study Population	No. of patients enrolled	Number and location of centers
Controlled Studies to Support Efficacy and Safety							
COCA4vs10001	NCT01746940	Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled	Single topical application of cocaine HCl topical solution 4% at a maximum of 160 mg or cocaine HCl topical solution 10% at a maximum of 400 mg	Compare efficacy to placebo and characterize risk profile following topical pledget application of investigational test products to the nasal cavity	Adult subjects over 18 years of age with the identified need for a diagnostic procedure or surgery of or through the nasal mucous membranes. All diagnostic and therapeutic procedures and surgeries to or through accessible mucous membranes of the nasal cavities are eligible Average age 39 years	159 enrolled 156 completed 68 males 91 females	10 study sites, all located in the United States
COCA4vs10002	NCT02500836	Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled	Single topical application of cocaine HCl topical solution 4% at a maximum of 160 mg or cocaine HCl topical solution 10% at a maximum of 400 mg	Compare efficacy to placebo and characterize risk profile following topical pledget application of investigational test products to the nasal cavity	Adult subjects over 18 years of age with the identified need for a diagnostic procedure or surgery of or through the nasal mucous membranes. All diagnostic and therapeutic procedures and surgeries to or through accessible mucous membranes of the nasal cavities that merit the use of anesthesia are eligible.	646 enrolled 637 completed 253 males 393 females	16 study sites, all located in the United States

Trial Identity	NCT no.	Trial Design	Regimen, Schedule, and Route	Study Objectives	Study Population	No. of patients enrolled	Number and location of centers
					Average age 37.6 years		
Clinical Pharmacology Studies							
LNT-P6-733		Phase 1, Two-period crossover, Randomized, Double-blind, Placebo-controlled	Single topical application of cocaine HCl topical solution 4% at a maximum of 160 mg and cocaine HCl topical solution 10% at a maximum of 400 mg	Evaluate absorption and pharmacokinetics of cocaine and its major metabolites and vasoconstriction following topical pledget application of investigational test products to the nasal cavity	18 male and 18 female healthy adults Average age 29.4 years	36 enrolled 31 completed	1 study site, located in Quebec, Canada

5.2. Review Strategy

The Applicant has conducted one Phase 1 pharmacokinetic study, and two Phase 3 clinical studies, and because the marketing application is using the 505(b)(2) pathway, the Applicant is relying on pharmacokinetic, safety, and efficacy information in the published literature.

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

Studies performed by Cody Laboratories, Inc.

- Study COCA4vs10-001: Randomized, prospective, multi-site, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of 4% and 10% cocaine topical solutions versus placebo solution in adult subjects undergoing a diagnostic procedure or surgery of or through the nasal mucous membranes.
- Study COCA4vs10-002: Randomized, prospective, multi-site, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of 4% and 10% cocaine topical solutions versus placebo solution in adult subjects undergoing a diagnostic procedure or surgery of or through the nasal mucous membranes.
- Study LNT-P6-733: Single-center, randomized, single-dose, double-blind, laboratory-blinded, two-period, 6-sequence, crossover study to evaluate the pharmacokinetics of cocaine and its metabolites and to assess the effect of the investigational products on the nasal mucosa following topical application. A secondary objective was to evaluate nasal mucosa vasoconstriction, safety, and tolerability of cocaine HCl topical solution 4% compared to 10%.

Literature provided by Cody Laboratories, Inc.

The Applicant conducted published literature searches at various times during their drug product development program. The identified literature concerning the safety of topical cocaine solutions for use as an anesthetic during nasal surgery is comprised of the following:

- the results of surveys from otolaryngologists – the Applicant identified three papers with survey results that address the clinical safety profile of topical cocaine when used for nasal procedures
- the results of clinical studies – the Applicant identified five clinical studies in the published literature involving the use of cocaine in nasal procedures
- case reports of adverse events – many of the identified case reports involves adverse event reporting in persons with a known history of cocaine abuse

All referenced articles have been translated into English, when necessary, and submitted for review.

A summary of the findings in the published literature was not provided.

Review of the FAERS database

A review of the United States FDA Adverse Event Reporting System for cocaine from January 1,

2000, through November 30, 2016, identified 6,140 total cases. The majority of these cases were accidental or intentional overdoses in drug abusers or suicide victims and resulted in cardiac arrest with CNS and/or respiratory depression and hospitalization and/or death. These cases included patients who had ingested multiple substances in addition to cocaine, including CNS depressants and alcohol. Some reported cases were for congenital anomalies in infants born to mothers with a known history of cocaine abuse.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Phase III investigation of topical application of Cocaine HCl 4% and 10% on safety and efficacy in local (topical) anesthesia for diagnostic procedures and surgeries on or through accessible mucous membranes of the nasal cavities

6.1.1. Study Design

Overview and Objective

Study COCA4vs10-001, a Phase 3 study, was conducted by Cody Laboratories, Inc. to evaluate the safety and efficacy of cocaine HCl topical solutions, both 4% and 10%, as local anesthetics in subjects undergoing diagnostic procedures and surgeries through accessible mucous membranes of the nasal cavities in adult patients. The objectives of the study are as follows:

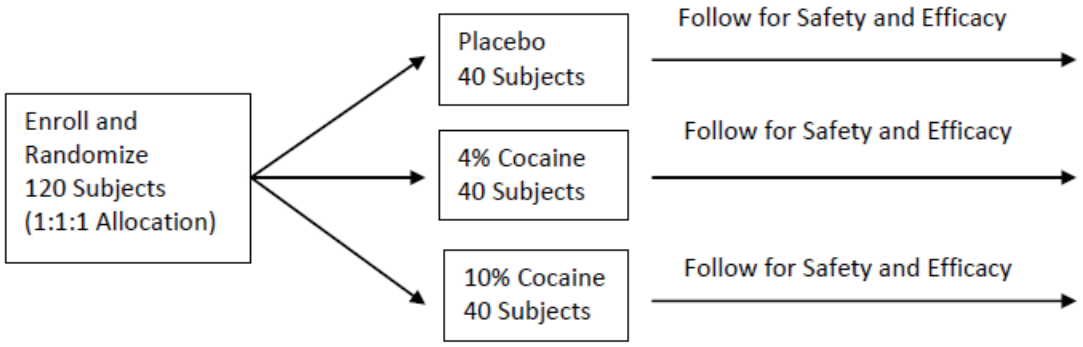
- Primary objective: (verbatim) To evaluate the efficacy of Cocaine HCl 4% formulation compared to placebo for anesthetizing the nasal mucosa prior to a single diagnostic procedure or surgery of or through the nasal cavities of one or both nostrils. The primary determinant of successful usage is superior analgesia compared to placebo achieved prior to a diagnostic procedure or surgery based on von Frey filament testing for each nostril that received the study drug application, and successful completion of the diagnostic procedure or surgery without the need for additional anesthesia or pain drugs during the diagnostic procedure or surgery.
- Secondary objectives: (verbatim)
  - To characterize the risk profile of Cocaine HCl 4% and 10% formulations when administered by cotton or rayon pledgets to the nasal mucosa
  - To determine the appropriate concentration of Cocaine HCl 4% or 10% to use for various procedures involving the nasal mucosa based on safety and efficacy findings
  - To monitor the nature and frequency of adverse events (AEs) associated with the use of Cocaine HCl Topical Solution.

Trial Design

This Phase 3 study conducted by the Applicant was a randomized, prospective, multi-site, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of 4%

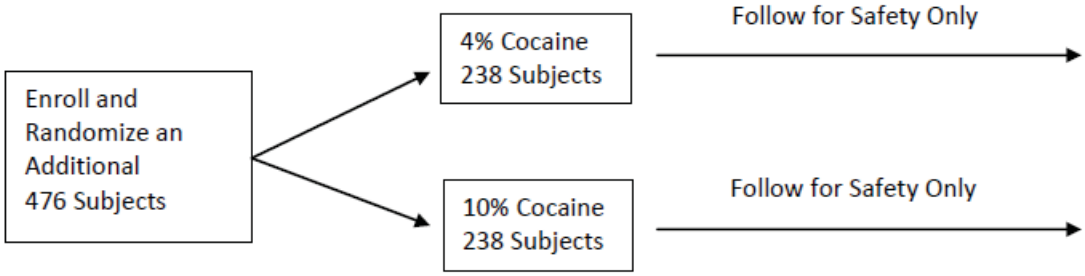
and 10% cocaine topical solutions compared to placebo for local anesthesia during diagnostic procedures and surgeries through the mucous membranes of the nasal cavities and was conducted under a SPA agreement. The first, or double-blind efficacy, phase of the study planned to enroll approximately 120 subjects in a 1:1:1 ratio (40 subjects per treatment arm) and was designed to evaluate the safety and efficacy of the administration of a single dose of cocaine HCl 4% or 10% compared to placebo. The second, or double-blind safety, phase of the study planned to enroll an additional 476 subjects (238 subjects per cocaine group) and was designed to evaluate the safety of the two cocaine HCl solutions. Refer to Figures 3 and 4 for pictorial representation of the double-blind efficacy and double-blind safety phases of the study.

Figure 3. Safety and Efficacy Portion



Source: Study COCA4vs10-001 – Protocol and Amendments, p. 10, Applicant's submission, NDA 209575

Figure 4. Safety Portion



Source: Study COCA4vs10-001 – Protocol and Amendments, p. 10, Applicant's submission, NDA 209575

Due to a lack of efficacy of the 4% solution identified in the interim analysis, after the efficacy-only phase was completed, the study was suspended prematurely and only an additional 36 subjects were enrolled in the safety phase, for a total of 156 subjects. The diagnostic procedures and surgeries performed included nasoendoscopy, pharyngoscopy, laryngoscopy, balloon sinuplasty, debridement, nasal polypectomy, and ear, nose, and throat examinations. Subjects in both phases of the study required anesthesia for a nasal diagnostic or surgical procedure, and did not receive general anesthesia or intravenous sedation for the procedure performed. Subjects were permitted an anxiolytic medication for purposes of lessening anxiety but not in sedating doses. The study consisted of a screening period up to seven days before

the procedure (Visit 1); a treatment period on the day of the diagnostic procedure or surgery (Visit 2); a follow-up phone call, or visit when necessary, one day (Visit 3) and seven days (Visit 4) following pledget removal. Refer to Table 11 and Figure 5 for additional information regarding the study schedule of events and the study design. There were 29 investigators participating in this study at 10 separate surgical centers located within the United States; there were no foreign sites for this study.

Table 11. Study Schedule for Screening, Qualification (Baseline), Anesthesia Application, and Study Procedure/Surgery

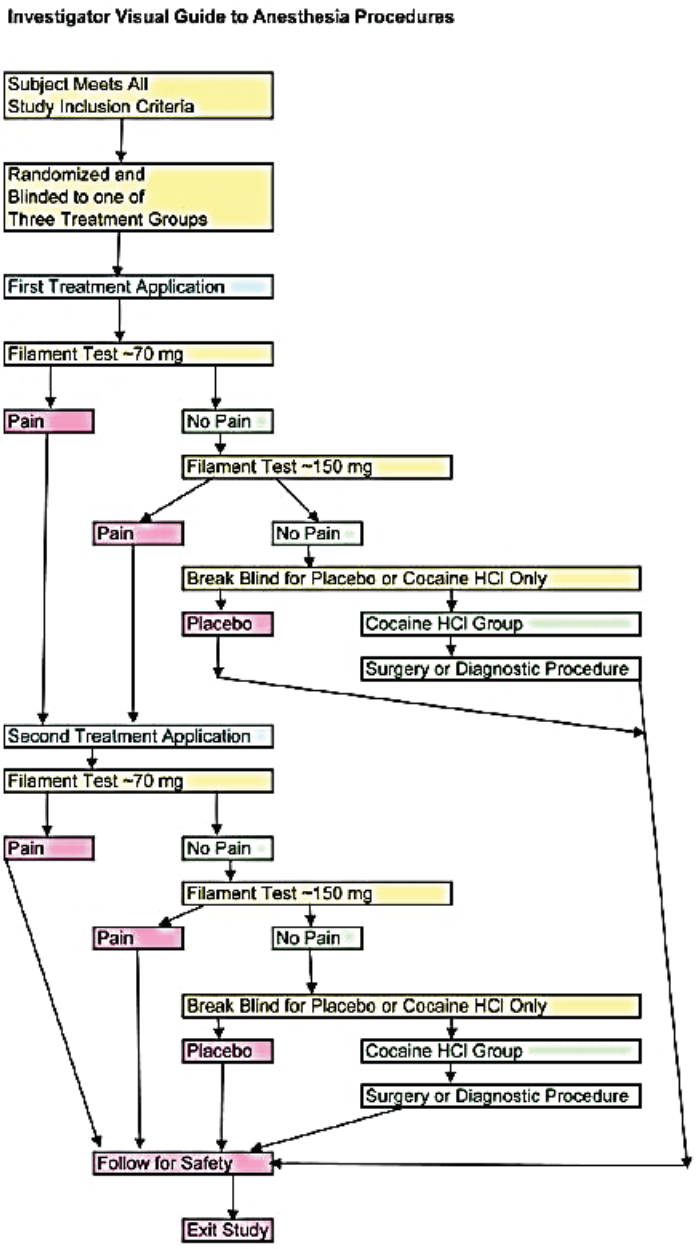
Study Period	Pre-Treatment	Treatment			Post-Procedure Follow-up	
Study Visit	Visit 1	Visit 2			Visit 3	Visit 4
Timeline	Day -6 Up to 7 days before Day 1	Day 1			Day 2	Day 8 7 days after Day 1
Procedures	Screening	Baseline	Study Drug Application	Procedure/Surgery	Assessments	Assessments
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Medical/Surgical History	X					
Demographics (Wt & Ht)	X					
Physical Examination	X					
Pregnancy Test/Drug Screen	X					
Clinical Laboratory Tests	X					
Vital Signs	X	X[a]	X[a]	X[a]		
12-lead ECG	X[b]			X[b]		
Monitoring ECG		X[c]	X[c]	X[c]		
Randomization		X[d]				
Monofilament Testing	X		X			
Study Drug Administered			X			
In-Procedure Pain Assessment				X		
Concomitant Treatments	X					
Adverse Events	X					

[a]Vital signs were collected on each subject at baseline just prior to administration of the study drug, and every 5 minutes ±2 minutes until the subject was discharged from phase 1 recovery and prior to final discharge.
[b]A 12-lead ECG was performed during screening, and at the time of discharge from phase 1 recovery.
[c]Monitoring ECGs were recorded just prior to (baseline) and after administration of the study drug and every 5 minutes ±2 minutes until the subject was discharged from phase 1 recovery. Repeat ECGs were performed after completion of procedures at the investigator's discretion.
[d]Subjects were randomized prior to any other procedures that were scheduled to occur at the baseline visit.
Source: CSR COCA4vs10-001, p. 38, Applicant's submission, NDA 209575

The screening visit included a complete history and physical exam, vital sign measurement (including heart rate, blood pressure, oxygen saturation, temperature, and respiratory rate), clinical laboratory testing (including serum chemistry, hematology, blood coagulation, cardiac enzymes, and urinalysis), baseline 12-lead ECG, and baseline single-lead ECG from the

monitoring device to be used on the day of the procedure.
Subjects who met eligibility criteria were enrolled and randomized, using a single permuted block scheme, on the day of treatment to receive placebo topical solution, cocaine HCl topical solution 4%, or cocaine HCl topical solution 10% via soaked cotton or rayon pledgets (measuring ½" x 3"). The study drugs were dosed as a single application of up to 4 mL of solution placed on cotton, or rayon, pledgets, and administered into the nose for 20 minutes prior to the procedure. The 4% solution was dosed up to a maximum of 160 mg and the 10% solution was dosed up to a maximum of 400 mg, depending on the number of pledgets applied. The exact dose of cocaine HCl administered was calculated by subtracting the volume of residual solution, after soaking the pledgets, from the original bottle volume. The dose administered was determined based on the procedure performed and subject variables including number of nares treated and was calculated based on the volume of solution absorbed onto the pledgets (residual volumes measured). A vFF test, with a 5.18, 15 g filament, was performed to the treated nasal mucosa to assess the success of anesthesia. A treatment success was defined as a subject-reported pain score of 0 on the 11-point numeric pain rating scale (NPRS), where 0 is no pain and 10 is severe pain. For subjects in the double-blind efficacy phase of the study, the blind to active treatment versus placebo was broken after the vFF test. Placebo subjects and cocaine failures could undergo a non-study procedure a minimum of 24 hours after pledget removal. The blind to cocaine treatment group remained.

Figure 5. Study Design



Source: CSR COCA4vs10-001 p. 29, Applicant's submission, NDA 209575

There were several communications between the Applicant and the Agency to gain agreement on the choice of an acceptable control group. The lack of FDA-approved anesthetic products for use on the nasal mucosa limited the number of possible treatment control groups and for ethical reasons, it was agreed that subjects treated only with a placebo solution should not undergo a procedure. Agreement was reached on breaking the blind to placebo versus active treatment after vFF testing. The use of two cocaine concentrations during the procedures would allow a comparison evaluation of the efficacy, and safety, results.

Study Endpoints

The primary efficacy endpoint was analgesic success immediately after application and sustained throughout the diagnostic procedure or surgery. This endpoint was evaluated for each nostril that received treatment using the following assessments:

- Prior to the procedure or surgery, no pain based on a 0 to 10 NPRS was reported during the vFF test
- During the procedure or surgery, no further analgesic treatment was required for the cocaine treatment groups

Subjects not meeting these criteria were considered treatment failures, were observed for up to 90 minutes post-pledget removal, and discharged with a plan for a non-study procedure to completed a minimum of 24 hours later. Refer to Table 12 for treatment success and failure definitions.

Table 12. Definition of Treatment Success and Failure (by Group and Procedures)

Treatment Group	Study Drug Application	von-Frey Monofilament Status*	After Study Drug Application	Sustained Analgesic Effect**	Endpoint Status
Placebo	Applied	0	Followed for Safety	-	Success
	Applied	>0	Followed for Safety	-	Failure
Cocaine HCl 4%	Applied	0	Procedure Begun	Yes	Success
	Applied	0	Procedure Begun	No	Failure
	Applied	>0	Followed for Safety	-	Failure
Cocaine HCl 10%	Applied	0	Procedure Begun	Yes	Success
	Applied	0	Procedure Begun	No	Failure
	Applied	>0	Followed for Safety	-	Failure

* >0 if at least 1 nostril exhibited any pain, 0 if all nostrils had no pain;
** `-` is not applicable (N/A)

Source: CSR COCA4vs10-001, p. 39, Applicant's submission, NDA 209575

Secondary efficacy endpoints were as follows:

- Analgesic success immediately after application
- Sustained analgesic success
- vFF test pain score

An additional secondary efficacy endpoint evaluating the adequacy of hemostasis was summarized by active treatment groups. This endpoint was assessed by individual investigators' response to the question, "Was adequate hemostasis achieved?". A yes or no answer was recorded. All no answers required additional explanation and consideration for recording lack of hemostasis as an adverse event.

Statistical Analysis Plan

Descriptive statistics were used for continuous data and included the number of subjects summarized, mean, standard deviation, median, and range. Summary statistics were presented by treatment group by phase, combined phases, and overall. Significance testing was one-sided using an α=0.025 level unless otherwise specified.

The primary efficacy analysis was performed using the intent-to-treat (ITT) population, which consisted of all subjects randomized and treated, and did not include subjects in the safety-only phase of the study. A secondary analysis of the primary efficacy endpoint was conducted using the per protocol (PP) population. The primary efficacy endpoint was evaluated as follows:

- placebo vs. cocaine topical solution 4%
- placebo vs. cocaine topical solution 10%
- there was no analysis performed between the two active treatments

Analyses of secondary efficacy endpoints were conducted using the ITT and PP populations and did not include subjects enrolled in the safety-only phase of the study.

Subgroup analyses were conducted on the following subject populations:

- sex
- age (<35 years of age, 35 to 65 years of age, >65 years of age)
- race (black, white, Asian, Native Hawaiian or Pacific Islander, and other)
- type of procedure (exploratory analysis)

Missing values for the NPRS pain intensity scores were imputed as treatment failures.

Protocol Amendments

There were no amendments made to the protocol during the conduct of clinical study.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant noted in Section 5, ETHICS, of the protocol that "this research was carried out in accordance with the International Conference on Harmonisation (ICH) E6, Good Clinical Practice".

Financial Disclosure

(b) (4), (b) (6), signed FDA form 3454 on September 1, 2017, 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 a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

A total of 159 subjects were enrolled and 156 subjects were randomized, received a study treatment, and completed both the efficacy and safety phases of the study, refer to Table 13. Three subjects withdrew from the study prior to randomization and are, therefore, not included in the individual treatment groups in the table below, but are included in the Overall group. One subject withdrew due to the physician leaving the site prior to the procedure, one for out-of-range blood pressure measurements, and one for inadvertent enrollment despite not meeting eligibility criteria. No subject withdrew or was removed from the study due to the occurrence of an adverse event.

Table 13. Subject Disposition (all randomized and withdrawn subjects)

	Cocaine HCl 4%		Cocaine HCl 10%		Placebo (N=40)	Overall (N=159)
	Efficacy (N=39)	Safety (N=18)	Efficacy (N=41)	Safety (N=18)		
Completed	39 (100%)	18 (100%)	41 (100%)	18 (100%)	40 (100%)	156 (98.1%)
Withdrawn	none	none	none	none	none	3 (1.9%)
Reason for Withdrawal						
Adverse Event	-	-	-	-	-	0
Subject Decision	-	-	-	-	-	1 (0.6%)
Physician Decision	-	-	-	-	-	1 (0.6%)
Other Reason	-	-	-	-	-	1 (0.6%)

Source: CSR COCA4vs10-001, p. 50 (PDF), Applicant's submission, NDA 209575

Protocol Violations/Deviations

The Applicant reported 20 major protocol deviations for six subjects; two subjects in each cocaine treatment group and two subjects in the placebo group. These were described as eight dosing deviations, five enrollment deviations, and seven study procedure deviations. Those deviations involving incorrect dosing regimen or violation of eligibility criteria are summarized in Table 14.

Table 14. Major Protocol Deviations Associated with Dosing Regimen and/or Lacking Eligibility Data

Subject ID	Issue/Category	Treatment	Issue Description
(b) (6)	Eligibility and Dosing	Cocaine 4%	Subject randomized in error due to exclusion #20 (serum potassium out of range) being met, and study medication not measured (height) prior to dispensing (dose administered determined by subtracting height of remaining drug bottle solution from original height). Multiple vital signs and ECGs not collected.
	Dosing and Eligibility	Cocaine 10%	Six pledgets used for dose application, randomized without PTT result, and study medication not measured (height) prior to dispensing (dose administered determined by subtracting height of remaining drug bottle solution from original height). Multiple vital signs not collected or collected out of window.
	Dosing	Placebo	Six pledgets used for dose application, pledgets retained for 23 minutes, and study medication not measured (height) prior to dispensing (dose administered determined by subtracting height of remaining drug bottle solution from original height). Multiple vital signs not collected.
	Dosing and Eligibility	Placebo	Six pledgets used for dose application, subject randomized in error, and study medication not measured (height) prior to dispensing (dose administered determined by subtracting height of remaining drug bottle solution from original height). Multiple vital signs not collected or collected out of window.

Source: CSR COCA4vs10-001, p. 53, Applicant's submission, NDA 209575

Other protocol deviations associated with missing or incorrectly collected vital sign, laboratory, or ECG data were identified in five subjects and were also distributed across both cocaine treatment groups and the placebo group. None of the reported protocol violations were thought to influence the safety or efficacy findings of the study. Of note, the Applicant did not record the time of the vFF test relative to the unblinding, making it hard to determine if any subjects were unblinded before the vFF test or at the same time. Dr. Feng Li, statistical reviewer, conducted a tipping point analysis to evaluate the potential impact of unblinding on the study results. The results from his analysis indicate that the statistical significance of cocaine 10% in comparison to placebo would be lost if the percentage of unblinding was more than 17% (refer to his review for a more complete discussion of the results of his additional analyses).

Table of Demographic Characteristics

Demographic and baseline characteristics are presented in Table 15. Briefly, 42.8% of subjects were male and 57.2% were female. The mean subject age was 38.96 years and while the majority of enrolled subjects were white, the placebo group had a higher percentage of white subjects than the cocaine treatment groups. The majority of subjects across all treatment groups were non-smokers.

Table 15. Demographic and Baseline Characteristics (Safety Population)

	Cocaine HCl 4%		Cocaine HCl 10%			
Characteristic	**Efficacy (N =39)**	**Total* (N = 57)**	**Efficacy (N =41)**	**Total* (N = 59)**	**Placebo (N = 40)**	**All Subjects (N = 159)**
Age (years), n						
Mean (SD)	39.49 (12.97)	39.26 (12.55)	39.34 (12.74)	40.98 (12.45)	34.58 (13.82)	38.96 (13.14)
Median	40.0	39.0	41.0	43.0	30.0	39.0
Sex, n (%)						
Male	19 (48.7)	27 (47.4)	17 (41.5)	22 (37.3)	17 (42.5)	68 (42.8)
Female	20 (51.3)	30 (52.6)	24 (58.5)	37 (62.7)	23 (57.5)	91 (57.2)
Race, n (%)						
American Indian or Alaska Native	1 (2.6)	1 (1.8)	0	0	0	1 (0.6)
Asian	1 (2.6)	2 (3.5)	1 (2.4)	1 (1.7)	1 (2.5)	4 (2.5)
Black or African American	6 (15.4)	9 (15.8)	8 (19.5)	15 (25.4)	2 (5.0)	26 (16.4)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White or Caucasian	31 (79.5)	45 (78.9)	32 (78.0)	43 (72.9)	37 (92.5)	128 (80.5)
Ethnicity, n (%)						
Hispanic or Latino	4 (10.3)	6 (10.5)	6 (14.6)	7 (11.9)	13 (32.5)	27 (17.0)
Not Hispanic or Latino	35 (89.7)	51 (89.5)	34 (82.9)	51 (86.4)	25 (62.5)	129 (81.1)
Not Reported	0	0	1 (2.4)	1 (1.7)	2 (5.0)	3 (1.9)
Weight (lb), n						
Mean (SD)	186.4 (45.39)	187.26 (48.97)	186.1 (46.97)	184.3 (44.14)	194.0 (55.13)	187.9 (48.62)
Median	179.0	178.0	176.0	179.0	184.0	180.0
History of Tobacco Use, n (%)						
Smoker	7 (17.9)	9 (15.8)	4 (9.8)	6 (10.2)	3 (7.5)	19 (11.9)
Non-Smoker	32 (82.1)	48 (84.2)	37 (90.2)	53 (89.8)	37 (92.5)	140 (88.1)

*Total includes subjects in both the efficacy and safety phases of the study
Source: CSR COCA4vs10-001, p. 56, Applicant's submission, NDA 209575

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

All subjects in the safety population had at least one prior medical condition. Medical histories reported in ≥10% of subjects included deviated nasal septum, hypertension, and headache. No subject reported a history of adrenal gland tumor, including pheochromocytoma, high fever associated with anesthesia, or hereditary pseudocholinesterase deficiency.

Most subjects had at least one concomitant medication. The following medications were used by ≥5% of subjects:

- Multivitamins
- Ibuprofen
- Omeprazole
- Fluticasone proprionate

Subjects were permitted to receive previously prescribed medications with the exception of those specifically listed in the exclusion criteria.

Sodium chloride solution, Chloraseptic spray, Chlorhexidine, Medrol, Norco, and ibuprofen were the most commonly used medications after the study procedure.

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

Treatment Compliance and Rescue Medication Use

The study drugs were administered to enrolled subjects by individual investigators, such that treatment compliance as assessed by subject-administration of medication was not applicable in this study.

No subject in either cocaine HCl treatment group required additional analgesic medication during the diagnostic or surgical procedure. All cocaine HCl treatment failures were identified during the vFF test, and therefore did not proceed to having a study procedure. Placebo subjects and cocaine HCl treatment failures had their procedure performed a minimum of 24 hours after pledget removal and anesthetics and analgesics were administered at the discretion of the investigators and were not provided.

Efficacy Results – Primary Endpoint

The proportion of subjects in both cocaine treatment groups demonstrating analgesic success was greater than those subjects who received placebo, refer to Table 16. All treatment failures were identified during the vFF test, therefore did not undergo a procedure. No subject failed due the need for additional analgesic medication administration. The confidence intervals are around the percentage of treatment successes for each group.

The number of subjects successfully treated with cocaine HCl 4% (21 out of 39 treated subjects), as reported by the Applicant, however, was not statistically significantly greater than those treated with placebo solution (15 out of 40 treated subjects). (b) (4) [redacted]. A generalized linear model analysis of the proportion of subjects with immediate and sustained analgesia was performed to assess the size of the difference in observed efficacy. The size of the difference between the cocaine HCl 4% treatment group and placebo was not statistically significan (b) (4) [redacted] The Applicant considered the lack of efficacy of the cocaine HCl 4% solution to be related to a large placebo response, use a low strength vFF for assessing analgesia, and no specific language for describing pain response. This reviewer also considered inconsistent dosing (discussed below) and whether the evaluated procedures differed between the cocaine groups. Given that all treatment failures were identified during the vFF testing, however, the procedure completed did not adversely impact the efficacy evaluation.

An analysis of the primary efficacy endpoint by procedure by treatment did not indicate a statistically significant difference in successful procedure completion between the two cocaine HCl solutions, albeit the numbers of subjects for procedures other than endoscopies were generally small.

Table 16. Immediate and Sustained Analgesia to the Nasal Cavities After the Application of Study Medication to the Nasal Mucosa - Efficacy (ITT) Population

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval	*p*- Value[a]
Cocaine HCl 4% (N=39)	21 (0.5385)	0.3718 to 0.6991	0.1088
Cocaine HCl 10% (N=41)	(b) (4) [redacted]		
Placebo (N=40)	15 (0.3750)	0.2273 to 0.5420	

Source: Table 14.2.1.1.
[a] *p*- values generated as one-sided from Fisher's Exact Test of equal treatment proportions, with each treatment arm tested against placebo at a one-sided alpha=0.0178 level of significance. [No covariate with factors for treatment, pooled site and treatment-by-pooled-study-site interaction available.]

Source: CSR COCA4vs10-001, p. 59 (PDF), Applicant's submission, NDA 209575

As previously mentioned, the total dose of cocaine administered was calculated based on the volume of solution remaining in the original bottle after pledgets were soaked, therefore, the dose was not consistent throughout the treatment groups. This inconsistency appears to have led to overlap in dosing between the two cocaine concentrations. For example, there were eight patients in the 10% treatment group who received 160 mg or less of cocaine HCl and 23 patients in the 4% treatment group who received greater than 100 mg. Additionally, there were 37 patients in the 4% treatment group who received less than 160 mg, which may be an additional explanation for the lack of efficacy of this concentration.

Subgroup Analyses

Subgroup analyses were performed for age, race, sex, and type of procedure. The following table, created by Dr. Feng Li, statistical reviewer, summarizes the analgesic success by subgroups. Note that the "other" race category included races other than white and black or African American. Cocaine-treated subjects had consistently higher analgesic success rates than placebo-treated subjects in all subgroups analyzed.

Table 17. Analgesic Success Rates by Sex, Race, and Age

		Placebo (N=40)		Cocaine 4% (N=39)		Cocaine 10% (N=41)	
Subgroup		**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Sex	Male	17	8 (47%)	19	14 (74%)	17	(b) (4)
	Female	23	7 (30%)	20	7 (35%)	24	
Race	White	37	15 (41%)	31	19 (61%)	32	
	Black	2	0	6	2 (33%)	8	
	Other	1	0	2	0	1	
Age	>=35	16	6 (38%)	23	12 (52%)	26	
	<35	24	9 (38%)	16	9 (56%)	15	

Source: Dr. Feng Li, statistical reviewer

Data Quality and Integrity

The preliminary report from an audit conducted by OSI, Division of Clinical Compliance Evaluation, has indicated that the reviewed data, including informed consent procedures, drug accountability records, and information related to study blinding and electronic source data, were reliable for Study COCA4vs10-001 and recommended accepting the clinical portion of the studies for further FDA review.

Efficacy Results – Secondary and other relevant endpoints

- Immediate analgesia
  Analysis of the secondary efficacy endpoint of immediate analgesic efficacy using the vFF test revealed (b) (4) no significant difference between the cocaine HCl 4% (21 out of 39 treated subjects) and placebo (15 out of 40 treated subjects) groups. Refer to Table 18 for additional efficacy information. An additional analysis of this secondary efficacy endpoint by procedure by treatmen (b) (4)

Table 18. Immediate Analgesia to the Nasal Cavities After the Application of Study Medication to the Nasal Mucosa

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval
Cocaine HCl 4% (N=39)	21 (0.5385)	0.3718 to 0.6991
Cocaine HCl 10% (N=41)	(b) (4)	
Placebo (N=40)	15 (0.3750)	0.2273 to 0.5420

Source: CSR COCA4vs10-001, p. 62 (PDF), Applicant's submission, NDA 209575

- Sustained analgesia

  Analysis of the secondary efficacy endpoint of sustained analgesia during the diagnostic procedure or surgery revealed a greater than 60% success rate (b) (4) This secondary endpoint was aimed at capturing subjects who may have reported 0 on the NPRS during vFF test, but required additional analgesic medication during performance of the procedure. The sustained analgesic response for the cocaine HCl 4% treatment group was 62% (24 out of 39 treated subjects) (b) (4) Refer to Table 19 for additional efficacy information. These results indicate a larger number of treatment successes than observed for the immediate analgesic secondary endpoint because there were five subjects (three in the cocaine HCl 4% treatment group and two in the cocaine HCl 10% treatment group) who underwent a procedure despite reporting >0 on the NPRS during the vFF test. And similar to the results from the analyses of the primary efficacy endpoint and the secondary efficacy endpoint of immediate analgesic success, there was no difference in treatment success by procedure by treatment, albeit the numbers of subjects per procedure were generally small.

Table 19. Sustained Analgesia to the Nasal Cavities After Application of Study Medication to the Nasal Mucosa

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval
Cocaine HCl 4% (N=39)	24 (0.6154)	0.4462 to 0.7664
Cocaine HCl 10% (N=41)	(b) (4)	

Source: CSR COCA4vs10-001, p. 63 (PDF), Applicant's submission, NDA 209575

- Pain intensity scores from vFF test

  Analysis of the secondary endpoint of pain intensity from the vFF test included an evaluation of subject-reported pain scores for each treatment for each nostril and combined nostrils. More procedures were performed on or through the right nostril than the left, and the analgesic success was reported higher for the right nostril. Lower numeric pain scores during vFF testing were reported by subjects in both cocaine treatment groups compared to those in the placebo group. Additionally, numeric pain scores reported by

(b) (4) by subjects in the cocaine HCl 4%, although statistical analyses were not performed. Refer to Table 20 for reported numeric pain scores by treatment by nostril(s).

Table 20. Numeric Pain Scores After Study Drug Application and von Frey Monofilament Test by Nostril by Treatment

	Left Nostril		Right Nostril		Combined Nostrils	
Treatment	n[a]	Mean[b] (SD)	n	Mean (SD)	n	Mean (SD)
Cocaine HCl 4%	24	1.13 (1.454)	30	0.77 (1.135)	54	0.93 (1.286)
Cocaine HCl 10%	(b) (4)					
Placebo	26	2.15 (2.275)	37	1.65 (1.844)	63	1.86 (2.031)

Source: Table 14.2.5.1.
[a] Denominator reflects the number of nostrils
[b] NPRS score, where 0=no pain and 10=unbearable pain

Source: CSR COCA410-001, p. 64 (PDF), Applicant's submission, NDA 209575

- Adequacy of hemostasis

  The adequacy of hemostasis was assessed by individual investigators and involved answering the question, "Was adequate hemostasis achieved?". All subjects, 100%, in both cocaine treatment groups were reported as having had adequate hemostasis. Refer to Table 21 for results for adequacy of hemostasis.

Table 21. Adequacy of Hemostasis After the Application of Study Medication to the Nasal Mucosa

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval
Cocaine HCl 4% (N=24)	24 (1.0000)	0.8575 to 1.0000
Cocaine HCl 10% (N=33)	(b) (4)	

Source: CSR COCA4vs10-001, p. 65 (PDF), Applicant's submission, NDA 209575

Dose/Dose Response

The primary efficacy findings indicate that (b) (4)

(b) (4)

(b) (4).

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted on this trial.

6.2. A Phase III investigation of topical application of Cocaine HCl 4% solution on safety and efficacy and Cocaine HCl 4% and 10% solution on safety in local (topical) anesthesia for diagnostic procedures and surgeries on or through accessible mucous membranes of the nasal cavities

6.2.1. Study Design

Overview and Objective

Study COCA4vs10-002, a Phase 3 study, was conducted by Cody Laboratories, Inc. to evaluate the safety and efficacy of cocaine HCl 4% topical solution as a local anesthetics in subjects undergoing diagnostic procedures and surgeries through accessible mucous membranes of the nasal cavities in adult patients. The objectives of the study are as follows:

- Primary objective: (verbatim) To demonstrate the immediate anesthetic efficacy of Cocaine HCl 4% treatment using a size 5.88 (60 gram) von Frey monofilament test performed 20 minutes after the application of study drug to the nasal mucosa and the sustained anesthetic efficacy of this Cocaine HCL 4% treatment using the lack of additional anesthesia or analgesia required for the remainder of a single diagnostic procedure or surgery through the nasal cavities compared to placebo.
- Secondary objectives: (verbatim)
  - Determine the safety and tolerability of Cocaine HCl 4% and 10% treatments as evaluated by vital signs, pulse oximetry, electrocardiograms (ECGs), and adverse events (AEs)
  - Demonstrate the immediate anesthetic efficacy of Cocaine HCl 10% treatment using a size 5.88 (60 gram) von Frey monofilament test performed 20 minutes after the application of study drug to the nasal mucosa and the sustained anesthetic efficacy of this Cocaine HCl 10% treatment using the lack of additional anesthesia or analgesia required for the remainder of a single diagnostic procedure or surgery through the nasal cavities compared to placebo (additional analysis)
  - Evaluate the immediate anesthetic efficacy of the Cocaine HCl 4% and 10% (additional analysis) treatments versus placebo using:
    - Von Frey monofilament test performed 20 minutes after the application of study drug to the nasal mucosa recorded as the Numeric Pain Rating Scale (NPRS, 0-10) score.

- Evaluate the sustained anesthetic efficacy of the Cocaine HCl 4% and 10% (additional analysis) treatments using:
  - Lack of additional anesthesia or analgesia required for the remainder of a single diagnostic procedure or surgery through the nasal cavities
- Evaluate the pain intensity for each nostril and combined nostrils from the Cocaine HCl 4% and 10% (additional analysis) treatments versus placebo using:
  - Von Frey monofilament test performed 20 minutes after the application of study drug to the nasal mucosa recorded as the NPRS score
- Need for additional anesthetic and/or analgesic therapy (rescue medication required) during the procedure
- Summarize the adequacy of hemostasis (additional analysis) as determined by the investigator.

This second Phase 3 study was conducted to evaluate the efficacy of the 4% topical solution and differed from Study COCA4vs10-001 in the following ways:

- A stiffer von Frey filament was used, 5.88 (60 gram) versus 5.18 (15 gram)
- The von Frey filament test was performed immediately prior to and immediately after the 20-minute application of the topical anesthetic
- Standardized language was given to the subjects to describe their pain
- The application of all 4 mLs of study drug to all four pledgets to improve uniformity of dosing and the selection of administered dose being depending on the number of pledgets inserted, versus the volume of remaining study drug solution

Trial Design

This Phase 3 study conducted by the Applicant was a randomized, prospective, multi-site, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of the administration of a single anesthetic dose of cocaine HCl topical solution, 4% or 10%, applied to pledgets and delivered to the nasal mucosa in men and women who were undergoing a single diagnostic or surgical procedure on or through accessible mucous membranes of the nasal cavities. This study was conducted under a SPA agreement.

A total of 646 subjects were randomized in a 2:2:1 fashion across the three treatments (cocaine HCl 4%, cocaine HCl 10%, and placebo). The study medication was dosed as a single 20-minute application of up to 4 mL absorbed on cotton (or rayon) pledgets prior to the diagnostic procedure or surgery. Specific instructions were provided to the investigators regarding the saturation of the pledgets with study drug solution. Each pledget absorbed 1 mL of solution and represented a 1 mL dose. Unlike the dosing calculations from Study COCA4vs10-001, which involved subtracting the volume of residual study drug, the dosing in this study was based on the number of pledgets applied to the nasal mucosa, as indicated in the table below:

Table 22. Cocaine Dosing for Study COCA4vs10-002

# of Pledgets Inserted	Cocaine HCl 4% Solution, mg dose	Cocaine HCl 10% Solution, mg dose
1	40	100
2	80	200
3	120	300
4	160	400

The majority of diagnostic procedures and surgeries performed included nasal endoscopy, transnasal laryngoscopy and pharyngoscopy, sinus endoscopy, and post-operative care including debridement. Subjects required topical anesthesia for a nasal diagnostic or surgical procedure, and did not receive general anesthesia or intravenous sedation for the procedure performed. Subjects were permitted an anxiolytic medication for purposes of lessening anxiety but not in sedating doses and only after the study drug application and vFF testing. The study consisted of a screening period up to ten days before the procedure (Visit 1); a treatment period on the day of the diagnostic procedure or surgery (Visit 2); a follow-up phone call, or visit when necessary, one day (Visit 3) and seven days (Visit 4) following pledget removal. Refer to Table 23 and Figure 3 for additional information regarding the study schedule of events and the study design. There were 29 investigators participating in this study at 10 separate surgical centers located within the United States; there were no foreign sites for this study.

Table 23. Study Schedule for Screening, Qualification (Baseline), Study Drug Application, and Study Procedure/Surgery

Study Period	Pre-Treatment	Treatment			Post-Procedure Follow-up	
Study Visit	Visit 1	Visit 2			Visit 3	Visit 4
Timeline	Day -10 Up to 10 days before Day 1	Day 1			Day 2	Day 8 7 days after Day 1
Procedures	Screening	Baseline	Study Drug Application	Procedure/ Surgery	Assessments	Assessments
Informed Consent and HIPAA Release	X					
Inclusion/Exclusion Criteria	X					
Medical/Surgical History	X					
Demographics (Wt & Ht)	X					
Physical Examination	X					
Clinical Laboratory Tests	X					
Urine Pregnancy	X	X				
Urine Drug Screen	X	X				
Vital Signs	X	X[a]	X[a]	X[a]		
12-lead ECG	X[b]			X[b]		
Monitoring ECG		X[c]	X[c]	X[c]		
Randomization		X[d]				
Monofilament Testing	X	X	X			
Study Drug Administered			X			
In-Procedure Pain Assessment				X		
Concomitant Treatments	X					
Adverse Events	X					
Study Termination						X

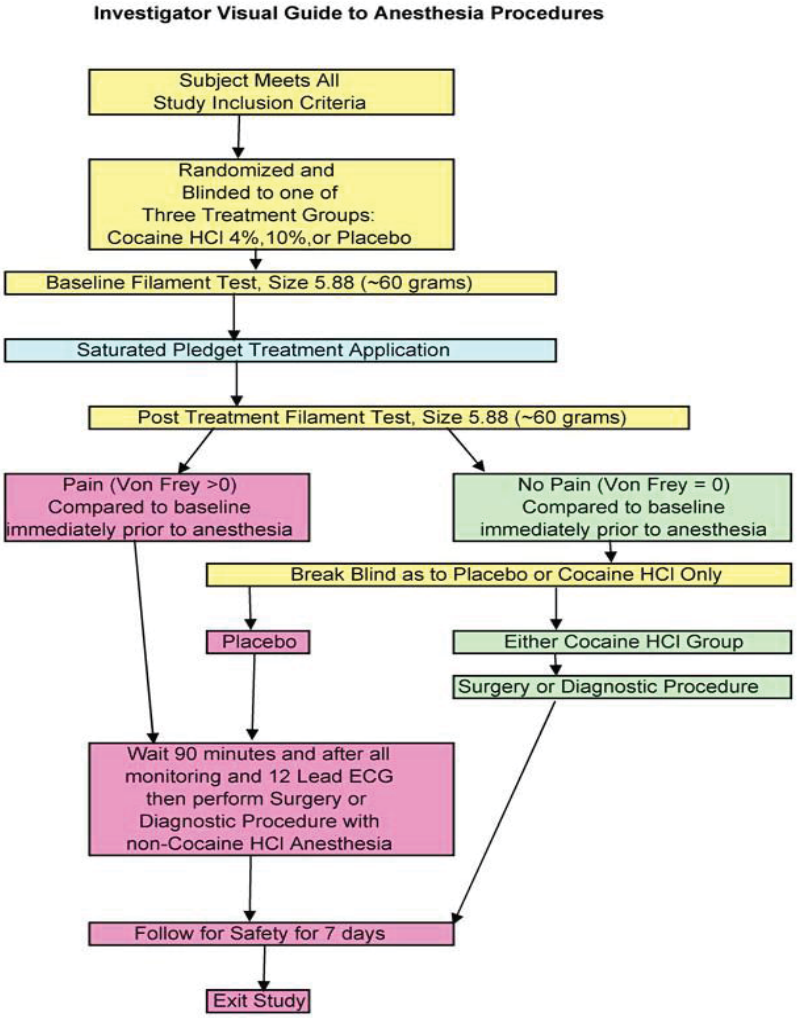
[a]Vital signs were collected on each subject at baseline just prior to administration of the study drug, and every 5 minutes ±2 minutes until the subject was discharged from phase 1 recovery and prior to final discharge.
[b]A 12-lead ECG was performed during screening, and at the time of discharge from phase 1 recovery.
[c]Monitoring ECGs were recorded just prior to (baseline) and after administration of the study drug and every 5 minutes ±2 minutes until the subject was discharged from phase 1 recovery. Repeat ECGs were performed after completion of procedures at the investigator's discretion.
[d]Subjects were randomized prior to any other procedures that were scheduled to occur at the baseline visit.
Source: CSR COCA4vs10-002, p. 50 (PDF), Applicant's submission, NDA 209575

The screening visit included a complete history and physical exam, vital sign measurement (including heart rate, blood pressure, oxygen saturation, temperature, and respiratory rate), clinical laboratory testing (including serum chemistry, hematology, blood coagulation, cardiac enzymes, and urinalysis), baseline 12-lead ECG, and baseline single-lead ECG from the

monitoring device to be used on the day of the procedure. An initial screening vFF test was performed on the anterior nasal septum.

Subjects who met eligibility criteria were enrolled and randomized, using a single permuted block scheme, on the day of treatment to receive placebo topical solution, cocaine HCl topical solution 4%, or cocaine HCl topical solution 10% via soaked cotton or rayon pledgets (measuring ½" x 3"). The dose administered was determined based on the procedure performed and subject variables including number of nares treated. A vFF test, with a 5.88 (60 gram) filament, was performed prior to application of study drug and subjects were instructed to "please remember the amount of sensation from this and any pain so you can compare this feeling to after the study drug is applied". Immediately after the 20-minute study drug application, the vFF test was repeated and subjects were asked, "Do you feel any pain compared to the test done just before the pledgets with drug product were applied? Ignore pressure and touch." Subjects who reported "no" answer to the question and were scored 0 on the 11-point numeric pain rating scale (NPRS), where 0 is no pain and 10 is severe pain. If a "yes" answer was given, the subject was asked, "Please tell me your pain score on a scale of 1 to 10 with 1 begin mild pain and 10 being unbearable pain. Ignore pressure and touch", and the pain score recorded. A treatment success was defined as a subject-reported pain score of 0. After the pre-procedure vFF testing was completed and pain scores recorded, the blind to active treatment versus placebo was broken, as previously agreed-upon. Placebo subjects and cocaine failures could undergo a non-study procedure a minimum of 90 minutes after pledget removal. The blind to cocaine treatment group remained.

Figure 6. Study Design



Source: CSR COCA4vs10-002, p. 36, Applicant's submission (PDF), NDA 209575

Study Endpoints

The primary efficacy endpoint was anesthesia success immediately after application and sustained throughout the diagnostic procedure or surgery, calculated for the cocaine HCl 4% topical solution and placebo treatment arms. This endpoint was evaluated for each nostril that received treatment using the following assessments:

- Prior to the procedure or surgery, no pain based on a 0 to 10 NPRS was reported during the vFF test after one application of the assigned treatment solution, cocaine HCl 4% or placebo topical solution
- During the procedure or surgery, no further anesthetic or analgesic treatment was required for the cocaine-treated subjects
- Cocaine HCl 10% was evaluated in a similar manner

Subjects not meeting these criteria were considered treatment failures and were observed for up to 90 minutes post-pledget removal, after which time they could undergo a non-study procedure under a topical anesthetic other than cocaine HCl. Refer to Table 24 for treatment success and failure definitions.

Table 24. Definition of Treatment Success and Failure (by group and whether a procedure was performed)

Treatment Group	Study Drug Application	Von Frey Monofilament Status*	After Study Drug Application	Sustained Analgesic Effect**	Endpoint Status
Placebo	Applied	0	Followed for Safety	-	Success
	Applied	>0	Followed for Safety	-	Failure
Cocaine HCl 4%	Applied	0	Procedure Begun	Yes	Success
	Applied	0	Procedure Begun	No	Failure
	Applied	>0	Followed for Safety	-	Failure
Cocaine HCl 10%	Applied	0	Procedure Begun	Yes	Success
	Applied	0	Procedure Begun	No	Failure
	Applied	>0	Followed for Safety	-	Failure
* >0 if at least 1 nostril exhibited any pain, 0 if all nostrils had no pain; ** `-` is not applicable (N/A)					

Source: CSR COCA4vs10-002, p. 51, Applicant's submission (PDF), NDA 209575

Secondary efficacy endpoints were as follows:

- Anesthetic success immediately after application of cocaine HCl 10% topical solution and sustained throughout the diagnostic procedure or surgery
- Anesthetic success immediately after application
- Sustained anesthetic success for both cocaine HCl topical solutions
- vFF test pain score

An additional secondary efficacy endpoint evaluating the adequacy of hemostasis was summarized by active treatment groups. This endpoint was assessed by individual investigators' response to the question, "Was adequate hemostasis achieved (yes or no)?". All no answers required additional explanation and consideration for recording lack of hemostasis as an adverse event. Exploratory analyses of the primary efficacy endpoint were performed by procedure by treatment group.

Statistical Analysis Plan

Descriptive statistics were used for continuous data and included the number of subjects summarized, mean, standard deviation, median, and range. Summary statistics were presented by treatment group by phase, combined phases, and overall. Significance testing was two-tailed using an α=0.05 level unless otherwise specified.

The primary efficacy analysis was performed using the intent-to-treat (ITT) population, which consisted of all subjects randomized and received study drug, and Fisher's Exact Test for cocaine HCl 4% topical solution and placebo treatment arms. A secondary analysis of the primary efficacy endpoint was conducted using the per protocol (PP) population.

Analyses of secondary efficacy endpoints were conducted using the ITT and PP populations.

Subgroup analyses were conducted on the following subject populations:

- gender
- age (<35 years of age, 35 to 65 years of age, >65 years of age)
- type of procedure

Summaries of immediate and sustained anesthetic success is provided by amount of study drug administered for each cocaine treatment group by procedure and overall. Subjects with missing primary efficacy endpoints were documented as treatment failures. There were no missing or censored pain scores imputed.

Protocol Amendments

There was one SPA Modification Agreement during the conduct of this study and was based on the unanticipated outcome of lack of efficacy of the cocaine HCl 4% topical solution in Study COCA4vs10-001. Significant changes to Study COCA4vs10-002 protocol included the following:

- change to a single phase trial evaluating the safety and efficacy of cocaine HCl 4% topical solution, cocaine HCl 10% topical solution, and placebo topical solution in a 2:2:1 ratio
- change back to dose blinding when breaking the blind for placebo and active treatment
- change back to the 0 to 10 pain scale
- additional standardized language regarding pressure and touch
- use of a stiffer vFF for testing
- dose of cocaine HCl administered calculated based on number of pledgets inserted
- screening time changed from seven to ten days prior to procedure, making total time in the study 17 days
- primary endpoint language edited to reflect treatment success versus placebo

Additional changes to the protocol included minor edits and clarifications.

Refer to Section 3.2 Summary of Presubmission/Submission Regulatory Activity and Table 3 for additional information on the regulatory history of this clinical study.

It does not appear there were any other protocol amendments for Study COCA4vs10-002.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant noted in Section 5, ETHICS, of the protocol that "this research was carried out in accordance with the International Conference on Harmonisation (ICH) E6, Good Clinical Practice consolidated guidance, 21 CFR 312 Investigational New Drug Application Regulations, and United States law and guidelines applicable to clinical research, and generally accepted principles for the ethical conduct of human research such as the Declaration of Helsinki regulations and guidelines".

Financial Disclosure

(b) (4), signed the FDA form 3454 on September 1, 2017, 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 a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

A total of 646 subjects were enrolled and 639 subjects randomized and received study drug, refer to Table 25. Nine subjects withdrew from the study early; three from the cocaine HCl 4% treatment group, five from the cocaine HCl 10% treatment group, and one from the placebo group. Seven of the nine subjects were randomized but did not receive study drug. One subject in the cocaine HCl 4% treatment group withdrew due to an adverse event, to be discussed in more detail in Section 8.4, Safety Results, of this review.

Table 25. Subject Disposition (all randomized and withdrawn subjects)

	Cocaine HCl 4% (N=259)	Cocaine HCl 10% (N=259)	Placebo (N=128)	Overall (N=646)
Completed (%)	256 (98.8)	254 (98.1)	127 (99.2)	637 (98.6)
Withdrawn (%)	3 (1.2)	5 (1.9)	1 (0.8)	9 (1.4%)
Reason for Withdrawal (%)				
Adverse Event	1 (0.4)	-	-	1 (0.2)
Subject Decision	1 (0.4)	2 (0.8)	-	3 (0.5)
Physician Decision	-	2 (0.8)	1 (0.8)	3 (0.5)
Other Reason	1 (0.4)	1 (0.4)	-	2 (0.3)
Source: Table 14.3.8.1				

Source: CSR COCA4vs10-002, p. 63 (PDF), Applicant's submission, NDA 209575

Protocol Violations/Deviations

Overall, there were 69 significant protocol deviations reported in 59 subjects as follows: 21 cocaine HCl 4%-treated subjects, 29 cocaine HCl 10%-treated subjects, and in 9 placebo-treated subjects. The overwhelming majority (53) were due to enrollment criteria violations and included the following:

- Systolic and/or diastolic blood pressure values above the stated protocol limits (N=16)
- ECG abnormalities including QRS or QTc intervals above the stated protocol limits (N=13)
- Laboratory values being outside the stated protocol limits (N=11)
- Use of prohibited concomitant medications (N=10)
- Incorrect treatment allocation via the IVRS (interactive voice response system) (N=3)

Other protocol violations were reported as dosing errors (6), processing issues (5), incomplete consent (4), and unblinding (1). The dosing errors included pledget insertion for greater than the stated protocol time of 20 minutes, a delay in hemodynamic monitoring, and incorrect number of pledgets saturated with study drug solution. The Applicant reported a single subject was unblinded to placebo versus active treatment prior to the second (after study drug administration) vFF test. Similar to the results reported for Study COCA4vs10-001, the Applicant did not record the time of the vFF tests relative to the unblinding, making it hard to determine if other subjects were unblinded either before the vFF test or at the same time. Dr. Feng Li, statistical reviewer, conducted a tipping point analysis to evaluate potential impact of unblinding on the study results. The results from his analysis indicate that the statistical significance of cocaine 4% in comparison to placebo would be lost if the percentage of unblinding was more than 44% and the statistical significance of the cocaine 10% in comparison to placebo would be lost if more than 56% of subjects were unblinded. It seems unlikely that such a large number of subjects would have been unblinded (refer to his review for a more complete discussion of the results of his additional analyses).

None of the reported protocol violations were thought to influence the safety or efficacy findings of the study.

Table of Demographic Characteristics

Demographic and other baseline characteristics are presented in Table 26. Briefly, 39% of subjects were male and 60.8% were female. The mean subject age was 37.57 years and the majority of subjects were white and non-smokers. The demographic characteristics were similar across the treatment and placebo groups with the exception that more subjects were male in the placebo group compared to the treatment groups.

Table 26. Demographic and Baseline Characteristics (Safety Population)

Characteristic	Cocaine HCl 4% (N=259)	Cocaine HCl 10% (N=259)	Placebo (N=128)	Overall (N=646)
Age (years), n				
Mean (SD)	38.42 (13.34)	37.50 (12.76)	36.01 (12.34)	37.57 (12.92)
Median	37.0	36.0	34.0	36.0
Sex, n (%)				
Male	90 (34.7)	103 (39.8)	60 (46.9)	253 (39.2)
Female	169 (65.3)	156 (60.2)	68 (53.1)	393 (60.8)
Race, n (%)				
American Indian or Alaska Native	-	2 (0.8)	-	2 (0.3)
Asian	9 (3.5)	12 (4.6)	10 (7.8)	31 (4.8)
Black or African American	43 (16.6)	30 (11.6)	12 (9.4)	85 (13.2)
Native Hawaiian or Other Pacific Islander	-	3 (1.2)	1 (0.8)	4 (0.6)
White or Caucasian	205 (79.2)	212 (81.9)	105 (82.0)	522 (80.8)
Ethnicity, n (%)				
Hispanic or Latino	36 (13.9)	36 (13.9)	17 (13.3)	89 (13.8)
Not Hispanic or Latino	220 (84.9)	222 (85.9)	108 (84.4)	550 (85.1)
Not Reported	-	-	1 (0.8)	1 (0.2)
Unknown	3 (1.2)	1 (0.4)	2 (1.6)	6 (0.9)
Weight (lb), n				
Mean (SD)	177.0 (46.9)	181.7 (47.1)	179.7 (43.8)	179.4 (46.4)
Median	174.0	175.0	175.0	175.0
History of Tobacco Use, n (%)				
Smoker	52 (20.1)	50 (19.3)	28 (21.9)	130 (20.1)
Non-Smoker	207 (79.9)	209 (80.7)	100 (78.1)	516 (79.9)

Source: CSR COCA4vs10-002, p. 72 (PDF), Applicant's submission, NDA 209575

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

All subjects in the safety population had at least one prior medical condition. Medical histories reported in ≥10% of subjects included deviated nasal septum, hypertension, and headache. No subject reported a history of adrenal gland tumor, including pheochromocytoma, high fever associated with anesthesia, or hereditary pseudocholinesterase deficiency.

Most subjects in the safety population used one concomitant medication. The following medications were used by ≥5% of subjects:

- Fluticasone
- Multivitamins
- Omeprazole
- Cetirizine
- ibuprofen

Less than 5% of subjects used dietary supplements.

Lidocaine with phenylephrine was the most frequently used additional topical anesthetic used in subjects who failed the vFF test.

Treatment Compliance and Rescue Medication Use

The study drugs were administered to enrolled subjects by individual investigators, such that treatment compliance as assessed by subject-administration of medication was not applicable in this study.

There were a total of three treatment failures that occurred during the study; i.e., subjects rated pain during vFF test 0, but experienced discomfort during the procedure. Two subjects were in the 4% cocaine HCl treatment group and one was in the 10% cocaine HCl treatment group.

Efficacy Results – Primary Endpoint

The proportion of subjects in both cocaine treatment groups having immediate and sustained anesthetic efficacy was greater than those subjects who received placebo, refer to Table 27. The vast majority of treatment failures were identified during the vFF test, therefore did not undergo a procedure. As previously mentioned, three subjects reported discomfort during the procedure.

The number of subjects successfully treated with cocaine HCl 4% (183 out of 258 treated subjects) was statistically significantly greater than the number of placebo-treated subjects (25 out of 127 treated subjects). (b) (4) The Applicant conducted the primary efficacy analyses on the ITT population, however, similar results were observed for the PP population. A generalized linear model analysis of the proportion of subjects with immediate and sustained anesthetic success was performed to assess the size of the difference in observed efficacy. The size of the difference between the cocaine HCl treatment groups and placebo are statistically significant, supporting the findings of the primary efficacy analyses. An exploratory analysis comparing the efficacy of the two cocaine concentrations resulted in a calculated p value of (b) (4) However, these results are not entirely supportive of a dose response relationship for two reasons. First, the results are driven by subject response during vFF testing, which may not be a reliable predictor of adequate surgical anesthesia, and second, this was not a prespecified analysis.

Table 27. Immediate and Sustained Anesthetic Success to the Nasal Cavities After the Application of Study Medication to the Nasal Mucosa - ITT Population

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval	*P* Value[a]
Cocaine HCl 4% (N=258)	183 (0.7093)	0.6498 to 0.7640	<0.0001[b]
Cocaine HCl 10% (N=254)	(b) (4)		
Placebo (N=127)	25 (0.1969)	0.1316 to 0.2767	

Source: Table 14.2.1.1, Table 14.2.1.5

[a] *P* values generated as one-sided from Fisher's Exact Test of equal treatment proportions, with each treatment arm tested against placebo at a one-sided alpha=0.0178 level of significance. [No covariate with factors for treatment, pooled site and treatment-by-pooled-study-site interaction available.] [b] An exploratory *P* value for 4% versus. 10% treatment was (b) (4)

Source: CSR COCA4vs10-002, p. 76 (PDF), Applicant's submission, NDA 209575

An analysis of the primary efficacy endpoint by procedure by treatment did not indicate a statistically significant difference in successful procedure completion between the two cocaine HCl solutions, albeit the numbers of subjects undergoing procedures other than nasal endoscopy were generally small. Refer to Section 7, Integrated Review of Efficacy Across Trials for a discussion of the efficacy results and evaluated procedures.

As previously mentioned, the total dose of cocaine administered was calculated based on the number of pledgets inserted in the nose. The dosing in this study appears to be more consistent than that used in Study COCA4vs10-001, however, not all subjects received the same number of pledgets, and hence not the same dose within each cocaine HCl treatment group. As indicated in Table 28, only 143 subjects received the maximum dose of cocaine HCL 4% (160 mg) and 148 subjects received the maximum dose of cocaine HCl 10% (400 mg). The remaining subjects received doses less than the maximum in 40 mg or 100 mg increments based on the solution concentration, 4% or 10% respectively.

Table 28. Cocaine Dose by Pledget Application

Cocaine HCl Dose (mg)	# of Subjects Treated*
4% topical solution	
• 80 mg	104
• 120 mg	12
• 160 mg	143
10% topical solution	
• 200 mg	99
• 300 mg	6
• 400 mg	148

*6 subjects did not have a dose of cocaine recorded

Subgroup Analyses

Subgroup analyses were performed for subject age, race, and sex. The following table, created by Dr. Feng Li, statistical reviewer, summarizes the anesthetic success by subgroups. Note that the "other" race category included races other than white and black or African American. Cocaine-treated subjects had consistently higher analgesic and anesthetic success rates than placebo-treated subjects in all subgroups analyzed.

Table 29. Anesthetic Success by Sex, Race, and Age

		Placebo (N=127)		Cocaine 4% (N=258)		Cocaine 10% (N=254)	
Subgroup		**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Sex	Male	59	13 (22%)	90	70 (78%)	102	(b) (4)
	Female	68	12 (18%)	168	113 (67%)	152	
Race	White	104	24 (23%)	204	147 (72%)	210	
	Black	12	0	43	29 (67%)	27	
	Other	11	1 (9%)	11	7 (64%)	17	
Age	>=35	61	11 (18%)	140	97 (69%)	131	
	<35	66	14 (21%)	118	86 (73%)	123	

Source: Dr. Feng Li, statistical reviewer

Data Quality and Integrity

The preliminary report from an audit conducted by OSI, Division of Clinical Compliance Evaluation, has indicated that the reviewed data, including informed consent procedures, drug accountability records, and information related to study blinding and electronic source data, were reliable for Study COCA4vs10-002 and recommended accepting the clinical portion of the studies for further FDA review.

Efficacy Results – Secondary and other relevant endpoints

- Immediate anesthetic efficacy
  Analysis of the secondary efficacy endpoint of immediate anesthetic efficacy using the vFF test revealed a statistically significant difference with both cocaine HCl treatment groups when compared to placebo. The observed immediate success for the cocaine HCl 4% treatment group was 72% (186 of 258 subjects), (b) (4) demonstrated a clinically significant larger proportion of subjects with immediate anesthetic success compared to placebo. Additionally, the proportion of immediate anesthetic successes (b) (4)

(b) (4)

Table 30. Immediate Anesthetic to the Nasal Cavities After the Application of Study Medication to the Nasal Mucosa - ITT Population

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval
Cocaine HCl 4% (N=258)	186 (0.7209)	0.6619 to 0.7748
Cocaine HCl 10% (N=254)	(b) (4)	
Placebo (N=127)	25 (0.1969)	0.1316 to 0.2767

Source: CSR COCA4vs10-002, p. 79 (PDF), Applicant's submission, NDA 209575

- Sustained anesthetic efficacy

  Analysis of the secondary endpoint of sustained anesthetic efficacy during the diagnostic procedure or surgery revealed (b) (4) . The sustained anesthetic response for the cocaine HCl 4% treatment group was 71% (184 of 258 subjects) (b) (4) Refer to Table 31 for additional efficacy information. (b) (4)

Table 31. Sustained Anesthetic to the Nasal Cavities After the Application of Study Medication to the Nasal Mucosa - ITT Population

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval
Cocaine HCl 4% (N=258)	184 (0.7132)	0.6538 to 0.7676
Cocaine HCl 10% (N=254)	(b) (4)	

Source: CSR COCA4vs10-002, p. 80 (PDF), Applicant's submission, NDA 209575

The Applicant presented additional immediate and sustained anesthetic efficacy information by cocaine dose as described below.

The proportion of immediate anesthetic efficacy successes by cocaine dose, mg, are as follows:

- 63% with cocaine HCl 80 mg (4% solution)
- 77% with cocaine HCl 160 mg (4% solution)
- (b) (4)
-

As previously indicated in Table 28, no subject received the lowest possible dose in each cocaine HCl treatment group, 40 mg or 100 mg for the 4% or 10% solution respectively. The Applicant stated that because the number of subjects who received a 3 mL dose, 120 mg for the 4% solution and 300 mg for the 10% solution, was so low, a meaningful evaluation of anesthetic efficacy could not be provided. Similar proportion results were observed for the secondary endpoint of sustained anesthetic efficacy.

- Pain intensity scores from vFF test

  Analysis of the secondary endpoint of pain intensity from the vFF test included an evaluation of subject-reported pain scores for each treatment for each nostril and combined nostrils. The number of procedures performed through the right and left nostrils was equivalent, however, the left nostril reportedly had lower mean NPRS scores. Lower numeric pain scores during vFF testing were reported by subjects (b) (4) (b) (4) compared to those in the placebo group. No significant difference was observed in subject-reported NPRS scores for the two most commonly performed procedures, nasal endoscopy and transnasal laryngoscopy. Refer to Table 32 for reported numeric pain scores by treatment by nostril(s).

Table 32. Numeric Pain Scores After Study Drug Application and von Frey Monofilament Test by Nostril by Treatment - ITT Population

	Left Nostril		Right Nostril		Combined Nostrils	
Treatment	n[a]	Mean[b] (SD)	n	Mean (SD)	n	Mean (SD)
Cocaine HCl 4%	215	0.64 (1.484)	206	0.71 (1.638)	421	0.68 (1.560)
Cocaine HCl 10%	206	(b) (4)				
Placebo	108	3.62 (2.498)	105	3.38 (2.525)	213	3.50 (2.525)

Source: Table 14.2.5.1.
[a] Denominator reflects the number of nostrils
[b] NPRS score, where 0=no pain and 10=unbearable pain

Source: CSR COCA4vs10-002, p. 81 (PDF), Applicant's submission, NDA 209575

- Adequacy of hemostasis

  Similar to the evaluation of hemostasis in Study COCA4vs10-001, the assessment was the response to the question, "Was adequate hemostasis achieved?". Subjects (b) (4) cocaine HCl treatment groups had adequate hemostasis; 100% of subjects in the 4% treatment group (b) (4). Refer to Table 33 for results for adequacy of hemostasis.

Table 33. Adequacy of Hemostasis After the Application of Study Medication to the Nasal Mucosa - ITT Population

Treatment	Success Achieved by Number of Subjects (Proportion of Subjects)	95% Exact Confidence Interval
Cocaine HCl 4% (N=186)	186 (1.0000)	0.9804 to 1.0000
Cocaine HCl 10% (N=212)	(b) (4)	

Source: CSR COCA4vs10-002, p. 83 (PDF), Applicant's submission, NDA 209575

Dose/Dose Response

(b) (4)

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted on this trial.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoint of immediate and sustained analgesic success in Study COCA4vs10-001 (b) (4) As previously mentioned, the lack of a statistically significant difference in the primary efficacy endpoint for 4% cocaine HCl and placebo may have been due to an unexpectedly high placebo response, use of a low strength vFF for evaluation of immediate analgesic success, and unclear language regarding experienced pain sensations. In Study COCA4vs10-002, (b) (4) The results of the integrated analysis of the primary efficacy endpoint for the Phase 3 studies indicate a statistically significant difference between 4% cocaine HCl topical solution

and placebo (b) (4) These results in combination with the long marketing history and clinical use of cocaine as a topical anesthetic for procedures of the nasal cavities support the approvability of this product, (b) (4)

7.1.2. Secondary and Other Endpoints

(b) (4) In Study COCA4vs10-001, statistical significance was not reached for the 4% cocaine HCl topical solution compared to placebo; however, Study COCA4vs10-002 did demonstrate a statistically significant difference between the 4% solution and placebo.

Analysis of the secondary efficacy endpoint of sustained analgesia/anesthesia revealed clinically meaningful success rates (b) (4)

The secondary endpoint of pain intensity scores from vFF in each nostril and combined nostrils varied between the Phase 3 studies, suggesting that a particular nostril does not appear to have a lower or higher pain threshold in response to the vFF test. (b) (4)

It does appear that hemostasis was adequate (b) (4) dditionally, the majority of procedures performed, would not likely lead to clinically relevant surgical bleeding.

7.1.3. Subpopulations

As previously discussed for both Phase 3 studies, there did not appear to be clinically significant differences in the evaluated subgroup success rates, however, the numbers for races other than white and black were quite low.

Analysis of immediate and sustained analgesic/anesthetic success was performed by procedure for each cocaine topical solution. There were no significant differences in the procedures

performed by treatment, albeit the number of procedures evaluated aside from nasal endoscopy was low.

7.1.4. Dose and Dose-Response

(b) (4)

The potential difference in efficacy between the cocaine treatment groups for sustained analgesic/anesthetic success, as assessed by the need for additional medication during the diagnostic procedure or surgery, was not evaluated in the Applicant's Phase 3 studies.

(b) (4)

ubjects in the 4% cocaine HCl treatment group who received a dose of 81 to 121 mg appear to have had a higher analgesic/anesthetic success rate than those who received other mg doses of the 4% topical solution. (b) (4)

The cocaine dosing in Study COCA4vs10-001 was variable and many subjects in the 4% treatment group received similar doses as those in the 10% treatment group, making the results of this study difficult to interpret.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Cocaine HCl topical solutions are used to provide rapid and predictable local anesthesia of the mucous membranes for the successful completion of non-invasive diagnostic and surgical procedures on or through the nasal cavities. Topical cocaine administration via pledget application provides adequate anesthesia of the mucous membranes for approximately 30 minutes, while limiting the systemic absorption of cocaine. Given the relatively short application time and predictable duration of anesthetic response, there is little clinical concern of long-term adverse reactions, tolerance, or withdrawal effects, all of which are commonly observed in situations of illicit use of cocaine.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

As previously mentioned, there is currently one FDA-approved cocaine topical solution, 4%. Approval of this cocaine HCl 4% solution would provide clinicians an additional approved topical anesthetic product for use during nasal diagnostic and surgical procedures. (b) (4)

(b) (4)

7.2.2. Other Relevant Benefits

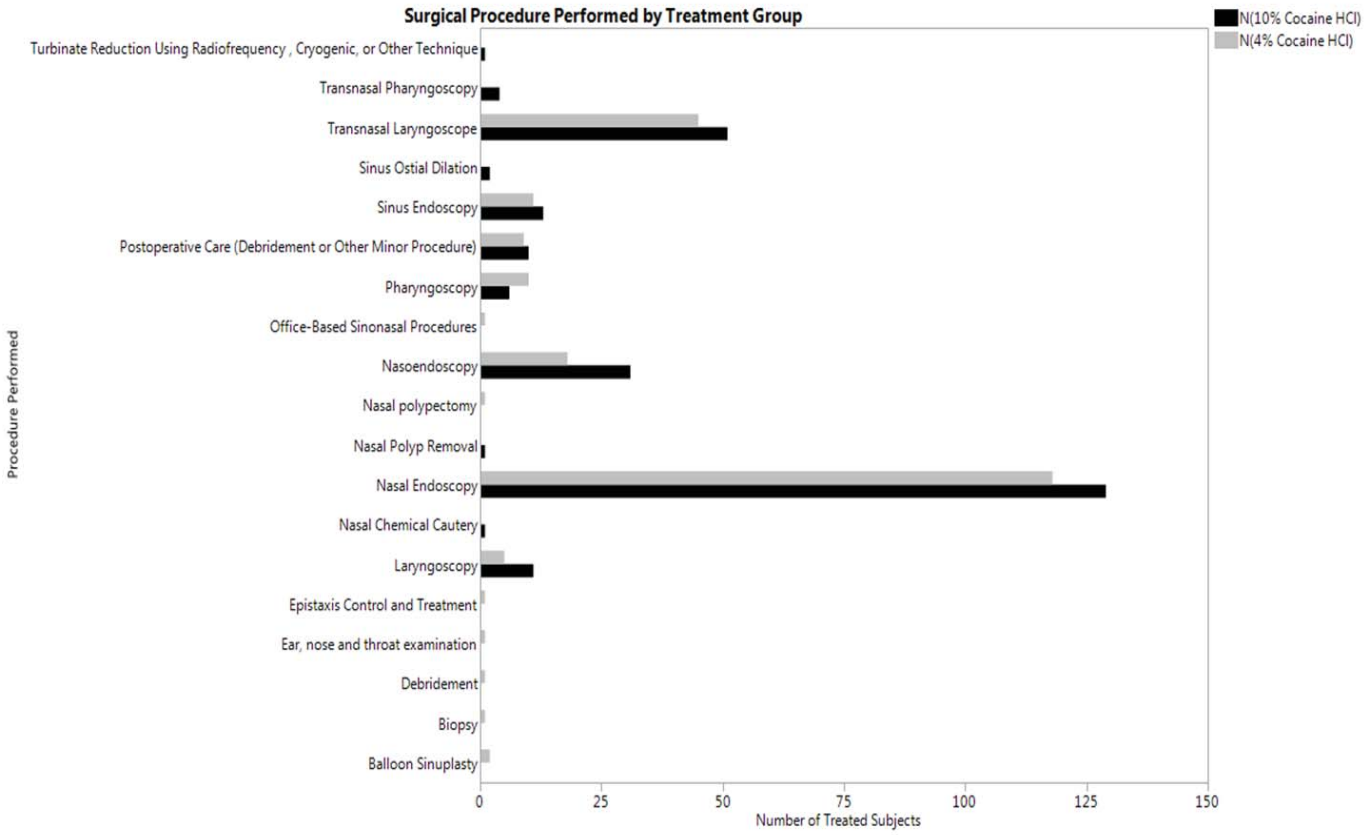
The Applicant did evaluate local vasoconstriction of the nasal mucosal blood vessels using laser Doppler in their Phase 1, PK study. The results support the known vasoconstrictive properties of cocaine and suggest an additional clinical benefit for its use in nasal surgery is to decrease nasal congestion and surgical bleeding, thereby improving visualization of the surgical field. In the Phase 3 clinical studies conducted by the Applicant, individual investigators were asked to assess the adequacy of hemostasis in cocaine-treated subjects who underwent a procedure. The results indicate that in the opinion of the investigators, adequate hemostasis was observed in the vast majority of subjects in both cocaine treatment groups.

An added benefit of all topically-applied local anesthetics is less trauma to the nasal mucosa and underlying structures. Administration of other widely used local anesthetics for nasal surgery, such as lidocaine with epinephrine, often involves mucosal injections, resulting in local tissue trauma and potentially increased bleeding.

7.3. Integrated Assessment of Effectiveness

The Applicant is seeking approval of both 4% and 10% cocaine HCl solutions for use as topical anesthetics during diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. In general, results from the Applicant's Phase 3 studies did demonstrate clinically relevant immediate and sustained topical anesthesia of the nasal mucosal membranes after application of (b) (4) The results from Study COCA4vs10-001 did not demonstrate a statistically significant difference in the primary efficacy endpoint for 4% cocaine HCl topical solution and placebo, which may have been due to an unexpectedly high placebo response, use of a low strength vFF, and unclear language regarding experienced pain sensations as discussed by the Applicant. The efficacy evaluations included patients undergoing a variety of procedures, which appear representative of those most commonly performed in an outpatient, office setting. There were not, however, a large number of procedures evaluated that are considered more invasive or more painful, as indicated in Figure 7.

Figure 7. Evaluated Diagnostic Procedures and Surgeries



During the drug development process, the Applicant was advised to (b) (4)

.

In response to an Information Request (IR) dated March 21, 2018, the Applicant provided (b) (4)

[redacted]

This additional rationale provided may not be adequate for the following three reasons. First,

(b) (4)

[redacted]

(b) (4)

[redacted] However, because the TQT evaluation was not adequate, I also do not recommend approval of 4% topical solution.

8. Review of Safety

8.1. Safety Review Approach

The Applicant conducted three clinical studies, one Phase 1 and two Phase 3 studies, with safety data that will be presented in this review. Because this application is a 505(b)(2), the Applicant is also relying on information in the published literature to support the safety of cocaine topical solutions for use as anesthetics in diagnostic procedures and surgeries on or through the nose.

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 both controlled 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 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 clinical 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 both the 4% and 10% cocaine topical solutions for use as topical anesthetics during diagnostic procedures and surgeries on or through the accessible mucous membranes of the nasal cavities. In the drug development program, the safety database included the intent-to-treat population with 841 subjects total. Three subjects, however, were not randomized resulting in 347 subjects exposed to the 4% solution and 341 subjects exposed to the 10% solution. As previously mentioned, there was overlap between the two treatment groups and the dose administered, suggesting potential overlap in the safety results reported, particularly in Study COCA4vs10-001. The mean dose of 4% cocaine HCl topical solution administered for the Phase 3 studies was 123.06 mg (range 41.6 to 166.4 mg) and the mean dose of 10% cocaine HCl topical solution was 308.4 mg (range 119 to 525 mg).The number of missing study drug doses reported was low; two missing from the 4% cocaine treatment groups, four missing from the 10% cocaine treatment groups, and two missing from the placebo groups across all studies.

The majority of subjects in all three clinical studies were exposed to intranasal cocaine solution or placebo for the recommended 20 minutes. A small number, eight subjects, were exposed for a period of time less than 20 minutes and 30 subjects were exposed for greater than 20 minutes. The AEs associated with the prolonged exposure were not clinically significantly different from those associated with the recommended treatment time and were most commonly documented as hypertension and diastolic hypertension.

Refer to Table 34 for cocaine exposure in the safety population.

Table 34. Safety Population Exposed to 4% and 10% Cocaine Topical Solutions

Individuals exposed to any treatment in this development program for the indication under review (N=692)				
Clinical Trials	**Phase/Design**	**Treatment Groups**	**# of Subjects Exposed**	**Surgical Population**
LNT-P6-733	I – PK, safety, tolerability, and vasoconstriction Two-period crossover	4% topical solution 10% topical solution Placebo solution	31 completed 4%, n=34 10%, n=32 Pbo, n=22	Healthy volunteers
COCA4vs10-001	3 – Efficacy and safety Prospective, randomized, double-blind, placebo-controlled	4% topical solution 10% topical solution Placebo solution	156 completed 4%, n=57 10%, n=59 Pbo, n=40	Subjects undergoing diagnostic procedures or surgeries on/through the nasal cavities
COCA4vs10-002	3 – Efficacy and safety Prospective, randomized, double-blind, placebo-	4% topical solution 10% topical solution Placebo solution	637 completed 4%, n=256 10%, n=254	Subjects undergoing diagnostic procedures or surgeries on/through the nasal

Individuals exposed to any treatment in this development program for the indication under review (N=692)				
	controlled		Pbo, n=127	cavities

8.2.2. Relevant characteristics of the safety population:

The safety population in the three clinical studies and the literature reviewed was a reasonably diverse adult population, including ASA physical status classification I – III. However, Caucasian, not Hispanic or Latino, middle-age, non-smoking adults was the primary demographic for the cocaine and placebo treatment groups in the Applicant's Phase 3 studies. Placebo subjects were younger (mean 35 years) compared to 4%-treated subjects (mean 39 years) and 10%-treated subjects (mean 41 years) in Study COCA4vs10-001 and females made up a larger percentage (mean 61%) of treated subjects in Study COCA4vs10-002.

8.2.3. Adequacy of the safety database:

Although the number of subject exposures in the Applicant's clinical development program appears adequate, the totality of the safety database is inadequate due to lack of a TQT evaluation in treated patients. This submission is a 505(b)(2) application relying the published literature for findings of safety in addition to the Applicant's clinical drug development program. Due to the recent approval of the 4% cocaine topical solution, Goprelto®, by Genus Life Sciences, Inc., the annual post-marketing surveillance program for topical cocaine is early in the reporting stages and there are currently no reports in the FAERS database regarding its use.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues regarding the data integrity or the quality of the submission. The information provided was organized and easy to locate.

8.3.2. Categorization of Adverse Events and Routine Clinical Tests

The clinical study reports (CSR) did provide definitions for adverse events (AE), FDA-defined serious adverse events (SAE), and treatment emergent adverse events (TEAE). Additionally, protocol-defined SAEs were provided by the Applicant in their safety analyses. The adverse events were categorized by severity and causality relationships were documented. A nasal cavity examination was performed in Study LNT-P6-733 and clinically significant changes were documented. Potential changes in smell post-treatment were not evaluated in the clinical studies conducted by the Applicant. The following safety information was provided in the CSRs:

LNT-P6-733 (refer to Section 4.5.3, Pharmacokinetics for further discussion of this study)
The safety assessments conducted during each of the two treatment periods of this study included monitoring for adverse events, vital sign measurements, 12-lead ECG evaluation, nasal

cavity examinations, and laboratory tests (refer to Table 6 for the schedule of all assessments). Vital sign monitoring included measurement of heart rate, respiratory rate, blood pressure, oxygen saturation, and body temperature. A 12-lead ECG was performed before each period of the study and approximately 1, 2, 4, and 6.5 hours post-pledget removal. The laboratory assessments included timed measurements of plasma and urinary pharmacokinetic parameters for cocaine and the metabolites, including BE, EME, ecgonine, and norcocaine, after bilateral intranasal administration of 4% and 10% cocaine topical solutions. Additional laboratory assessments included serology testing for Human Immunodeficiency Virus, Hepatitis B virus, and Hepatitis C virus; hematology; serum chemistry; urinalysis; and pregnancy screening. Assessments for alcohol and other substances of abuse were performed at the screening visit and prior to each treatment period.

Study COCA4vs10-001

Safety assessments were performed during both the double-blind efficacy and the safety only phases and included monitoring for adverse events, vital sign measurements, single lead ECG monitoring, and 12-lead ECG evaluations prior to study drug treatment and prior to discharge from recovery. Vital sign measurements and ECG monitoring were performed throughout the study drug application and the diagnostic procedure or surgery, and during the recovery period. Laboratory assessments performed during the screening visit included serum chemistry, hematology, blood coagulation, cardiac enzymes, and urinalysis. There were no specific nasal mucosal or smell assessments performed during this study. Additional assessments performed during additional follow-up visits on Days 2 (Visit 3) and 8 (Visit 4) were at the discretion of the investigator. Refer to Table 11 for the complete schedule of assessments.

Study COCA4vs10-002

Safety assessments were performed throughout the study and included monitoring for adverse events, vital sign measurements, single lead ECG monitoring, and 12-lead ECG evaluations prior to study drug treatment and prior to discharge from recovery. Vital sign measurements and ECG monitoring were performed throughout the study drug application and the diagnostic procedure or surgery, and during the recovery period. Laboratory assessments performed during the screening visit included serum chemistry, hematology, blood coagulation, cardiac enzymes, and urinalysis. There were no specific nasal mucosal or smell assessments performed during this study. Additional assessments performed during additional follow-up visits on Days 2 (Visit 3) and 8 (Visit 4) were at the discretion of the investigator. Refer to Table 23 for the complete schedule of assessments.

8.4. Safety Results

8.4.1. Deaths

There were no subject deaths reported during the Applicant's Phase 3 studies or throughout the drug development program. Review of the published literature and the FAERS database has not identified any deaths related to topical cocaine administration for the purposes of

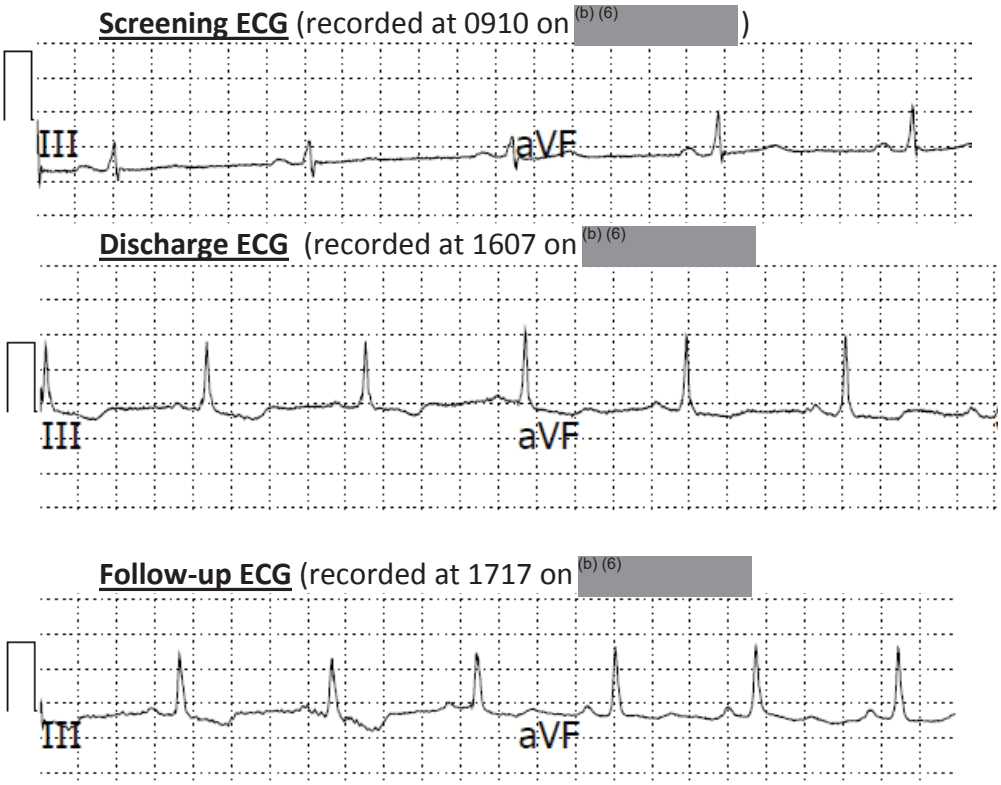
anesthesia during nasal surgery. The deaths that have been reported in the FAERS database, where cocaine was listed as the primary suspect or was reported, are associated with the illicit use of cocaine.

8.4.2. Serious Adverse Events

The Applicant provided the regulatory definitions for an SAE and also provided protocol-defined SAEs, which included Grade 3 or greater vital sign measurements, and will be discussed further in Section 8.4.4, Significant Adverse Events. There was one FDA-defined SAE, myocardial ischemia, in Study COCA4vs10-001. The subject narrative included the following information:

- Subject (b) (6) was a 49 year-old African American male with a past medical history of anemia, anxiety, and nasal congestion who presented for nasoendoscopy. He had no prior history of hypertension or cardiac disease. His current daily medications included pseudoephedrine (Claritin-D), ativan, brain prep pills, cholecalciferol, and fish oil. Screening laboratory results and 12-lead ECG were within normal limits. There is a discrepancy regarding the cocaine dose he received. The Compliance and/or Drug Concentration Data Listing, Study COCA4vs10-001, p. 14,(PDF), indicates that he received 388 mg of cocaine HCl, 3.88 mL of 10% topical solution at 1352 on Nov. 4, 2014. Appendix 2, SAE Medical Summaries Study COCA4vs10-001, p. 183 (PDF), indicates he received 305 mg of cocaine HCl, 3.05 mL of 10% topical solution on the same day and time. At unspecified time points, there were changes observed on continuous single-lead ECG monitoring, described as "isolated T wave inversion" and "isolated ST depression". The 12-lead ECG performed prior to discharge, at 1607, had similar changes of ST segment depression and T wave inversion, noted in the inferior leads. The subject was reportedly asymptomatic and was discharged from recovery with planned follow-up on (b) (6). The ECG performed on (b) (6), was reportedly within normal limits (refer to Figure 8 for relevant 12-lead ECGs from screening, at the time of discharge, and at the follow-up visit). Repeat laboratory testing on the follow-up visit indicated an increase in creatine kinase MB isozyme from 0.5 ng/mL to 3.3 ng/mL, still within normal limits. The Troponin-I was within normal limits. The subject did not require treatment and the event relationship was reported as possibly related to the study drug administration. Refer to Table 35 for relevant vital signs on day of procedure.

Figure 8. ECG for Subject (b) (6) with Myocardial Ischemia



Source: CSR Study COCA4vs10-001, Applicant's submission, NDA 209575

Table 35. Measured Relevant Vital Signs on Day of Procedure

Measured Parameter	Baseline Value	Peak Value	Discharge Value
Heart rate (bpm)	81	90 (@1415)	77 (@1556)
Systolic blood pressure (mmHg)	131	162 (@ 1531)	145 (@ 1556)
Diastolic blood pressure (mmHg)	79	103 (@1415)	81 (@ 1556)

It is reassuring that this subject reportedly recovered and did not suffer a myocardial infarction with irreversible myocardial damage; however, additional information, including a more extensive history and physical examination, laboratory evaluations, and continuous ECG monitoring, could have assisted in elucidating the cause of the SAE.

Protocol-defined SAEs will be discussed in detail in Section 8.4.4, Significant Adverse Events.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were two subjects in Study COCA4vs10-002 who withdrew due to an adverse event. The following are summaries of the subject narratives provided:

- Subject (b) (6) , a 24 year-old Caucasian female with significant past medical history of

allergic rhinitis, hypothyroidism, and ovarian cystectomy, received 80 mg, 2 mL of cocaine HCl 4% topical solution. She complained of anxiety within 10 minutes of pledget insertion and developed systolic hypertension requiring pledget removal. Her peak heart rate (HR) was recorded at 30 minutes post-pledget insertion and was 97 bpm (baseline 73 bpm). Her peak systolic blood pressure was 170 mmHg (baseline 127 mmHg) 10 minutes post-pledget insertion and peak diastolic blood pressure was 111 mmHg (baseline 90 mmHg) 25 minutes post-pledget insertion. She did not undergo her scheduled procedure and withdrew from the study.

- Subject (b) (6) a 39 year-old Caucasian female with significant past medical history of eczema, headaches, laryngitis, neck pain, seasonal allergies, anemia, bronchitis, and nasal congestion received 80 mg, 2 mL of cocaine HCl 4% topical solution. She did not have a procedure performed for the documented reason, as stated in the Subject Disposition Data Listing, p. 8 (PDF), of "the drug product application was interrupted and the procedure was not performed". However, in the Summary of Clinical Safety, this subjects' withdrawal was documented as due to moderate intermittent paroxysmal sinus tachycardia and hypertension. Review of the vital sign data does indicate that the patient developed tachycardia within 10 minutes of pledget insertion. Her baseline heart rate was reported as 80 bpm, rose to 112 bpm at the 10-minute time point, and peaked at 156 bpm at the 15-minute time point. Systolic blood pressure measurements at 10 and 15 minutes, during the initial and peak heart rate changes, were 121 mmHg and 118 mmHg (slight increases over the 117 mmHg baseline value), respectively. Diastolic blood pressure measurements at the same time points were 88 mmHg and 87 mmHg, respectively (baseline value 78 mmHg). There were no reported clinically significant changes in other measured vital sign parameters or in the ECG recording. She completed the required 90-minute recovery period and was discharged with stable vital signs as follows: heart rate 92 bpm, systolic blood pressure 124 mmHg, and diastolic blood pressure 66 mmHg. There were no other documented adverse events for this subject.

Three subjects in Study COCA4vs10-002 treated with cocaine HCl 10% required premature removal of pledgets due to adverse events but did complete the scheduled procedure. Those subjects and the reason for early pledget removal are as follows:

- Subject (b) (6) – moderate nausea and diastolic hypertension
- Subject (b) (6) – mild intermittent paroxysmal hypertension and paroxysmal tachycardia
- Subject (b) (6) – moderate vasovagal syncope with bradycardia

There were five subjects (14%) in Study LNT-P6-733 who withdrew from the study after treatment. None were reported as due to the occurrence of an adverse event, but were categorized as follows: three withdrew their consent and two were withdrawn due to protocol violations. Of the three who withdrew consent after treatment 1, they all appeared to have increases in measured hemodynamic parameters and one subject had three out-of-range heart rate measurements; i.e., greater than 100 beats per minute. There was no additional information provided for the two subjects withdrawn due to protocol deviations.

8.4.4. Significant Adverse Events (Protocol-Defined SAEs)

The Applicant summarized other protocol-defined serious adverse events during Study COCA4vs10-001. While these AEs did not meet the FDA criteria for an SAE, the Applicant felt they needed additional explanation. There were 29 subjects who experienced 33 severe, Grade 3 protocol-defined SAEs and most of these included clinically relevant changes in measured hemodynamic parameters. None of these resulted in withdrawal of a subject from the study, except those previously discussed, and none resulted in treatment discontinuation. Some changes in vital signs were reported as monitoring errors; i.e., inaccurate measurement not corroborated with other parameters or with repeat measurement. Additional information regarding the observed vital sign changes will be discussed in Section 8.4.7, Vital Signs.

In Study COCA4vs10-002, there were four subjects who experienced four severe (Grade 3) TEAEs; three were in the cocaine HCl 4% treatment group and one subject in the cocaine HCl 10% treatment group. There were also two subjects treated with cocaine HCl 10% (400 mg) who experienced ST segment elevation. One subject experienced mild, asymptomatic ST segment elevation on a single monitoring ECG 1.5 hours after study drug application. The final, pre-discharge ECG was reported as 'normal'. The other subject experienced mild, asymptomatic ST segment elevation 2 hours after study drug application. The 12-lead ECG obtained 10 minutes after the observed ST segment change was read as 'otherwise normal'. No additional follow-up was provided for either subject.

No subject who received placebo solution experienced a Grade 3 TEAE in this study.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following discussion will contain a summary of the adverse events by study and within the entire safety population.

LNT-P6-733

There were no deaths, SAEs, or discontinuations due to an AE. There were a total of 280 treatment-emergent adverse events (TEAEs) documented in 34 subjects. The number of TEAEs was similar for both concentrations of cocaine HCl topical solution, but higher than reported for the placebo group. The majority, 95%, of TEAEs were reported as mild intensity and 93% were reported as related to study drug administration. There was one moderate TEAE reported with Test-1 dosing, cocaine HCl 4% solution, and 12 TEAEs reported with Test-2 dosing, cocaine HCl 10% solution. No subject dosed with placebo solution experienced a moderate TEAE. There was a single severe TEAE described as somnolence, possibly related to dosing with Test-2, which was resolved by the end of the study. The most common TEAEs were dysgeusia and hypoaesthesia of the mouth, pharynx, and teeth, and were felt to be expected clinical findings after administration of a topical anesthetic. There were a total of 16 TEAEs of palpitations, with a larger number reported with Test-2 dosing compared to Test-1 dosing, 11 versus 5, and none reported with placebo dosing. Additionally, there were three TEAEs for chest discomfort

reported with Test-2 dosing compared to none reported for either Test-1 or placebo dosing. All TEAEs were reported as resolved at the end of the study, with the exception of two; one related to nasal congestion and one related to a positive urine leukocyte esterase.

Study COCA4vs10-001

There were no deaths or AE discontinuations in this study. There was one FDA-defined SAE, previously described. Table 36 includes the TEAEs that occurred during the study by treatment group in both the efficacy and safety phases.

Table 36. General Summary of Treatment Emergent Adverse Events

	n (%)			
	Cocaine HCl 4% Total* (N = 57)	**Cocaine HCl 10% Total* (N = 59)**	**Placebo (N = 40)**	**Overall (N= 159)**
Subjects reporting any TEAE	53 (93.0)	55 (93.2)	35 (87.5)	143 (89.9)
Total number of TEAEs	85	104	57	246
Subjects reporting a severe TEAE[a]	12 (21.1)	10 (16.9)	7 (17.5)	29 (18.2)[c]
Total number of severe TEAEs[a,b]	14	11	8	33[c]
Subjects reporting a TEAE related to study drug[d]	49 (86.0)	56 (94.0)	8 (20.0)	113 (71.1)[c]
Total number of treatment-related TEAEs	70	88	13	171c
Subjects reporting an FDA-criteria SAE	0	1	0	1[c]
Total number of FDA-criteria SAEs	0	1	0	1[c]
Subjects who died	0	0	0	0
Life Threatening/Disabling TEAE (protocol-defined SAEs)	0	0	0	0
Subjects reporting a TEAE leading to discontinuation	0	0	0	0

Source: Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.4.
* Total is a combination of the Efficacy treatment (Phase 1) and Safety database treatment (Phase 2)
[a] Treatment-emergent AEs Grade 3 are equivalent to a severe classification. [b] Serious treatment-emergent AEs (SAEs) were defined in the protocol as grade 3 (severe) or grade 4 (life threatening) AEs; No grade 4 TEAEs were reported. [c] Sum of Cocaine HCl 4% Total, Cocaine HCl 10% Total and Placebo.[d] Classified as possibly, probably or definitely related.

Source: CSR Study COCA4vs10-001, p. 72 (PDF), Applicant's submission, NDA 209575

A total of 143 subjects (89.9%) had a least one TEAE and most (71.1%) were reported as possibly, probably, or definitely related to study drug treatment. Fifty-three subjects (93%) experienced 85 TEAEs in the cocaine HCl 4% treatment group, 55 subjects (93.2%) experienced 104 TEAEs in the cocaine HCl 10% treatment group, and 35 subjects (87.5%) experienced 57 TEAEs in the placebo group. While the number of severe TEAEs was higher in the cocaine HCl 4% treatment group, the percentage of overall TEAEs related to study drug was higher in the cocaine HCl 10% treatment group. Additionally, the dosing in Study COCA4vs10-001 was inconsistent and there was likely overlap, such that a subject in the cocaine HCl 4% treatment group may have received a dose consistent with that administered in the cocaine HCl 10%

treatment group, and vice versa. This suggests that the safety (and efficacy) results may not be reflective of the true safety profile of the two cocaine topical solutions.

Twenty-nine subjects overall (18.2%) experienced a total of 33 Grade 3 TEAEs, or protocol-defined SAEs. Twelve subjects (21.1%) experienced 14 Grade 3 TEAEs in the cocaine HCl 4% treatment group, 10 subjects (16.9%) experienced 11 Grade 3 TEAEs in the cocaine HCl 10% treatment group, and 7 subjects (17.5%) experienced 8 Grade 3 TEAEs in the placebo group. All other TEAEs were reported as mild or moderate in severity. The Applicant also reported TEAEs by study phase; i.e., efficacy and safety phases. The numbers of TEAEs across both cocaine HCl treatment groups were similar, but the number of subjects in the safety phase of the study was small.

The most common TEAE reported in ≥1% of subjects in all treatment groups was hypertension. More subjects who received cocaine HCl 10% topical solution experienced hypertension compared to subjects who received cocaine HCl 4% topical solution. Increased heart rate was the second most common TEAE reported and was experienced by more subjects in the cocaine HCl 4% group than in the cocaine HCl 10% group. In response to the clinical issues outlined in the 74-day letter, the Applicant clarified the number of subjects in each treatment group who experienced tachycardia greater than 100 bpm *and* experienced increases in heart rate greater than 20 bpm, a more clinically relevant heart rate assessment during cocaine exposure. The additional tabular data indicates that six subjects in the cocaine HCl 4% treatment group, five subjects in the cocaine HCl 10% treatment group, and no subject in the placebo group experienced those heart rate changes.

Refer to Table 37 for TEAEs by preferred term and system organ class for all treatment groups.

Table 37. All TEAEs Occurring in 1% of Subjects by Preferred Term and System Organ Class

	n (%)					
	Cocaine HCl 4%		Cocaine HCl 10%			
System Organ Class Preferred Term	Efficacy (N=39)	Total (N=57)	Efficacy (N=41)	Total (N=59)	Placebo (N=40)	Overall (N=159)
Subjects reporting any TEAE	35 (89.7)	53 (93.0)	38 (92.7)	55 (93.2)	35 (87.5)	143 (89.9)
Cardiac disorders	0	3 (5.3)	3 (7.3)	4 (6.8)	2 (5.0)	9 (5.7)
Bradycardia	0	2 (3.5)	1 (2.4)	1 (1.7)	0	3 (1.9)
Myocardial ischemia*	0	0	0	1 (1.7)	0	1 (0.6)
Tachycardia	0	1 (1.8)	2 (4.9)	2 (3.4)	1 (2.5)	4 (2.5)
Investigations	9 (23.1)	19 (33.3)	13 (31.7)	20 (33.9)	12 (30.0)	51 (32.1)
Blood pressure increased	0	1 (1.8)	0	0	1 (2.5)	2 (1.3)
Heart rate decreased	3 (7.7)	3 (5.3)	4 (9.8)	8 (13.6)	5 (12.5)	16 (10.1)
Heart rate increased	6 (15.4)	16 (28.1)	10 (24.4)	14 (23.7)	7 (17.5)	37 (23.3)
Respiratory, thoracic and mediastinal disorders	1 (2.6)	3 (5.3)	3 (7.3)	6 (10.2)	4 (10.0)	13 (8.2)
Hyperventilation	1 (2.6)	2 (3.5)	0	1 (1.7)	2 (5.0)	5 (3.1)
Nasal septum deviation	0	0	1 (2.4)	1 (2.4)	0	2 (1.3)
Vascular disorders	33 (84.6)	50 (87.7)	37 (90.2)	52 (88.1)	29 (72.5)	131 (82.4)
Diastolic hypertension	3 (7.7)	4 (7.0)	2 (4.9)	2 (3.4)	2 (5.0)	8 (5.0)
Hypertension	32 (82.1)	47 (82.5)	37 (90.2)	52 (88.1)	28 (70.0)	127 (79.9)
Hypotension	2 (5.1)	4 (7.0)	1 (2.4)	1 (1.7)	3 (7.5)	8 (5.0)

Source: Table 14.3.1.1. * Occurrence is <1% overall, but included due to severity
Adverse events were coded using MedDRA, version 17.0.

Source: CSR Study COCA4vs10-001, p. 75 (PDF), Applicant's submission, NDA 209575

Three subjects discontinued the study due to reported non-study drug reasons, including physician left the surgery center prior to procedure, baseline vital sign measurements out of range, and mistaken randomization.

Study COCA4vs10-002

There were no deaths or FDA-defined SAEs in this study. There were two subjects in the cocaine HCl 4% treatment group who withdrew due to an adverse event, previously discussed. Table 38 includes the TEAEs that occurred during the study by treatment group.

Table 38. General Summary of Treatment Emergent Adverse Events

	n (%)			
	Cocaine HCl 4% (N = 259)	**Cocaine HCl 10% (N = 259)**	**Placebo (N = 128)**	**Overall (N= 646)**
Subjects reporting any TEAE	218 (84.2)	237 (91.5)	94 (73.4)	549 (85.0)
Total number of TEAEs	301	368	125	794
Subjects reporting a severe TEAE[a]	3 (1.2)	1 (0.4)	0	4 (0.15)[c]
Total number of severe TEAEs[a]	3	1	0	4[c]
Subjects reporting a TEAE related to study drug[b]	200 (77.2)	232 (89.6)	17 (13.3)	449 (69.5)[c]
Total number of treatment-related TEAEs[b]	229	291	19	539[c]
Subjects reporting an SAE[e]	0	0	0	0[c]
Subjects reporting a TEAE leading to discontinuation[e]	2	0	0	2

Source: Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.4.
[a] No grade 4 TEAEs were reported.. [b] Classified as possibly, probably or definitely related. [c] No SAEs, no life threatening/disabling, and no deaths were reported. [d] Classified in MedDRA as TEAE, while described as an AE and other reason for discontinuation in Table 3 (Subject Disposition)

Source: CSR COCA4vs10-002, p. 89 (PDF), Applicant's submission, NDA 209575

A total of 549 subjects (85%) had at least one TEAE and most (67.9%) were reported as possibly, probably, or definitely related to study drug treatment. More subjects in the cocaine HCl 10% treatment group experienced TEAEs (91.5%) than subjects in the either the cocaine HCl 4% treatment group (84.2%) or the placebo group (73.4%). As previously mentioned, there were a total of four subjects, three in the cocaine HCl 4% treatment group and one in the cocaine HCl 10% treatment group who experienced a severe TEAE (Grade 3); however, more TEAEs in the cocaine HCl 10% treatment group were reported as related study drug, when compared to those in either the 4% treatment group or placebo group.

Similar to the findings in Study COCA4vs10-001, the most common TEAE reported in ≥1% of subjects in all treatment groups was hypertension. More subjects who received cocaine HCl 10% topical solution experienced hypertension compared to subjects who received cocaine HCl 4% topical solution or placebo solution. Tachycardia was the second most common TEAE reported and was experienced by more subjects in the cocaine HCl 4% group than in the cocaine HCl 10% group. In response to the clinical issues outlined in the 74-day letter, the Applicant clarified the number of subjects in each treatment group who experienced tachycardia greater than 100 bpm *and* experienced increases in heart rate greater than 20 bpm, a more clinically relevant heart rate assessment during cocaine exposure. The additional tabular data indicates that 18 subjects (7%) in the cocaine HCl 4% treatment group, 43 subjects (16.6%) in the cocaine HCl 10% treatment group, and two subjects (1.5%) in the placebo group experienced those heart rate changes.

Refer to Table 39 for TEAEs by preferred term and system organ class for all treatment groups.

Table 39. All TEAEs Occurring in ≥1% of Subjects by Preferred Term and System Organ Class

	n (%)			
	Cocaine HCl 4% (N = 259)	**Cocaine HCl 10% (N = 259)**	**Placebo (N = 128)**	**Overall (N= 646)**
Subjects reporting any TEAE	218 (84.2)	237 (91.5)	94 (73.4)	549 (85.0)
Total number of TEAEs	301	368	125	794
Cardiac disorders	31 (12.0)	47 (18.1)	10 (7.8)	88 (13.6)
Bradycardia	8 (3.1)	1 (0.4)	5 (3.9)	14 (2.2)
Sinus Tachycardia	6 (2.3)	9 (3.5)	0	15 (2.3)
Tachycardia	12 (4.6)	28 (10.8)	1 (0.8)	41 (6.3)
Tachycardia paroxysmal	2 (0.8)	6 (2.3)	1 (0.8)	9 (1.4)
Investigations	13 (5.0)	30 (11.6)	8 (6.3)	51 (7.9)
QRS prolonged (ECG)	4 (1.5)	8 (3.1)	3 (2.3)	15 (2.3)
QT Interval prolonged (ECG)	7 (2.7)	10 (3.9)	3 (2.3)	20 (3.1)
ST segment elevation (ECG)*	0	2 (0.8)	0	2 (0.3)
Heart rate increased	2 (0.8)	7 (2.7)	1 (0.8)	10 (1.5)
Musculoskeletal and connective tissue disorders	1 (0.4)	8 (3.1)	0	9 (1.4)
Exostosis**	1 (0.4)	8 (3.1)	0	9 (1.4)
Respiratory, thoracic and mediastinal disorders	18 (6.9)	20 (7.7)	4 (3.1)	42 (6.5)
Nasal septum deviation**	11 (4.2)	16 (6.2)	2 (1.6)	29 (4.5)
Nasal turbinate hypertrophy**	3 (1.2)	1 (0.4)	3 (2.3)	7 (1.1)
Vascular disorders	203 (78.4)	224 (86.5)	86 (67.2)	513 (79.4)
Diastolic hypertension	2 (0.8)	4 (1.5)	1 (0.8)	7 (1.1)
Hypertension	201 (77.6)	220 (84.9)	85 (66.4)	506 (78.3)
Source: Table 14.3.1.1. *Occurrence is <1% overall, but included due to potential severity. Adverse events were coded using MedDRA, version 17.0. **All events are pre-existing conditions, unrelated to study drug treatment.				

Source: CSR COCA4vs10-002, p. 91 (PDF), Applicant's submission, NDA 209575

8.4.6. Laboratory Findings

The Phase 3 studies did not evaluate laboratory data post-treatment, with the exception of cardiac enzyme evaluations for the subject with cardiac ischemia (refer to Section 8.4.2, Serious Adverse Events). 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

There were clinically significant vital sign changes observed in subjects treated with the cocaine topical solutions compared to those treated with placebo solution in the Phase 3 studies. The

observed changes, particularly increases in heart rate and diastolic blood pressure measurements, occurred in a larger number of subjects treated with 10% cocaine solution compared to those treated with 4% cocaine solution, and as previously discussed, many were classified as adverse events.

Heart Rate

Table 40 outlines the clinically significant heart increases observed in the Phase 3 studies, individually and combined. Specifically, the data presented includes those subjects who were tachycardic (with heart rates greater than 100 bpm) *and* experienced heart rate increases of greater than 20 bpm and those subjects who experienced increases of greater than 30% above baseline measurements. The parameters selected for inclusion in the table represent the clinically relevant changes measured intra-operatively that may result in a pharmacological intervention. While the percent change may appear to be a more meaningful parameter for heart rate data analysis, inclusion of those with tachycardia eliminates those subjects whose baseline heart rate may be low, such that a greater than 30% increase above that value may not present a clinically significant situation, depending on individual co-morbidities. Of note, the placebo subjects' vital sign data was not pooled due to the different randomization ratios employed in the two Phase 3 studies.

Table 40. Observed Heart Rate Changes, Phase 3 Studies

Clinical Study	Heart Rate >100 bpm *and* increases >20 bpm (n, %)	Heart Rate >30% increase (n, %)
COCA4vs10-001		
• 4% (N=57)	6 (11%)	15 (26%)
• 10% (N=59)	5 (8%)	15 (25%)
• Pbo (N=40)	0 (0%)	9 (23%)
COCA4vs10-002		
• 4% (N=256)	19 (7%)	51 (20%)
• 10% (N=254)	48 (19%)	78 (31%)
• Pbo (N=127)	2 (2%)	14 (11%)
Combined		
• 4% (N=313)	25 (8%)	66 (21%)
• 10% (N=313)	53 (17%)	93 (30%)

Source: Adapted from Applicant's submission, NDA 209575, and reviewer's analyses

This table demonstrates a clinically significant increase in heart rate in both cocaine treatment groups compared to placebo and a larger effect of the 10% cocaine solution on heart rate increases. Intraoperative increases of more than 20 bpm with tachycardia would likely result in a pharmacological intervention; e.g., increased anesthetic or analgesic administration or treatment with a beta-blocker. Increases of greater than 30% above baseline values may also result in an intervention, depending on the pre-existing medical conditions. In certain patient populations, such as those with underlying coronary artery disease, these increases may not be well-tolerated and could result in myocardial ischemia or infarction.

Systolic and Diastolic Blood Pressure

Table 41 outlines the clinically significant changes in measured systolic and diastolic blood pressure observed in the Phase 3 studies, individually and combined. Specifically, the data presented includes those subjects who were hypertensive *and* experienced increases of greater than 30% above baseline values.

Table 41. Systolic and Diastolic Blood Pressure Changes

Clinical Study	Systolic Blood Pressure >140 mmHg *and* increases >30% (n, %)	Diastolic Blood Pressure >90 mmHg *and* increases >30% (n, %)
COCA4vs10-001		
• 4%	2 (4%)	12 (21%)
• 10%	2 (3%)	9 (15%)
• Pbo	0 (0%)	6 (15%)
COCA4vs10-002		
• 4%	11 (4%)	24 (9%)
• 10%	12 (5%)	35 (14%)
• Pbo	3 (2%)	8 (6%)
Combined		
• 4%	13 (4%)	36 (11%)
• 10%	14 (4%)	44 (14%)

Source: Reviewer's analyses

This table demonstrates clinically significant increases in systolic and diastolic blood pressure in both cocaine treatment groups compared to placebo. Diastolic blood pressure appears to be affected more than systolic blood pressure after treatment with both concentrations of cocaine topical solution, and in Study COCA4vs10-002, the increases appear to be larger in a small subset of patients treated with 10% topical solution compared to those observed after treatment with 4% solution. Hypertensive measurements to this degree intraoperatively would likely result in a pharmacological intervention; e.g., increased anesthetic or analgesic administration or treatment with an antihypertensive medication. In certain patient populations, such as those with underlying coronary artery disease, these increases may not be well-tolerated and could result in myocardial ischemia or infarction.

As previously mentioned, the cocaine dosing in Study COCA4vs10-001 was calculated based on residual solution and was inconsistent within the treatment arms. This resulted in some subjects in the 4% treatment group receiving a potential 10% cocaine dose and those in the 10% treatment group receiving a potential 4% cocaine dose. This may be one explanation as to why the measured hemodynamic parameters in this study are inconsistent within treatment arms and differ from those measured in Study COCA4vs10-002.

Due to the increases in heart rate and blood pressure, most notably observed in Study COCA4vs10-002, an analysis using the MedDRA Adverse Event Diagnosis (MAED) Tool was

conducted and the following table (42) includes those results. While the MAED analysis results are exploratory only and should be interpreted with caution, the results do provide information regarding the AEs which may require additional exploration and those which may be observed with higher frequencies than in the placebo groups. The analysis results for Study COCA4vs10-001 are not shown, but indicate only a single significant odds ratio for the preferred term hypertension for the comparison between the 10% cocaine topical solution and placebo (odds ratio of 3.2 with confidence intervals of 1, 10.6).

Table 42. MAED Analyses for Specific Preferred Terms for Study COCA4vs10-002

Preferred Term	Treatment Comparisons	Odds Ratio (confidence intervals)	Risk Ratio (confidence intervals)
HTN	• 4% vs. pbo • 10% vs. pbo • 10% vs. 4%	1.8 (1.1, 2.8) 2.9 (1.7, 4.9) 1.6 (1, 2.6)	1 (1.3, 1.8) 1.3 (1.1, 1.5) 1.1 (1, 1.2)
Tachycardia	• 4% vs. pbo • 10% vs. pbo • 10% vs. 4%	- 7.6 (1.9, 67) 2.5 (1.2, 5.5)	- 13.8 (1.9, 100.6) 2.3 (1.2, 4.5)

- only significant odds and risk ratios were included
HTN: hypertension; pbo: placebo
Source: Reviewer's analyses

In summary, heart rate and blood pressure changes observed with administration the 10% topical solution are greater and more clinically significant than those observed with the 4% topical solution.

Respiratory Rate, Temperature, and Oxygen Saturation

There was an observed decrease from baseline in respiratory rate of approximately one breath per minute across all treatment arms, and there was no return to baseline in the 10% cocaine HCl group; however, no decrease was clinically significant and there was no corresponding decrease in oxygen saturation. The average change from baseline body temperature was approximately a 0.5° F increase across all treatment arms during pledget insertion and into the recovery period. These increases were not clinically significant but did appear to be more consistent in subjects treated with the cocaine topical solutions when compared to placebo subjects. There were no clinically significant changes reported in oxygen saturation across all treatment arms.

8.4.8. Electrocardiograms (ECGs)

In the Phase 3 studies, screening and post-dose (once Phase 1 discharge criteria were met) 12-lead ECG were analyzed. Single-lead ECG monitoring was performed prior to study drug administration and every 5 minutes thereafter until Phase 1 discharge criteria were met. There were no reports of asystole, ventricular tachycardia, arrhythmia, complete heart block, appearance of Q waves, or change in J point. There were no clinically significant arrhythmias aside from sinus tachycardia reported, which was previously discussed. The QT analysis

submitted by the Applicant will be discussed in Section 8.4.9, but observations regarding increases in QRS and QT_c duration will be briefly presented here. In the Phase 3 studies, there were 14 subjects in the 10% cocaine HCl group who experienced an AE of prolongation of the QRS interval or QT_c interval or both. This is in contrast to six subjects in the 4% cocaine HCl group and three subjects in the placebo group who experienced the same AEs. It is reassuring that the prolongation of cardiac depolarization and repolarization did not result in result in clinically significant arrhythmias reported in these clinical studies; however, the increased number of subjects in the cocaine treatment groups experiencing these ECG changes is concerning. Furthermore, because subjects with a past medical history of cardiac disease or an abnormal ECG were excluded from participation in these studies, the observed adverse events are being attributed to the study drug treatment.

8.4.9. **QT**

(b) (4)

(b) (4) there were subjects in the Phase 3 studies, primarily Study COCA4vs10-002, with documented QT prolongation (eight subjects treated with cocaine HCl 10%, five subjects treated with cocaine HCl 4%, and two subjects treated with placebo solution). Prolongation of the QT interval (and the subsequent development of a ventricular arrhythmia) is not an ECG finding that is only observed in the setting of chronic exposure to "triggering" medications. This is an ECG finding that is commonly observed in the operating room in response to a single administration of known "triggering" medications. Cocaine HCl does arguably have a relatively short half-life, but assumptions cannot be made about the plasma concentrations relative to prolongation of the QT interval. And lastly, because cocaine HCl topical solution has until recently been a marketed unapproved drug product, there is not a large post-marketing safety database, including the information expected from the regular annual reporting required after NDA approval, to support its safety profile with respect to cardiac conduction and the QT interval.

(b) (4) the Applicant did not conduct a dedicated

study to evaluate the potential effect of topical cocaine solution on ventricular repolarization observed as a prolongation of the QT interval. In lieu of conducting a dedicated study, the Applicant conducted a subpopulation analysis consisting of data from 12-lead ECG recordings captured during the screening visit and post-procedure once Phase 1 discharge criteria were met, during the Phase 3 studies. Continuous single-lead ECG monitoring was performed during the diagnostic procedure or surgery, however, the QT intervals could not be calculated from that captured data. The CDER Division of Cardiovascular and Renal Products (DCRP) QT Interdisciplinary Review Team (QT-IRT) was consulted for input regarding the adequacy of the Applicant's proposed QT evaluation. The team concluded that the submitted ECG data from the two Phase 3 studies is not adequate to satisfy the thorough QT evaluation requirements. Below is the language from the review completed by Dr. Christine Garnett:

ECG data were collected in two phase 3 studies in patients and in one healthy volunteer study, however, the ECG data submitted from these studies are not adequate to satisfy the TQT requirement because two reasons.

> *1. Patient ECG data: Both phase 3 studies included collection of 12-lead ECGs at screening and after phase 1 recovery (> 90 min post-dose). The timing of the 12-lead ECGs that were collected is not adequate to permit quantification of the effects of cocaine on the QTc interval as the T_{max} of cocaine is ~30 min. In addition, monitoring ECGs were collected, which appears to cover the time of peak cocaine concentration, but no QT data was submitted from these ECGs. An IR was sent to the Applicant (DARRTS 02/20/2018) requesting submission of these data. The Applicant responded to the IR stating that no quantitative ECG measurements were collected from these ECGs per the SPA-approved Case Report Forms (NDA 209575, sequence 0010).*
> *2. Healthy volunteer ECG data: The first post-dose ECG in this study was ~1 h 20 min postdose and does therefore not capture the time of peak cocaine concentration. Additionally, the study did not include a positive control or sufficiently high exposures to* (b) (4)*.*

In addition, we note that the peak plasma concentration of cocaine following the maximum recommended dose (400 mg) exceeds the supratherapeutic dose included in the TQT study for another cocaine containing product GOPRELTO (NUMBRINO: 433 ng/mL; GOPRELTO: 146 ng/mL).

Because the QT evaluation was not acceptable, conclusions cannot be made regarding the potential for either concentration of cocaine topical solution to have an impact on the QT or other ECG-measured intervals; therefore, a dedicated study is needed to inform the clinical risk of developing a cardiac rhythm disturbance due to a prolonged QT interval.

A teleconference was held with the Applicant on March 12, 2018, to discuss potential options for fulfilling the TQT evaluation requirement. The possibilities to satisfy the TQT requirement include supportive information resulting from a published literature review, additional subgroup analyses, or a TQT study.

On April 30, 2018, the Applicant submitted a TQT study protocol for review. The following key

comments were conveyed to the Applicant on June 13, 2018:

- Because of the anticipated changes in heart rate (see our next comment) we recommend that you remove the supratherapeutic dose and instead include the therapeutic dose (4%, 160 mg).
- A dose dependent increase in heart rate was observed in your previous clinical studies, as noted in the "Integrated Summary of Safety" submitted with your NDA. You will, therefore, need to consider the use of alternative methods for assessing changes in the QT interval, such as QTcI (individualized QT correction). To support alternative methods, it is important that drug-free baselines are available from a wide enough span of heart rates to cover treatment changes in heart rate, within each individual. One way to achieve this could be to have the subjects undergo postural maneuvers (e.g. unsupported sitting and standing) on drug-free visits. In addition, it is also important to account for QT/RR hysteresis prior to deriving the individual QT/RR relationship to avoid bias when estimating the individual QT/RR relationship. For additional information, please see "Methodologies to characterize the QT/corrected QT interval in the presence of drug induced heart rate changes or other autonomic effects" (Garnett, C. et al., Am Heart J 2012;163(3):912-30).

As of the date of this clinical review, the TQT evaluation had not been completed and is the basis for the CR action for Numbrino™ 4%. (b) (4)

8.5. Analysis of Submission-Specific Safety Issues

The Applicant did not specifically evaluate changes in nasal mucosa or smell in the Phase 3 studies beyond what was reported during the routine post-procedure follow-up on days 1 and 7. In review of the reported AEs, it does not appear there were clinically significant changes in either nasal mucosa or smell as a result of cocaine treatment. During Study LNT-P6-733, a pre- and post-study drug administration physical examination was conducted and all subjects had a normal examination at screening and at the end of the study.

8.6. Safety Analyses by Demographic Subgroups

Demographic subgroups that were analyzed for safety in this NDA included gender, age, and race. There do not appear to be differences in the incidence of TEAEs for males and females. Specifically, 87.3% of male subjects and 85.7% of female subjects experienced a TEAE. Because the overall number of SAEs was low, there was on stratification of AE severity by gender.

The age subgroup was analyzed by those <35 years, 35 to 65 years, and >65 years. The Applicant reported no clinically meaningful differences between the TEAE rates across these age groups, although noted that the number of subjects in the >65 year-old group was low

(N=13). This may be true, however, 100% of subjects in the >65 year-old group experienced a TEAE compared to 85.1% of subjects in the <35 year old group and 87.1% of subjects in the 35 to 65 year-old group. Furthermore, 100% of the subjects in the >65 year-old group treated with a cocaine topical solution experienced hypertension, compared to 50% of placebo subjects in the same age group.

The majority of subjects across the drug development program were white, 80.5%, or African American, 13.9%. Other races included American Indian or Alaska Native (N=3), Asian (N=36), and Native Hawaiian or other Pacific Islander (N=4). Because the number of participating subjects of other races were small, comparisons between them is not meaningful.

This reviewer is concerned about the incidence of TEAEs in subjects with low body weight. The recommended dosing for topical cocaine has been previously reported as 1 to 3 mg/kg of cocaine HCl (Fleming *et al*, 1990). This suggests that 160 mg of the 4% cocaine HCl would exceed the maximum recommended dose for subjects weighing <53 kg and 400 mg of the 10% cocaine HCl solution would exceed the maximum recommended dose for subjects weighing <133 kg. Arguably, the recommended dosing may be conservative, however, there did appear to be a larger number of subjects weighing ≤70 kg treated with cocaine HCl topical solutions who experienced a clinically significant increase in heart rate. Specifically, in Study COCA4vs10-002, there was a larger number of subjects who weighed 70 kg or less in both cocaine treatment groups who experienced increases in heart rate ≥30% above baseline, compared to subjects who weighed 100 kg or more.

8.7. Specific Safety Studies/Clinical Trials

The Applicant did not conduct additional safety studies.

8.8. Additional Safety Explorations

8.8.1. Human Reproduction and Pregnancy

The Applicant did not evaluate the effect of 4% or 10% cocaine HCl topical solution administration on human reproduction or pregnancy. There have been no clinical trials evaluating therapeutic cocaine use in pregnant women.

8.8.2. Pediatrics and Assessment of Effects on Growth

There have been no clinical trials evaluating the safety and efficacy of cocaine topical solutions in the pediatric population. The Applicant submitted an initial pediatric study plan (iPSP) on October 21, 2015 and it was agreed upon on October 14, 2016. The Applicant and the Agency agreed that (b) (4) The proposed pediatric studies evaluating 4% cocaine HCl are as follows:

- (b) (4)

The Applicant plans to submit a partial waiver for the 0 to <8 year-old cohort, however, at the time of this review the complete package to justify the waiver request had not been submitted. The Pediatric Review Committee, with input from the Division, agrees with a partial waiver for this age group, however, the agreed-upon required information needs to be submitted for a thorough evaluation. The outstanding information is to include actual use data, advice from key opinion leaders, and surveys of practitioners on the current use/utility of topical cocaine in pediatric subjects, with emphasis on 0 to <8 years of age.

The partial waiver request will provide supportive information indicating the use of cocaine topical solutions in children younger than 8 years of age is very small based on the following considerations:

- subjects <8 years of age are unlikely to cooperate with indicated procedures
- additional sedation or anesthesia is necessary for successful completion of the indicated procedures
- descriptions regarding the extent and degree of topical anesthesia is difficult or not possible
- variable dosing in younger subjects may result in safety issues

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 10% 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 10% 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% and 10% cocaine topical solutions, 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 monitored and recorded residual solution not absorbed by the cotton or rayon pledgets.

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

As previously mentioned, in December, 2017, 4% cocaine HCl topical solution, manufactured by Genus Lifesciences, Inc., gained FDA marketing approval. Prior to that date, both cocaine HCl topical solutions were marketed unapproved products with a long history of clinical use in nasal and sinus surgery. While it has only recently been formally regulated by the Agency, there have been no reports of serious adverse events related to its therapeutic use. 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 should remain similar to those reports in the published literature.

8.9.3. Additional Safety Issues From Other Disciplines

Aside from the inadequate TQT evaluation, the clinical pharmacology review team had an additional concern related to the use of cocaine HCl topical solutions in subjects with hepatic impairment. The Applicant did not evaluate the safety of cocaine HCl topical solutions in this patient population, either through a clinical study or comprehensive review of the published literature. Because the apparent systemic exposure is higher with this 4% solution than with the approved Goprelto®, and exposure with use of the 10% solution is even higher, a clinical evaluation in patients with hepatic impairment is needed. The clinical pharmacology review team is recommending changes to the product label, indicating it should not be used in patients with liver impairment, until a clinical study can be completed, as will be outlined in a post-marketing requirement (PMR).

8.10. Integrated Assessment of Safety

In addition to the results from their clinical studies, the Applicant is relying on pharmacokinetic and safety information for cocaine topical solutions in the published literature. Specifically, the systemic exposure results from Study LNT-P6-733, while different from those reported with the approved product, are supported by pharmacokinetic information in the referenced published articles. Additionally, the reported safety findings in the Applicant's clinical development program are consistent with those reported in the reviewed published literature, most commonly increased heart rate, tachycardia, increased blood pressure, and transient hypertension. The Applicant's integrated safety database included 347 subjects exposed to 4% cocaine HCl topical solution and 341 subjects exposed to 10% cocaine HCl topical solution. The safety population included 841 subjects enrolled, but three subjects withdrew prior to randomization. Additional safety concerns surrounding the nasal administration of the cocaine HCl solutions are the potential clinical effects on the nasal mucosa and on the ability to smell.

The Applicant reported a larger percentage of subjects in both cocaine treatment groups who experienced an AE compared to those in the placebo group and a larger number of those AEs were described as possibly or probably related to cocaine administration compared to placebo treatment. Additionally, there appeared to be larger percentage of subjects in the 10% cocaine HCl treatment group who experienced an AE compared to those in the 4% cocaine HCl treatment group and those classified as definitely related were reported for more 10%-treated subjects than for 4%- or placebo-treated subjects, as indicated in Table 43. However, because the randomization schemes differed between the studies, the interpretation of pooled safety data may not be entirely accurate due to Simpson's paradox. There were no deaths reported and a single SAE in the 10% cocaine HCl treatment group, as previously discussed in Section 8.4.2, Serious Adverse Events.

Table 43. Adverse Events Summary, All Clinical Studies

Safety Population (N=841)				
	Treatment Group			
	Cocaine HCl 4% (N=352)	Cocaine HCl 10% (N=354)	Placebo (N=192)	Overall (N=841)
Subjects with at Least One AE	300(85.2%)	323(91.2%)	133(69.3%)	726(86.3%)
Maximum AE Severity Grade				
1-Mild	266(75.6%)	280(79.1%)	122(63.5%)	639(76.0%)
2-Moderate	19(5.4%)	31(8.8%)	4(2.1%)	53(6.3%)
3-Severe	15(4.3%)	12(3.4%)	7(3.6%)	34(4.0%)
4-Life Threatening or Disabling	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
5-Death Related to AE	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Highest Relationship of AE to Study Drug				
Not Related	37(10.5%)	33(9.3%)	108(56.3%)	174(20.7%)
Possibly	204(58.0%)	208(58.8%)	24(12.5%)	410(48.8%)
Probably	48(13.6%)	65(18.4%)	1(0.5%)	114(13.6%)
Definitely	11(3.1%)	17(4.8%)	0(0.0%)	28(3.3%)
Subjects Experiencing at Least One SAE	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)
Subjects Withdrawn Due to an AE	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)
Deaths	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

Source: ISS, p. 27 (PDF), Applicant's submission, NDA 209575

The SOC with the largest number of reported TEAEs for the Phase 3 studies was vascular disorders, and hypertension was the most frequently reported TEAE. The reported incidence of hypertension was higher for subjects in the 10% cocaine HCl treatment group compared to subjects in the 4% cocaine HCl treatment group and subjects in the placebo group. Additionally, it appears that the degree of increases in diastolic blood pressure were higher in a subset of patients in Study COCA4vs10-002 treated with the 10% cocaine HCl solution, as previously discussed in Section 8.4.7, Vital Signs. These findings are not surprising given the sympathomimetic actions of cocaine. The primary safety concerns associated with cocaine HCl topical administration are elevations in systolic, diastolic, and mean arterial blood pressure. In clinical practice, either increases or decreases of greater than 30% above or below baseline values are typically considered clinically relevant. Measured increases to that degree generally result in a clinical intervention, such as increasing the depth of anesthesia or administration of a vasoactive medication if indicated. It appears there were more subjects who experienced such increases in diastolic blood pressure across both cocaine treatment groups compared to the number who experienced increases in systolic blood pressure. This suggests that cocaine may exert a greater effect on the vasculature during diastole of the cardiac cycle.

The cardiac disorders SOC had the second largest number of reported TEAEs during the Phase 3 studies, and included tachycardia, sinus tachycardia, and palpitations. Subjects treated with

10% cocaine HCl solution experienced a larger number of tachycardia, sinus tachycardia, and palpitation TEAEs compared to subjects treated with either 4% cocaine HCl or placebo solutions. As previously discussed in Section 8.4.7, Vital Signs, increases in heart rate of greater than 30% above baseline are clinically significant and would generally result in a pharmacological intervention.

Additional safety analyses were performed by cocaine dose administered and duration of pledget insertion. For dose administered, the milligram dose categories and percentages of patients who received the corresponding dose are as follows:

- 4% cocaine HCl topical solution
  - 0 to <41 mg (0)
  - 41 to <81 mg (34%)
  - 81 to <121 mg (10%)
  - 121 to ≤160 mg (56%)
- 10% cocaine HCl topical solution
  - 0 to <101 mg (0)
  - 101 to <201 mg (34%)
  - 201 to <301 mg (9%)
  - 301 to ≤400 mg (58%)

For the most commonly reported TEAE, hypertension, there does not appear to be a dose-response relationship across the 4% cocaine HCl doses administered. The Applicant reported a decrease in the incidence of hypertension associated with increasing administered doses of 10% cocaine HCl. In review of the analyzed data presented, that does appear to be the case, and while there may not be an adequate explanation for that finding, it is important to note that different dosing between the two groups did result in an increased incidence of hypertension, as well as other TEAEs. Additionally, there does appear to be a dose-response relationship within the cocaine treatment groups for the incidence of severe adverse events and the largest milligram doses of 10% cocaine HCl administered resulted in the highest incidence of TEAEs reported as definitely related to study drug.

There does appear to be a dose-response relationship with increasing doses of both 4% and 10% cocaine HCl for the adverse event of tachycardia.

The vast majority (>90%) of subjects had study drug pledgets applied for 17 to 23 minutes, so an analysis looking for differences in the occurrence of TEAEs across different pledget application times would likely not result in additional information for consideration. There were two subjects reported to have the pledgets applied for greater than 23 minutes, 26 and 27 minutes, both of which experienced hypertension.

There was a single subject across the entire clinical development program who experienced an SAE. While this low number is reassuring, it is still concerning given that he had no significant past medical history and no apparent risk factors for cardiac disease, suggesting careful patient selection may not mitigate the risk for an adverse cardiac event. Additionally, there were a large number of subjects who experienced clinically relevant increases in measured

hemodynamic parameters, particularly those treated with 10% cocaine HCl solution. Because subjects with a known history of cardiac disease, including coronary artery disease, irregular heart rhythm, and uncontrolled hypertension, and abnormal screening ECG were excluded from participation in the clinical studies conducted by the Applicant, it is not known how intranasal cocaine administration would be tolerated in these populations. Furthermore, the number of subjects evaluated in the >65 year-old age cohort in the Phase 3 studies was low (N=13), and according to the Centers for Disease Control and Prevention, National Center for Health Statistics, the prevalence of hypertension in 2015-2016, a well-documented risk factor for cardiac disease, was highest among patients >60 years of age (Fryar *et al*, 2017).

In summary, the safety concerns related to administration of these cocaine topical solutions are the following: the impact of cocaine treatment on the QT interval; clinically significant increases in measured hemodynamic parameters; the number of reported TEAEs; higher systemic exposure compared to FDA-approved Goprelto® (greater than 10-fold higher C_{max} after administration of 10% cocaine HCl topical solution); and the uncharacterized hemodynamic and adverse event profile in patients with a history of cardiac disease or known risk factors. Additionally, the single SAE is concerning given the apparent absence of cardiac risk factors in the subject's past medical history.

The additional safety concerns regarding changes in nasal mucosa and smell were not specifically evaluated during the Phase 3 studies, but there did not appear to be clinically significant changes that would have been documented during the routine post-procedure follow-up visits or phone calls. Furthermore, the pharmacology/toxicology review team did not identify these issues during review of the nonclinical data.

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. Prescription Drug Labeling

The proposed label for Numbrino™ 4% topical solution underwent several extensive revisions. The major edits, by section, are included below.

Section 1 Indications and Usage
The proposed indication for 4% cocaine HCl topical solution is too broad and does not accurately reflect the procedures and surgeries for which the product was evaluated in the Applicant's Phase 3 studies. Edits were made to more completely describe the degree of anesthesia to be expected with 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
The suggested edits to this section further clarify the composition and size of the pledgets recommended for use with this product. Additionally, edits were made to describe pledget preparation consistent with that used in Study COCA4vs10-002. The maximum recommended dose was also included.

Section 5 Warnings and Precautions
The suggested edits to this section further clarify the following clinical concerns:

- the risk of hypertension and tachycardia associated with administration of 4% cocaine HCl topical solution
- the potential for a positive cocaine toxicology screening test

Section 6 Adverse Reactions
The suggested edits to this section clarify the risks of cardiovascular-related adverse reactions, including hypertension and tachycardia. Tabular representations of adverse reactions for the individual Phase 3 study results were incorporated into this section and all percentages were rounded to the nearest whole number, with the exception of percentages less than 1%.

Section 7 Drug Interactions
The clinical pharmacology review team made several edits to this section to more accurately reflect those drug products most likely to cause an adverse drug interaction.

Section 8 Use in Special 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 8.6, Hepatic Impairment and Section 8.7, Renal Impairment. Refer to those reviews for complete labeling recommendations.

Section 14 Clinical Studies
This section was edited to include the efficacy findings from Study COCA4vs10-002. Because of the anticipated approval of Numbrino™ 4% (b) (4)

Additionally, the results of the subjective hemostasis evaluation, investigator observation, were included in this section of the label.

11. Risk Evaluation and Mitigation Strategies (REMS)

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

12. Postmarketing Requirements and Commitments

As previously discussed, the clinical pharmacology review team will request a PMR for evaluation of administration of cocaine HCl topical solution in patients with hepatic impairment. Refer to the review by Dr. Deep Kwatra for additional information.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): COCA4vs10-001, COCA4vs10-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
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): 0		
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		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Appears this way on the original

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RENEE L PETIT-SCOTT
07/19/2018

RIGOBERTO A ROCA
07/19/2018